

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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**National Institute for
Health Research**

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¹Infectious Diseases Unit, Vaccine Evaluation Centre, University Hospitals of Leicester NHS Trust and Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK

²Department of Health Sciences, University of Leicester, Leicester Medical School, Leicester, UK

³Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK

⁴Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK

⁵Health Protection Agency, Centre for Infections, London, UK

⁶Health Economics and Decision Science (HEDS), School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK

⁷Department of Microbiology, University Hospitals of Leicester NHS Trust, Leicester, UK

*Corresponding author

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Abstract

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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¹Infectious Diseases Unit, Vaccine Evaluation Centre, University Hospitals of Leicester NHS Trust and Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK

²Department of Health Sciences, University of Leicester, Leicester Medical School, Leicester, UK

³Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK

⁴Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK

⁵Health Protection Agency, Centre for Infections, London, UK

⁶Health Economics and Decision Science (HEDS), School of Health and Related Research (SchARR), University of Sheffield, Sheffield, UK

⁷Department of Microbiology, University Hospitals of Leicester NHS Trust, Leicester, UK

*Corresponding author karlgnicholson@doctors.org.uk

Background: Western industrialised nations face a large increase in the number of older people. People over the age of 60 years account for almost half of the 16.8 million hospital admissions in England from 2009 to 2010. During 2009–10, respiratory infections accounted for approximately 1 in 30 hospital admissions and 1 in 20 of the 51.5 million bed-days.

Objective: To determine the diagnostic accuracy and clinical effectiveness and cost-effectiveness of rapid molecular and near-patient diagnostic tests for influenza, respiratory syncytial virus (RSV) and *Streptococcus pneumoniae* infections in comparison with traditional laboratory culture.

Methods: We carried out a randomised controlled trial (RCT) to evaluate impact on prescribing and clinical outcomes of point-of-care tests (POCTs) for influenza A and B and pneumococcal infection, reverse transcriptase-polymerase chain reaction (RT-PCR) tests for influenza A and B and RSV A and B, and conventional culture for these pathogens. We evaluated diagnostic accuracy of POCTs for influenza and pneumococcal infection, RT-PCR for influenza and sputum culture for *S. pneumoniae* using samples collected during the RCT. We did a systematic review and meta-analysis of POCTs for influenza A and B. We evaluated ease and speed of use of each test, process outcomes and cost-effectiveness.

Results: There was no evidence of association between diagnostic group and prescribing or clinical outcomes. Using PCR as 'gold standard', Quidel Influenza A + B POCT detected 24.4% [95% confidence interval (CI) 16.0% to 34.6%] of influenza infections (specificity 99.7%, 95% CI 99.2% to 99.9%); viral culture detected 21.6% (95% CI 13.5% to 31.6%; specificity 99.8%, 95% CI 99.4% to 100%). Using blood culture as 'gold standard', BinaxNOW pneumococcal POCT detected 57.1% (95% CI 18.4% to

90.1%) of pneumococcal infections (specificity 92.5%; 95% CI 90.6% to 94.1%); sputum culture detected 100% (95% CI 2.5% to 100%; specificity 97.2%, 95% CI 94.3% to 98.9%). Overall, pooled estimates of sensitivity and specificity of POCTs for influenza from the literature were 74% (95% CI 67% to 80%) and 99% (95% CI 98% to 99%), respectively. Median intervals from specimen collection to test result were 15 minutes [interquartile range (IQR) 10–23 minutes] for Quidel Influenza A + B POCT, 20 minutes (IQR 15–30 minutes) for BinaxNOW pneumococcal POCT, 50.8 hours (IQR 44.3–92.6 hours) for semi-nested conventional PCR, 29.2 hours (IQR 26–46.9 hours) for real-time PCR, 629.6 hours (IQR 262.5–846.7 hours) for culture of influenza and 84.4 hours (IQR 70.7–137.8 hours) and 71.4 hours (IQR 69.15–84.0 hours) for culture of *S. pneumoniae* in blood and sputum, respectively. Both POCTs were rated straightforward and undemanding; blood culture was moderately complex and all other tests were complex. Costs and quality-adjusted life-years (QALYs) of each diagnostic strategy were similar. Incrementally, PCR was most cost-effective (78.3% probability at a willingness to pay of £20,000/QALY). Few patients were admitted within a timescale conducive to treatment with a neuraminidase inhibitor according to National Institute for Health and Care Excellence guidance.

Limitations: The accuracy study was limited by inadequate gold standards.

Conclusions: All tests had limitations. We found no evidence that POCTs for influenza or *S. pneumoniae*, or PCR for influenza or RSV influenced antimicrobial prescribing or clinical outcomes. The total costs and QALYs of each diagnostic strategy were similar, although, incrementally, PCR was the most cost-effective strategy. The analysis does not support routine use of POCTs for either influenza or pneumococcal antigen for adults presenting with acute cardiopulmonary conditions, but suggests that conventional viral culture for clinical diagnosis should be replaced by PCR.

Trial registration: Current Controlled Trials ISRCTN21521552.

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List of abbreviations

3WS	Three Winters Study	hMPV	human metapneumovirus
A&E	accident and emergency	HPA	Health Protection Agency
AFC	Agenda for Change	HR	hazard ratio
ANOVA	analysis of variance	HRG	Healthcare Resource Group
ARI	acute respiratory infection	HRQoL	health-related quality of life
AUC	area under the curve	HSV	herpes simplex virus
BHQ	black hole quencher	ICD-10	<i>International Classification of Diseases, Tenth Edition</i>
BMI	body mass index	ICER	incremental cost-effectiveness ratio
BTS	British Thoracic Society	IF	immunofluorescence
CAP	community-acquired pneumonia	ILI	influenza-like illness
cDNA	complementary deoxyribonucleic acid	IQR	interquartile range
CEAC	cost-effectiveness acceptability curve	ITT	intention to treat
CI	confidence interval	ITU	intensive treatment unit
CLIA	Clinical Laboratory Improvement Amendments	i.v.	intravenous
COPD	chronic obstructive pulmonary disease	MAU	Medical Admissions Unit
CPAP	continuous positive airway pressure	MCMC	Markov chain Monte Carlo
CPE	cytopathic effect	MCSD	minimum clinically significant difference
CRF	case report form	MeSH	medical subject heading
CrI	credible interval	MGB	minor groove binder
DH	Department of Health	MMLV	Moloney murine leukaemia virus
DNase	deoxyribonuclease	MRC-5	Medical Research Council 5 cells
dNTP	deoxynucleotide triphosphate	MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
EoU	ease of use	NA	not applicable
EQ-5D	European Quality of Life-5 Dimensions	NI	neuraminidase inhibitor
EuroQoL	European quality of life	NICE	National Institute for Health and Care Excellence
FDA	US Food and Drug Administration	NPT	near-patient test
GP	general medical practitioner	NPV	negative predictive value
HA	haemagglutinin	PCR	polymerase chain reaction
HAd	haemadsorption	PLC/PRF5	primary liver cells
HAI	haemagglutination inhibition	POC	point of care
		POCT	point-of-care test

PPV	positive predictive value	RSV	respiratory syncytial virus
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses	RT	reverse transcriptase
		RT-PCR	reverse transcriptase-polymerase chain reaction
PSSRU	Personal Social Services Research Unit	SBCMV	soil-borne cereal mosaic virus
QALY	quality-adjusted life-year	SD	standard deviation
QoL	quality of life	SE	standard error
QUADAS	quality assessment tool for diagnostic accuracy studies	SROC	summary receiver operating characteristic
RCT	randomised controlled trial	STARD	Standards for Reporting Diagnostic Accuracy
RETCIF	rapid enhanced tissue culture immunofluorescence	TS	total score
RFT	rapid flu test	TtR	time to reporting
RMK	Rhesus monkey kidney	UHL	University Hospitals of Leicester
RNA	ribonucleic acid	VSOP	virology standard operating procedure
RNAse	ribonuclease	VTM	virus transport medium
ROC	receiver operating characteristic		

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 health 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

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Chapter 1 Background and rationale

Elderly demographics

Western industrialised nations face a large increase in the number of older people. In 2006 there were about 200,000 more children of < 16 years of age than people at state pension age in the UK. However, in 2007, for the first time ever, the population at state pension age exceeded the number of children. And, despite increases to state pension age, the population at state pension age is projected to exceed the number of children of < 16 years by 400,000 in 2016, and by over 2 million in 2031.¹ Annual figures published by the NHS Information Centre reveal that people aged > 60 years accounted for almost half of all of the 16.8 million hospital admissions (finished consultant episodes) in 2009–10.^{2,3} During 2009–10, infections of the respiratory tract accounted for about 1 in 30 of all hospital admissions in England and 1 in 20 of the 51.5 million bed-days.⁴ Preparation for this population growth, including the prevention and care of illness, is of paramount importance.

Acute respiratory illness

Illness surveys conducted in general practice indicate an overwhelming importance of acute respiratory illness in comparison with other conditions. During the most recent (Fourth) National Morbidity Study, a higher proportion of people (31%) consulted for respiratory conditions at least once during the year than for diseases in any other single *International Classification of Diseases* (ICD) chapter.⁵ Overall, 67% of patients who saw their general medical practitioner (GP) with a respiratory condition did so because of an acute infection, i.e. \approx 20% of all consultations in primary care occur because of acute respiratory infections (ARIs), which are mostly viral. The rates of acute respiratory illness were highest among small children. They were lowest among subjects aged 45–64 years and then increased with age, and the percentage that was graded as ‘serious’ reached \approx 25% in those aged > 65 years.

Owing to the increasing severity of acute respiratory illness in older people, the number of hospital admissions in England for influenza, pneumonia and other acute lower respiratory infections (ICD-10 codes J10–J18, J20–J22) is approximately three times higher for people aged \geq 75 years than in younger people (*Figure 1*).⁴ Annual figures published by the NHS Information Centre reveal that among those aged > 75 years the number of admissions for influenza and pneumonia and other lower respiratory tract infections has doubled to almost 200,000 in England over the last 10 years (see *Figure 1*).⁴

The average length of stay for acute respiratory conditions increases progressively with age.⁶ Although the average length of stay for pneumonia has fallen during the last 20 years, it is 10–15% longer in those aged > 65 years than in younger adults (*Figure 2*).⁷ The annual number of pneumonia and influenza deaths (ICD-10 codes J10–J18) in England and Wales increases with increasing age and exceeds 1000 per annum in each of the 5-year age bands in those aged > 70 years (*Figure 3*). 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* – which are key aetiological agents of acute respiratory illness and, collectively, are responsible for considerable morbidity and mortality in the elderly.

There is a paucity of information on the relative incidence of influenza, RSV and pneumococcal disease among elderly cardiopulmonary admissions. Falsey *et al.*⁸ evaluated the number of hospitalisations for RSV infection relative to influenza in several thousand elderly people admitted to six hospitals in New York

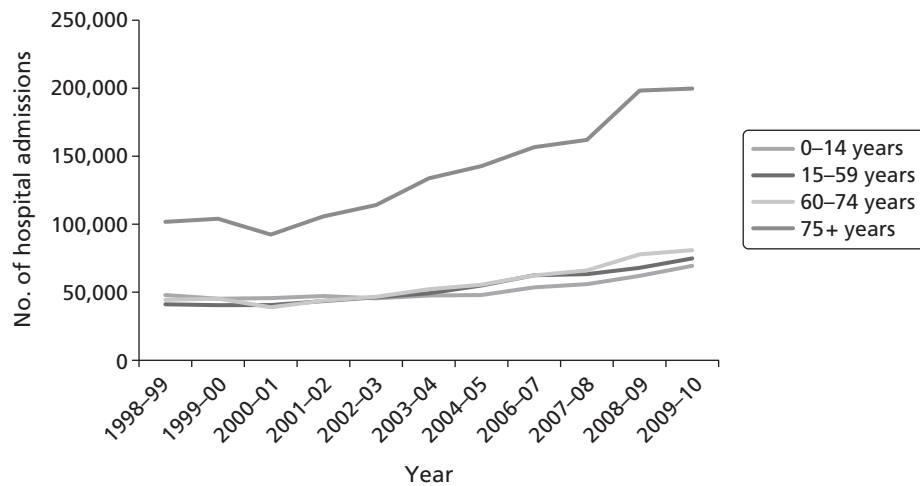


FIGURE 1 Annual number of admissions by age to NHS hospitals in England for 'Influenza and Pneumonia' (ICD-10 codes J10-J18), and 'Other acute lower respiratory infections' (J20-J22), years 1998-99 to 2009-10. Source: www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=202 (accessed 30 October 2010).

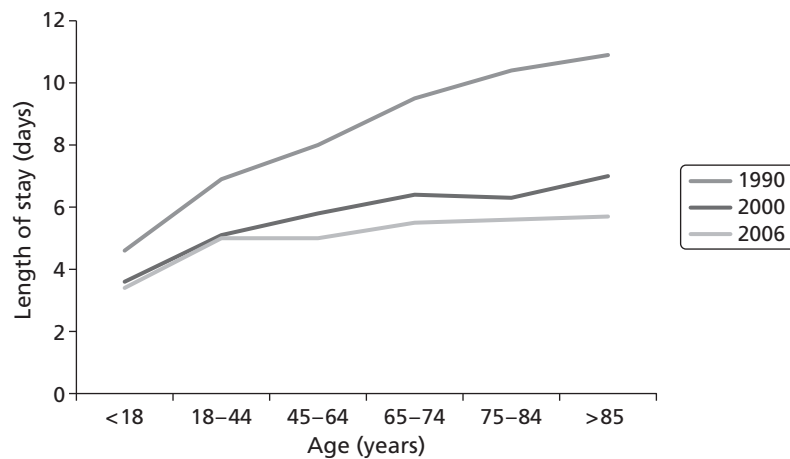


FIGURE 2 Average length of stay for 'pneumonia' in short-stay hospitals, by age: USA, 1990, 2000 and 2006. Source: www.cdc.gov/nchs/data/has/has09.pdf#102oryID=202 (accessed 30 October 2010).

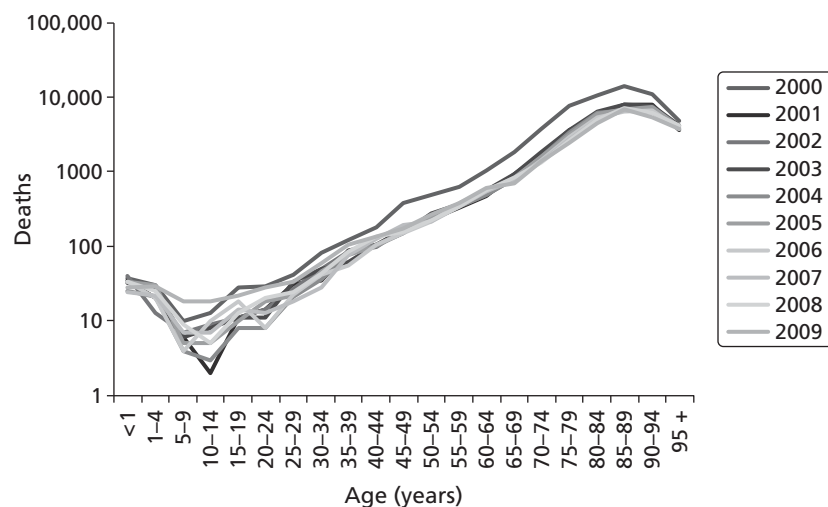


FIGURE 3 Annual number of pneumonia and influenza deaths (ICD-10 codes J10-J18) in England and Wales, years 2000-9 (compiled from annual ONS mortality statistics).

State between November and April 1989–1992. This and other studies suggest that RSV may be found in up to 5% of patients hospitalised with acute respiratory disease,^{9–13} although with molecular diagnostic tests, the number identified may be higher. Previous studies^{8–10,12,13} indicate that about 10% of cardiopulmonary admissions have influenza but the number of admissions is influenced by the severity of epidemics, which have been generally mild since 1999/2000, including the recent 2009 H1N1 pandemic. None of these studies was conducted in the UK, and referral and admission practices may differ in the UK from those elsewhere. About one-third of all patients who are hospitalised in Northern Europe with community-acquired pneumonia (CAP) have *S. pneumoniae* infection.¹⁴ *S. pneumoniae* is the most common microbiological cause of CAP,^{15,16} including the UK,¹⁷ and is the most commonly identified cause of CAP death.¹⁶

Influenza

About 20% of children and 5% of adults worldwide develop symptomatic influenza A or B each year.¹⁸ Although influenza A and B viruses circulate virtually every winter, quantification of the burden of influenza on consultations, emergency department examinations, hospital admissions and mortality has been difficult because influenza lacks pathognomonic features, it co-circulates with other respiratory pathogens, and it causes a range of non-specific complications, such as exacerbations of chronic cardiopulmonary disease. Indeed, during 2009, many hospital admissions with confirmed influenza A H1N1 infection presented with an exacerbation of asthma.¹⁹ During outbreaks, sentinel schemes, such as the Royal College of General Practitioners network in England, report increased consultation rates for influenza-like illness (ILI) and other respiratory syndromes that are strongly associated with excess mortality. In England and Wales, an estimated 6200–29,600 people died during each of the epidemics between 1975–6 and 1989–90.²⁰ These estimates are about 10 times the number of death certifications for influenza, suggesting that influenza is responsible for many ‘hidden deaths’. About 90% of influenza-associated excess deaths are among people aged ≥ 65 years.¹⁸ Although there are age-related increases in deaths from seasonal influenzal illness in both ‘at-risk’ and ‘low-risk’ groups,²¹ most deaths and hospitalisations occur in elderly people with chronic cardiopulmonary disorders.

The burden of influenza on winter admissions is poorly reflected by hospital activity analysis – as shown by our recent study of rapid molecular diagnosis of paediatric admissions in Leicester. We found that very few children with influenza were diagnosed or coded correctly.²² Moreover, analysis of hospital activity statistics for Leicester for winters 2002–3 and 2003–4 showed that only 2 of 5614 cardiopulmonary admissions among the elderly had a confirmed diagnosis of influenza. These local observations suggest that hospital activity data may grossly underestimate the true burden of influenza in hospitals, and the infrequency with which influenza is diagnosed may explain why hospital doctors consider conventional diagnostic virology for respiratory pathogens to be unhelpful.

Respiratory syncytial virus

Respiratory syncytial virus infection produces incomplete protection and reinfection is common. Like influenza, RSV infection in the elderly has no pathognomonic features, and cannot be distinguished from other respiratory virus infections clinically. Evidence indicates that RSV may be severe in the elderly, causing a spectrum of illness including pneumonia.^{8,23,24} Outbreaks in residential care facilities causing severe morbidity and mortality are well documented. Pneumonia occurs in 5–55% of cases and mortality of up to 20% is described.^{8,23} Because RSV has traditionally been considered a paediatric infection, evidence of the virus in community-dwelling elderly or admissions with cardiopulmonary disorders is usually not sought.

Community-acquired pneumonia and *Streptococcus pneumoniae*

Invasive pneumococcal disease and CAP exhibit a distinct winter seasonality that may be attributed to climatic conditions, crowding, air pollution, and respiratory virus activity, including influenza, RSV and rhinoviruses.^{25–27} In Leicester, weekly admissions data for 1352 cases of CAP admitted during the winters of 2002–3 and 2003–4 showed two peaks of 5 and 6 weeks’ duration during 2002–3 and a 14-week peak during 2003–4, confirming the seasonal pattern and its possible association with respiratory virus activity. Bacterial pneumonia is a well-recognised complication of influenza, and pneumococcus was the most

common microbe associated with life-threatening and fatal 2009 pandemic H1N1 infection. Between 9.5% and 48% of CAP may involve co-infection of typical and atypical organisms.²⁸ Of the 148 cases of *S. pneumoniae* infection identified by Porath *et al.*,²⁹ 100 had co-pathogens identified, usually 'atypicals'. Although the clinical importance of polymicrobial infection is uncertain, mixed infection may be associated with a more complicated course.³⁰ The overall mortality from CAP can be substantial – in one meta-analysis involving 33,148 patients with CAP, it was 12.3% for patients with *S. pneumoniae*, 9% for influenza, and 5% for RSV.¹⁶ Treatment cannot await the results of conventional microbiological tests, so an empiric regimen is necessary, which in the UK typically includes a β -lactam antibiotic, with or without a macrolide.¹⁷

It is possible that a positive point-of-care (POC) pneumococcal antigen test result could lead to the prescription of a single antimicrobial agent, placing patients with polymicrobial infection that includes *S. pneumoniae* at increased risk of death. Oosterheert *et al.*³¹ undertook a systematic review to assess whether treatment with a β -lactam plus macrolide or quinolone monotherapy is truly superior to β -lactam treatment alone. Eight relevant studies were selected. In six, significant reductions in mortality were found; in one, a reduction in hospital length of stay was found; and in another no beneficial effects could be demonstrated for treatment regimens with fluoroquinolone monotherapy or combinations of β -lactams and macrolides. The studies supporting the recommended treatment regimen were designed as non-experimental cohort studies and confounding may have influenced the results. The authors concluded that a randomised controlled trial (RCT) is warranted to circumvent the methodological flaws in the designs of the available studies.

Diagnostic tests

Diagnostic tests for influenza

Viral isolation and haemagglutination inhibition antibody testing are standard methods for influenza diagnosis but have drawbacks. Virus isolation by culture from respiratory secretions may take a week or more – for example, a median of 8 days in one recent study;²¹ it requires specialised laboratory facilities, and the results cannot be provided soon enough to influence treatment decisions or infection control. Serology provides a retrospective diagnosis.³² Neither test alone is considered a reference standard for influenza diagnosis, as each lacks sensitivity, but culture and serology have been used together as the reference standard in assessment of molecular tests.³³

Tests for rapid diagnosis of influenza A and B virus by immunofluorescence (IF) of exfoliated nasopharyngeal cells have shown variable sensitivity (40–100%) and specificity (86–99%);³⁴ they require specialist equipment and expertise, and are labour intensive. Rapid, near-patient tests (NPTs) for influenza vary in complexity, sensitivity and specificity.¹⁸ They can potentially aid clinical management, but their value in the hospital setting in influencing prescribing and infection control of adults is unclear. We used the Quidel® QuickVue Influenza A + B test (Quidel, San Diego, CA, USA) due to its apparent ease and speed of use, and reports of its sensitivity and specificity.¹⁸ However, its diagnostic accuracy in the elderly is unclear. Molecular diagnosis of influenza by reverse-transcriptase [reverse transcriptase-polymerase chain reaction (RT-PCR)] provides improved sensitivity and specificity, allows accurate detection, and facilitates the subtyping of influenza.³⁵ Like virus culture, multiplex polymerase chain reaction (PCR) offers the potential to identify several pathogens (e.g. influenza subtypes A/H1N1, A/H3N2 and B; RSV types A and B) in one sample and in one reaction.^{35,36} The technique is used routinely within the specialist diagnostic facilities of the Centre for Infections, Colindale, London, where it has a sensitivity of 92% and specificity of 84%.³³

Diagnostic tests for respiratory syncytial virus

Factors contributing to underestimations of the incidence and burden of RSV in the elderly include virus lability; the brief period of virus shedding and low titre of virus in nasal specimens during reinfection; the relative insensitivity of standard diagnostic tests – including the complement fixation test (CFT), virus culture (even when performed under rigorous conditions including bedside inoculation),³⁷ and rapid

antigen detection tests [IF and Directigen® enzyme immunoassay (Becton Dickinson, Franklin Lakes, NJ, USA)] in the elderly,^{37,38} and the frequent co-circulation of RSV with influenza.^{22,24} Multiplex RT-PCR has emerged as a sensitive and specific method of detecting RSV infection.³⁶ Examination of nose and throat swabs by multiplex RT-PCR from 167 elderly subjects (age ≥ 65 years) who presented to their GP with ILI during the winters of 1995–6, 1996–7 and 1997–8 showed that 15% had RSV.³⁹ These investigators detected one RSV infection for every two influenza infections, suggesting that the previously unrecognised burden of RSV in the elderly may be substantial.

Diagnostic tests for *Streptococcus pneumoniae*

Diagnosis of pneumococcal pneumonia is complicated by the lack of a diagnostic reference standard that is highly sensitive and specific. Despite being the single most important pathogen causing CAP, *S. pneumoniae* is undoubtedly underdiagnosed owing to limitations of conventional tests. Limitations of Gram stain and culture of sputum include failure to obtain sputum for culture – a fraction of patients produce sputum;²⁸ the overall diagnostic yield of sputum examination is very low (< 25%),⁴⁰ and isolation of *S. pneumoniae* from sputum may represent colonisation. Blood cultures have been considered as a standard in patients with CAP,⁴¹ but positive cultures are found in < 10% of patients with CAP, particularly those with low-severity CAP or have started antibiotics already.^{17,41,42} The test is often unhelpful, as positivity becomes evident no earlier than 24 hours after obtaining the specimen, and results typically have little influence on therapeutic decisions and outcomes.^{41,43–45} However, a review of patients with confirmed pneumococcal pneumonia found that 42% of patients with positive blood culture results had their treatment changed as a result.⁴⁶ As the overall prevalence of β -lactam resistance remains low in the UK, rapid near-patient testing for pneumococcal infection could influence therapeutic decisions.

Measurement of pneumococcal antibodies has not proven reliable for diagnosing pneumococcal pneumonia.⁴⁷ PCR appears to be more sensitive than blood culture but most studies have tested only a small number of samples, and have not compared different sample types from the same patients.⁴⁸ Murdoch *et al.*⁴⁸ used a nested PCR to target the pneumolysin gene in multiple sample types from 474 adults with CAP. The authors concluded that the pneumolysin PCR adds little to existing diagnostic tests and that it was less sensitive than the rapid urine antigen test. Other investigators have evaluated different PCR methods on sputum – in general they have had good sensitivity but poor specificity, whereas PCRs that have been developed to evaluate blood have had poor sensitivity but good specificity.⁴⁹ The detection of *S. pneumoniae* antigens in the urine of patients with pneumonia has been extensively studied using a variety of techniques. Although the performance of most tests has been somewhat disappointing, the BinaxNOW® urinary antigen test (Binax, Portland, ME, USA) that we used is simple to perform; it can detect the C polysaccharide cell wall antigen common to all *S. pneumoniae* strains and it provides results within 15 minutes. It has sensitivity of 80% or more in adults and children when positive blood cultures are used as reference standard.^{50–54}

Rationale for the study

The three respiratory pathogens, influenza, RSV and *S. pneumoniae*, are responsible for considerable morbidity and mortality, and become increasingly important as pathogens with advancing age and comorbidity. The elderly population of the UK is rapidly increasing in life expectancy and size. People aged > 60 years now account for almost half of the annual number of all hospital admissions, placing huge pressure on the health-care system. RSV and influenza can exacerbate chronic cardiopulmonary disease in adults of working age, adding to the demand for hospital beds and pressure on health-care providers to discharge patients at the earliest opportunity, preferably before admission to a hospital ward.

Vaccines and drugs to prevent RSV transmission and illness are unlikely to be available for use within the next decade. Vaccines against influenza and pneumococcal infection provide incomplete protection. Many pathogens can cause CAP, and the appreciable risk of death from CAP demands that treatment is given

empirically at the earliest opportunity. Early treatment with neuraminidase inhibitors (NIs) – within 48 hours of onset of illness – is considered essential.

Conventional diagnostic tests, especially viral culture, provide information too late to influence care and containment decisions. They are expensive and require specialised facilities and expertise. Blood cultures are often negative in patients with CAP caused by the pneumococcus; the result is also influenced by antecedent antimicrobial treatment. Treatment of CAP is usually empirical.

Compared with other diagnostic tests, the rapid point-of-care tests (POCTs) offer the greatest potential to influence antibiotic prescribing, ameliorate illness and prevent nosocomial transmission – but only if the tests are sufficiently sensitive and specific. PCR could provide comparable benefits if its longer turnaround time is compensated for by better test performance.

This study was designed to evaluate the ease and speed of use of the different tests, assess their costs, and identify whether they provide clinical and health-economic benefits, and rationalise the use of single-roomed accommodation.

The three diagnostic strategies assessed in this study were (1) POCTs for influenza A and B and pneumococcal infection; (2) RT-PCR tests for influenza A and B, and RSV A and B; and (3) conventional culture for these pathogens.

Chapter 2 Methods

Study design

We undertook a prospective RCT and economic evaluation of rapid POC, molecular and conventional diagnostic tests for influenza, RSV and *S. pneumoniae* in the management and outcome of acute cardiopulmonary admissions in the elderly (age ≥ 65 years) and 'high-risk' individuals with underlying chronic heart or lung disease, including asthma, who were 18–64-years of age at the time of presentation in two teaching hospitals in the UK. A summary of the protocol for the study is provided in *Appendix 1*. A copy of the full protocol is available from the Principal Investigator, Karl Nicholson.

Setting

The participating hospitals were Glenfield General Hospital and Leicester Royal Infirmary in the University Hospitals of Leicester (UHL) NHS Trust, Leicester, a city in the English East Midlands. The UHL NHS Trust serves a population of approximately one million subjects of all ages. It is the only facility within the county of Leicestershire that provides inpatient emergency medical care to the population of Leicestershire. The laboratory tests were carried out in the Department of Microbiology, Leicester Royal Infirmary.

Participants

We recruited people presenting to medical admissions units, or any ward accepting acute medical admissions, 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'/ILI, 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.

The inclusion and exclusion criteria for participants are shown in *Box 1*.

Recruitment

Medical and nursing staff on medical admissions units and wards providing acute medical care to patients with acute cardiopulmonary conditions identified eligible patients. Research nurses provided trial information and obtained signed informed consent from the patient or signed informed assent from a relative or carer.

Randomisation

Participants were then randomly allocated to one of three diagnostic study groups: (1) NPTs for pneumococcal infection and influenza; (2) rapid molecular tests for influenza and RSV; or (3) conventional laboratory diagnostic tests. Their investigations, medical care and discharge planning was provided as usual by the medical and nursing teams on the medical admissions units and other wards, not by the investigators. The randomisation process enabled the investigators to evaluate the role of the diagnostic tests on clinical outcomes. Ultimately, all diagnostic tests were performed on specimens from all subjects, providing the means to compare diagnostic accuracy.

BOX 1 Participant inclusion and exclusion criteria**Inclusion criteria**

- Written informed consent, or written informed assent by a relative or carer.
- Men or women aged ≥ 65 years, or 18–64 years, with underlying chronic heart or lung disease including asthma.
- Acute exacerbation of chronic cardiopulmonary illness,* or acute cardiopulmonary illness or ILI of ≤ 168 hours' duration, including pneumonia, influenza or ILI, exacerbations of COPD, bronchitis, asthma, congestive heart failure and cardiac arrhythmia.
- Recruitment within 16 hours of initial medical assessment.
- Able to comply with the study protocol.
- Access to a telephone.

Exclusion criteria

- Angina or suspected myocardial infarction.
- Previously recruited within 28 days of the current admission.
- Enrolment in a trial of antimicrobial therapy.

*These are provisional or suspected clinical diagnoses that have been made either by the referring GP or by the admitting medical team. In general, participants had at least one respiratory symptom and one systemic symptom or two or more respiratory symptoms from at least two of the following bullet points:

Respiratory symptoms

- Sore throat and/or hoarseness.
- Nasal symptoms (stiffness, and/or runny nose, and/or thick nasal discharge, or sneezing).
- Cough (new or increased).
- Sputum (new or increased).
- Wheezing (new or increased).
- Difficulty breathing/shortness of breath (new or increased).
- Chest pain with breathing.

Systemic symptoms

- Feverishness/sweating.
- Chills, shivers or rigors.
- Tiredness or fatigue.
- Decrease or loss of appetite.
- Headache.
- Muscle or body aches.
- Generally feel unwell.

The trial statistician generated randomisation codes, stratified by centre and using randomly permuted block sizes of 9, 12 or 15, which were not revealed to any person before randomisation. The randomisation code allocated participants in the ratio 1 : 1 : 1 to one of the three study groups. It was provided in sequentially numbered sealed study envelopes, which were stored securely (within a locked filing cabinet, within a locked office, within a locked department). The randomisation code for an individual patient became known to the research nurse only when signed informed consent or assent was obtained. The randomisation codes were then checked by the trial statistician against the master copy to ensure that the sequences concurred. It was not revealed to the participants or to the medical and nursing team providing care.

Planned interventions

Participants were randomised to receive:

- diagnostic assessment using rapid near-patient diagnostic tests (Quidel for influenza, and BinaxNOW for the pneumococcal antigen), *or*
- rapid molecular tests (for influenza A and B and RSV A and B), plus laboratory pneumococcal antigen testing, *or*
- conventional laboratory diagnostic assessment, notably culture for influenza A and B, RSV A and B, and *S. pneumoniae*, and serology for influenza A and B.

Although all tests were eventually carried out on all participants, clinicians were provided with rapid test results relating only to their randomisation group.

Collection of samples for microbiological analyses

Identical samples were taken from each person but were processed differently depending on the randomisation (Box 2).

BOX 2 Specimen processing

Rapid 'near-patient' test group

- *Blood culture* Undertaken by the admitting medical team or research nurse, and transported to/processed in the laboratory according to local protocols.
- *Paired (acute and convalescent) sera* An 'acute' venous blood sample was collected and transported to the laboratory, where the serum was separated and stored. A convalescent sample was collected, where possible, up to 90 days after admission. Acute and convalescent sera from participants were batched and tested at the HPA Centre for Infections for antibodies to seasonal strains of influenza A and B.
- *Freshly expectorated sputum* Sputum was collected from participants with a productive cough and cultured in the laboratory using standard operating procedures.
- *Freshly voided urine* Collected and tested on the ward, by a research nurse, for pneumococcal soluble antigen using the near-patient BinaxNOW *S. pneumoniae* test, according to the manufacturer's instructions (see Appendix 2).

BOX 2 Specimen processing (*continued*)

- *Nasopharyngeal swabs* A nasal swab sample was collected from the nostril that presented the most secretion (if any) under visual inspection. This specimen was analysed on the ward by a research nurse for the presence of influenza A and B antigen using the near-patient QuickVue Influenza A+B test (www.cliawaived.com/web/items/pdf/QDL-20183-Quidel_Influenza_Tests_Insert~619file1.pdf). A nasopharyngeal specimen was collected for deferred molecular testing and conventional virus culture using the opposite nostril to that used previously. The protocol for collecting and transporting nasopharyngeal specimens is provided in *Appendix 3*. The nasopharyngeal specimen was transported to laboratory (and stored at 4 °C if received after hours), where one aliquot was cultured for influenza A and B and RSV using standard operating procedures, and another was stored at –80 °C and analysed by deferred molecular diagnostic tests for influenza A and B and RSV A and B.

Molecular diagnostic group

- *Blood culture* Undertaken and processed as above.
- *Paired (acute and convalescent) sera* Collected and processed as above.
- *Freshly expectorated sputum* Collected from participants with a productive cough and processed as for the 'near patient test group'.
- *Freshly voided urine* Collected and transported to laboratory, where it was tested promptly for the presence of pneumococcal soluble antigen using the near-patient BinaxNOW *S. pneumoniae* test.
- *Nasopharyngeal swabs* Nasopharyngeal swabs were collected as for the 'near-patient test group'. They were transported to the laboratory and stored at 4 °C if they were received after hours. The nasal swab sample was stored at –20 °C for deferred testing for the presence of influenza A and B antigen using the near-patient QuickVue Influenza A+B test. An aliquot of the nasopharyngeal specimen was analysed promptly by molecular diagnostic tests for influenza A and B and RSV A and B. Another aliquot was cultured for influenza A and B and RSV using standard operating procedures.

Conventional test group

- *Blood culture* Undertaken and processed as for 'near-patient test group'.
- *Paired (acute and convalescent) sera* Collected and processed as for 'near-patient test group'.
- *Freshly expectorated sputum* Collected from participants with a productive cough and processed as for the 'near-patient test group'.
- *Freshly voided urine* Collected and transported to laboratory where it was stored at –20 °C for deferred testing for the presence of pneumococcal soluble antigen using the near-patient BinaxNOW *S. pneumoniae* test.
- *Nasopharyngeal swabs* Nasopharyngeal swabs were collected as 'near-patient test group' and transported to the laboratory as above. One aliquot was cultured for influenza A and B and RSV using standard operating procedures, and another was stored and analysed by deferred molecular diagnostic tests for influenza A and B and RSV A and B. The nasal swab sample was stored at –20 °C for deferred testing for the presence of influenza A and B antigen using the near-patient QuickVue Influenza A+B test.

Participants in each group gave a venous blood sample on entry to the study for blood culture if it had not been collected already by the medical team. Blood cultures were processed in the laboratory according to local protocols. Serum from an 'acute' blood sample was collected from participants in each group on entry to the study and stored for titration of antibodies against influenza A and B in paired 'acute' and 'convalescent' sera. It was originally planned that the 'convalescent' sample would be collected 10 days after admission. Because many people were discharged within 10 days of admission, we amended the protocol to collect 'convalescent' sera up to 30 days, and subsequently up to 90 days, after admission. Acute and convalescent sera were processed in the Influenza Laboratory at the Health Protection Agency (HPA) Centre for Infections, Colindale, London.

On entry to the study we collected freshly expectorated sputum for Gram stain and culture from participants in each study group with a productive cough. Freshly voided urine was collected from all participants on entry to the study and processed in the BinaxNOW *S. pneumoniae* test, as shown in Box 2, and according to the manufacturer's instructions (see Appendix 2). One nasal swab (collected from one nostril only), one nasal swab (collected from the opposite nostril) and one throat swab were collected on entry to the study (see Appendix 3), and were processed as shown in Box 2.

EuroQol quality-of-life assessment (European Quality of Life-5 Dimensions)

We assessed patients using the European quality of life (EuroQol) assessment at baseline on admission, and 7 and 28 days later. The EuroQol European Quality of Life-5 Dimensions tool (EQ-5D)⁵⁵ has been used in many cost-effectiveness studies^{56,57} and is recommended for use in the economic evaluation of health-care technologies within the UK in guidance issued by the National Institute for Health and Care Excellence (NICE).⁵⁸ It defines health in five dimensions: morbidity, self-care, usual activities, pain or discomfort, anxiety or depression. Each dimension has three levels: no problems, a moderate problem, or a severe problem. Health states defined by the level chosen for each dimension can be scored using utility weights reflecting the values from a representative sample of the UK population.⁵⁹ These utilities are scaled so that full health = 1 and death = 0, and they allow for severe health states for which health-related quality of life (HRQoL) is valued lower than death. The EQ-5D was self-completed by participants or was done by proxy if the participant was incapable of completing the self-administered questionnaire or providing a verbal response. Where patients were discharged, the EQ-5D was assessed by telephone interview of the patient, by postal questionnaire or by proxy.

Record-keeping

The mainstay of the record-keeping for this study was the case report form (CRF) (see Appendix 5). Individual CRFs were stored in locked filing cabinets in a secure University of Leicester research laboratory within Leicester Royal Infirmary.

The CRFs captured basic demographic data (including details of residential status, smoking habits, alcohol consumption, household contacts, influenza and pneumococcus immunisation status during the previous 3 years, and hospital admissions during the period 1 September to 30 April of the previous winter), the date and time of admission, the randomisation group, GP details, symptoms of the presenting illness, examination findings on admission, past medical history, and provisional diagnosis information on recruitment. The CRFs also recorded information on prescribed medication, oxygen and intravenous (i.v.) fluids, investigations, isolation status, complications, transfer to the intensive care unit, duration of stay, deaths, quality of life (QoL), and the timing of specimen collection and test results. Information was collected from the participant by research staff on recruitment and during follow-up visits, from medical case notes, computerised hospital records, and by post, and was entered into the CRF. Clinical and QoL data, together with laboratory findings, were entered into a database written in Microsoft Access 2000 (Microsoft Corporation, Redmond, WA, USA), which was maintained on University of Leicester mainframe computers, behind electronic firewalls allowing limited access with passwords. This proved a secure and confidential way of maintaining the records.

Near-patient tests

BinaxNOW *Streptococcus pneumoniae* test

Urine was tested for *S. pneumoniae* antigens using the BinaxNOW *S. pneumoniae* urinary antigen tests according to the manufacturer's instructions. The principles of the test and the test procedure are described in

Appendix 2. Freshly voided urine samples were collected from participants in each study group, as described in *Box 2*. Briefly, the test swab provided by the manufacturer was dipped into the urine specimen at room temperature, so that the specimen completely covered the swab head. The swab was removed from the urine and then placed into the bottom hole (the swab well) of the test device, and pushed upwards so that the swab tip was visible in the top hole. Three drops of the reagent was added to the bottom hole and the adhesive cover was immediately removed from the right edge of the test device, which was then closed and sealed. A positive-control swab (containing heat-inactivated *S. pneumoniae*) and an *S. pneumoniae* negative-control swab were also provided. The results were read 15 minutes later. A positive test result was indicated by the appearance of a pink-to-purple coloured line for both the specimen and positive control. A negative test result was indicated by a colour reaction to only the positive control.

Quidel QuickVue Influenza A + B test

Nasopharyngeal specimens collected as described in *Box 2* were tested for influenza type A and type B antigens using the Quidel QuickVue Influenza A + B test, according to the manufacturer's instructions. The principles of the test and the test procedure are described at www.cliawaived.com/web/items/pdf/QDL-20183-Quidel_Influenza_Tests_Insert~619file1.pdf.

Molecular diagnostic tests

We used molecular diagnostic tests that were developed at the Centre for Infections, HPA (London, UK), and the HPA Laboratory, Cambridge.

Ribonucleic acid extraction from clinical and control samples

Swab samples in virus transport medium (VTM) were vortexed vigorously for 1 minute to dislodge material attached to the swab. Each sample was mixed with 2 ml of amphotericin B (Fungizone®, Gibco®, New York, NY, USA) (2.5 µg/ml concentration) then vortexed to mix before removal of an aliquot for nucleic acid extraction. Viral ribonucleic acid (RNA) was extracted from nasopharyngeal specimens that were collected, transported and stored, as described in *Box 2*. During the first study season, viral RNA was manually extracted from 150-µl aliquots of nasopharyngeal specimen using the guanidium isothiocyanate method described by Boom *et al.*,⁶⁰ with a final elution volume of 30 µl. Although this method provided high-quality RNA for PCR, subsequent work was performed using an automated nucleic acid extraction platform (X-tractorGene, Corbett Robotics, Australia) with a guanidine isothiocyanate reagent pack (Sigma-Aldrich, St Louis, MO, USA) according to the manufacturer's specifications. Briefly, manual cell lysis was performed by adding 100 µl of sample digest buffer and 360 µl of lysis buffer to a 180-µl nasopharyngeal sample aliquot. The entire 640-µl volume was then transferred into a lysis block, which was placed in X-tractorGene for automated processing, providing a final elution volume of 50 µl.

Positive-control viruses and two negative controls were included with each extraction. The control viruses were influenza strains A/Taiwan/1/86 (H1N1), A/Moscow/10/99 (H3N2) and B/Panama/45/90; RSV strains Long (RSV A) and N2 (RSV B); and human metapneumovirus (hMPV). The no-template controls were VTM and deoxyribonuclease (DNase)/ribonuclease (RNase)-free water. The controls were made as quality-controlled batches, stored at -80 °C and then undergoing the same lysis procedure and nucleic acid extraction described above.

Reverse transcription

Synthesis of complementary deoxyribonucleic acid (cDNA) from extracted RNA was primed using random hexamers and Moloney murine leukaemia virus (MMLV) reverse transcriptase (RT) as described by Stockton *et al.*,³⁶ prior to amplification by either the multiplex semi-nested conventional PCR or real-time PCR methods. In a 40-µl reaction, 22.2 µl of RNA was added to a RT mix containing 20 mM Tris-HCl, 50 mM KCl, 7.5 mM MgCl₂, 100 mM of each deoxynucleotide triphosphate (dNTP), 5.3 nM of a random hexamer

(Promega, Madison, WI, USA), 1.6 U of ribonuclease inhibitor (RNasin) (Promega) and 200 U of MMLV transcriptase (Invitrogen, Carlsbad, CA, USA). The mixture was incubated at room temperature for 10 minutes, at 37 °C for at least 45 minutes, at 95 °C for 5 minutes and then quenched on ice for at least 1 minute.

Polymerase chain reaction tests

Different PCR assays were used to detect influenza A and B and RSV A and B during the 3-year study that took into account ongoing technological advances and availability. The method applied during the first year of the study used conventional PCR. Subsequently, real-time PCR methods were applied to facilitate rapid, high throughput of specimens.

Semi-nested multiplex conventional PCR During the first year of the study, detection and subtyping of influenza A H1 and H3, influenza B, and RSV A and RSV B were carried out by conventional, semi-nested PCR targeting the haemagglutinin (HA) region of the influenza genome, and the N and P regions of RSV in a multiplex reaction as described by Stockton *et al.*³⁶ For primary PCR, 20 µl of cDNA was added to the master mix to make up a final reaction volume of 100 µl. For secondary PCR, 2 µl of the primary PCR product was added to 48 µl of reaction master mix for a final volume of 50 µl. Secondary PCR amplicons were visualised using ethidium bromide following gel electrophoresis on 1.2% agarose (Roche, Mannheim, Germany). Band patterns were compared against positive-control viruses for influenza and RSV. Negative controls included DNase/RNase-free water and VTM.

HPA Cambridge one-step quadriplex real-time RT-PCR During the second year of the study, we used a one-step quadriplex PCR to detect influenza A and B according to the National Standard Method virology standard operating procedure (VSOP) 25.⁶¹ This assay amplified 5 µl of extracted RNA template in a 25-µl reaction volume with generic primers targeting the conserved region of the matrix gene for influenza A/B detecting all known influenza subtypes (H1–H15) and influenza B, and includes a bacteriophage MS2 internal control. The specificity of this assay was evaluated against a panel of influenza A (subtypes H1–H15), influenza B strains and a respiratory panel of pathogens to ensure specificity of the assay for influenza type A, influenza A subtype H5 and influenza type B. All samples were analysed in duplicate, and both results had to be concordant for a definitive positive or negative diagnosis. Data analysis was performed using the Rotor Gene software versions 6.0.41 and 6.1.71 (Corbett Research, Australia). This method and all other real-time PCR methods in the study used a Rotor-Gene real-time PCR machine (Corbett Research, Australia), and master mix and enzyme kits purchased from Invitrogen (Carlsbad, CA, USA). Forward and reverse primers were obtained from Eurofins (London, UK); probes tagged with minor groove binders (MGBs) were synthesised by Applied Biosystems (ABI, Warrington, UK) and probes labelled with Cy5 and Rox were purchased from Metabion (Martinsried, Germany).

HPA Colindale, one-step influenza multiplex real-time RT-PCR During the third year of the study, we detected H1 and H3 subtypes of influenza A and influenza B using a one-step multiplex PCR according to the National Standard Method VSOP 50 as described by Stephenson *et al.*⁶² but with minor modifications. This assay amplified 7.5 µl of extracted RNA template in a 25-µl reaction volume, with primers and probes targeting conserved regions of the HA gene of H1, H3 and B viruses, and includes a soil-borne cereal mosaic virus (SBCMV) internal control. All samples were analysed in duplicate, and both results had to be concordant for a definitive positive or negative diagnosis. Primers and probes tagged with black hole quencher (BHQ) were obtained from Eurofins (London, UK); other probes tagged with MGB were purchased from ABI. Modifications included substitution of the fluorophores VIC to JOE and NED to Cy5. Data analysis was performed using the Rotor-Gene software version 6.1.71.

HPA Colindale, One-step real-time RT-PCR for RSVA and RSVB and hMPV, and two-step real-time, multiplex PCR for RSVA, RSVB, and hMPV We used one-step real-time RT-PCR for RSVA, RSVB, and hMPV during the second year of the study, and a two-step RT-PCR for these pathogens, according to the HPA SOP V-5381/01–06. The same primers and probes were used in both the one-step and two-step assays

and targeted conserved regions of the respective nucleocapsid genes in RSV A, RSV B and hMPV⁶³ and both assays included an SBCMV internal control. In the one-step method, 7.5 µl of extracted RNA template was used in a 25 µl total reaction volume. In the two-step assay, 22.2 µl of extracted RNA was added to 17.8 µl RT mix and then 2.5 µl of the cDNA product was added to 22.5 µl reaction mix for a total volume of 25 µl. All samples were analysed in duplicate with results validated as positive or negative where both replicates were concordant. Probes tagged with BHQs and primers were purchased from Eurofins (London, UK).

Conventional diagnostic tests

Virus culture

Nasopharyngeal samples were processed in the laboratory according to local protocols. Two cell lines were used for viral culture: primary liver cells (PLC/PRF5) (a continuous primary liver carcinoma line)⁶⁴ and Medical Research Council 5 cells (MRC-5) from human fetal lung.⁶⁵

Approximately 0.25 ml of the nasopharyngeal specimen in VTM was inoculated into monolayered PLC/PRF5 and MRC-5 cells in culture tubes and incubated, stationary, at 33 °C overnight. Tubes negative for cytopathic effect (CPE) after 24 hours were reincubated, with rolling at two to three revolutions per minute, at 33 °C in fresh maintenance medium.

MRC-5 cell culture tubes were observed until 28 days after inoculation. Those that were CPE positive were confirmed and subtyped by IF using group-specific antibodies, whereas those that were CPE negative were reincubated and observed up to 28 days after initial inoculation. If contamination occurred during this period, the original samples were filtered and reinoculated into fresh culture tubes. If the cell monolayer sheet appeared to be of poor quality then cells were scraped off the tubes, transferred into a fresh culture tube and reincubated and analysed for up to another 28 days.

PLC/PRF5 cell culture tubes were observed for CPE twice weekly and haemadsorption (HAd) was concurrently performed using human red blood cells type O. CPE- and/or HAd-positive tubes were confirmed and subtyped by IF, whereas those that were negative were reincubated and observed for up to 14 days post initial inoculation. As with MRC-5 tubes, contaminated tubes were filtered and reincubated, whereas those with poor cell sheets were scraped off and transferred into fresh culture tubes for analysis up to another 14 days.

Haemagglutination inhibition

Antibody responses were titrated by the Respiratory Virus Unit, Centre for Infections, HPA (London, UK), by haemagglutination inhibition (HAI) assay using established protocols. Sera were tested at an initial dilution of 1/8 and were given serial two-times dilutions to establish end point titres. Acute and convalescent sera were tested in parallel, in duplicate, under masked conditions using A/New Caledonia/20/99 (H1N1), A/California/7/2004 (H3N2), and B/Malaysia/2506/04 (a descendant of the B/Victoria/2/87 lineage) as test antigens during the 2005–6 season; A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/04 during the 2006–7 season; and A/Solomon Islands/03/2006 (H1N1), A/Brisbane/10/2007 (H3N2), and B/Florida/4/2006 (a descendant of the B/Yamagata/16/88 lineage) during the 2007–8 season. A fourfold or greater rise in antibody titre was considered a significant rise.

Blood cultures

Blood cultures bottles were incubated using the BacT/ALERT 3D automated blood culture system (bioMérieux, Durham, NC, USA) according to local protocols. Bottles flagging positive growth were

removed and a drop of the blood culture broth was Gram stained and examined under the microscope. Blood culture broth with Gram-positive cocci in chains were inoculated onto blood agar plates and incubated aerobically and anaerobically at 37 °C. Primary antibiotic susceptibility for streptococci to include optochin were also set up on blood agar and Iso-sensitest agar (Oxoid, Basingstoke, UK), and incubated aerobically at 37 °C. The presence of *S. pneumoniae* was confirmed by demonstrating streptococci in the Gram stain of colonies, negative catalase test and susceptibility to optochin.

Gram stain and microscopy of sputum

Sputum was examined by Gram stain and microscopy according to local protocols. Briefly, sputum smears on slides were flame heated to fix, and then stained in the following order: Crystal violet, Gram's iodine, ethanol and carbol fuchsin. Microscopic analysis was performed using immersion oil and bright-field microscopy. Samples positive for Gram-positive cocci, Gram-positive bacilli, Gram-negative cocci and Gram-negative bacilli were rated, subjectively, using a '+' system, whereby the lowest copy number receives one + and confluent samples are given ++++. The presence of epithelial cells and white blood cells was also observed and reported.

Sputum culture

Sputum was cultured on blood and chocolate agar according to local protocols. Samples were diluted with equal volume of sterile saline, homogenised and inoculated onto chocolate agar with bacitracin, and blood agar with optochin. Plates were incubated aerobically in CO₂ at 37 °C, were read at 24 hours and 48 hours. *S. pneumoniae* were identified by Gram stain showing streptococci, negative catalase test and susceptibility to optochin.

Outcome measures

Clinical

Impact of test result on prescribing:

- Time, from admission to first administration of 'narrow-spectrum' antibiotics.
- Time, from admission to first administration of oral antibiotics.
- Time, from admission to prescription of 'no antibiotics' (oral or i.v.) administered to patients with influenza or RSV.
- Proportion of patients in each group who are prescribed NIs.

Impact of test result on duration of hospitalisation:

- For all patients in each diagnostic group.
- For patients in each diagnostic group with:
 - Influenza.
 - RSV.
 - *S. pneumoniae* infection.

Fever duration during first 10 days of hospitalisation

- Time, from admission until patients became apyrexial, for:
 - All patients in each group.
 - Patients with *S. pneumoniae* infection.

Supplemental oxygen dependence and continuous positive airway pressure dependence during first 10 days of hospitalisation

Admissions to intensive care and ventilator support during first 10 days of hospitalisation

Deaths within 28 days of hospitalisation

- For all patients in each diagnostic group.
- Overall, for patients with:
 - Influenza.
 - RSV.
 - *S. pneumoniae* infection.

Quality of life:

- For all patients in each diagnostic group.
- For patients in each diagnostic group with influenza, RSV and *S. pneumoniae* infection.

Use of isolation facilities by patients with influenza and RSV, and inappropriate use by those with *S. pneumoniae* infection

Financial

Costs of the diagnostic tests

Care costs

Cost savings arising from the use of diagnostic tests

Total NHS costs

Incremental cost per case detected and cost per QALY

Laboratory

Diagnostic accuracy: sensitivity, specificity, and positive and negative predictive values

Ease of use of diagnostic tests

Speed of use of diagnostic tests

Cost per case detected

Antimicrobial spectrum of activity

Broad-spectrum antibiotics

The following antibiotics, or classes of antibiotics, for the purposes of this study, were considered to be broad-spectrum antibiotics, i.e. having activity against Gram-positive *and* Gram-negative pathogens, with or without anaerobic organisms:

- Cephalosporins.
- Co-amoxiclav (Augmentin®, GSK).
- Piperacillin with tazobactam (Tazocin®, Pfizer).
- Carbapenems [imepenem with cilastatin (Primaxin®, MSD), meropenem (Meronem®, AstraZeneca), ertapenem (Invanz®, MSD)].

- Quinolones [ciprofloxacin (Ciproxin®, Bayer), levofloxacin (Tavanic®, Sanofi-aventis), moxifloxacin (Avelox®, Bayer), etc.].
- Tetracyclines [doxycycline (non-proprietary), oxytetracycline (non-proprietary), minocycline (non-proprietary)].
- Cotrimoxazole (non-proprietary).
- Clarithromycin and azithromycin (non-proprietary).
- Clindamycin (non-proprietary).

Narrow-spectrum antibiotics

The following antibiotics, or classes of antibiotics, are considered to be narrow-spectrum antibiotics, i.e. predominantly having activity against either Gram-positive or Gram-negative organisms, or anaerobic organisms:

Gram-positive antibiotics

- Benzylpenicillin (and penicillin V).
- Flucloxacillin.
- Amoxicillin (and ampicillin).
- Erythromycin.
- Vancomycin.
- Rifampicin.
- Fusidic acid.
- Linezolid.
- Daptomycin.

Gram-negative antibiotics

- Gentamicin and other aminoglycosides.
- Aztreonam.
- Trimethoprim.
- Nitrofurantoin.

Anaerobic antibiotics

- Metronidazole.

Where multiple agents are used together, they are classified as broad spectrum if either is a broad-spectrum agent, or if together they cover Gram-negative and Gram-positive organisms, with or without anaerobes.

Sample size

Statistical power of the Three Winters Study (3WS) was estimated for one laboratory end point (sensitivity/specificity), the primary clinical end point (i.e. length of stay), and one secondary end point (i.e. appropriate isolation levels).

The initial sample size calculation proposed that if the average sensitivity/specificity of the tests is assumed to be 80% and a 20% dropout rate was assumed then 2752 patients *in total* would enable the sensitivity/specificity to be estimated to within two standard errors (SEs), i.e. 7.6% if the disease prevalence was 5% and 5.4% if the prevalence was 10%.

In terms of clinical end points, 2752 patients *in total* would also enable a minimum clinically significant difference (MCSD), between diagnostic policies, of 1 day in the mean length of stay [assuming standard

deviation (SD) = 6 days] to be detected at the 5% significance level with over 80% power, assuming a 20% dropout rate and adjusting for the fact that there are three groups. In total 2752 patients would also enable a MCSD, between diagnostic policies, of an improvement in appropriate use of isolation facilities from 5% to 15% to be detected at the 1% significance level with over 95% power, assuming a 20% dropout rate and adjusting for the fact that there are three groups.

Clearly, the initial sample size calculation was driven by the desire to estimate the sensitivity/specificity with a sufficient level of precision but that this depended crucially upon the disease prevalence. Consequently, the sample size calculation was revisited in 2007 after the first two winters' data were available. During 2005–6, the overall disease prevalence was 18.7%, and during 2006–7 it was 10.3%, giving a combined disease prevalence across the first two winters of 13.2%. Consequently, if the average sensitivity/specificity was 80% and the dropout rate continued to be 20% then 1200 patients *in total* would enable the sensitivity/specificity to be estimated to within, i.e. two SE, 7.8% assuming a prevalence of 13%. Hence, the required sample size was revised to 1200 patients *in total*, as this still enabled both a MCSD of 1 day in mean length of stay (SD = 6 days) to be detected at the 5% significance level with over 80% power, and a MCSD of an improvement in appropriate use of isolation facilities from 5% to 15% to be detected at the 1% significance level with over 95% power, both assuming a 20% dropout rate and allowing for the fact that there are three groups.

Statistical methods

Statistical analyses were carried out using Stata version 11 (StataCorp LP, College Station, TX, USA). The study was analysed as an intention-to-treat (ITT) study; effectively all patients were analysed according to the group to which they were randomly allocated, regardless of whether they were in fact managed according to the results of their designated diagnosis method.

For continuous, non-time-to-event, outcomes the three intervention groups were compared using either parametric [analysis of variance (ANOVA)] or non-parametric (Kruskal–Wallis) test as appropriate, and summary statistics were reported as means (SD) and medians [interquartile range (IQR)], respectively. For categorical outcomes, the three interventions groups were compared using either Pearson's chi-squared test or Fisher's exact test, as appropriate. For time-to-event outcomes, these were reported as median (IQR) for each of three intervention groups, and compared formally using Cox proportional hazards regression models to allow for censoring/death and reported as hazard ratios (HRs) [and associated 95% confidence intervals (CIs)]. For the primary outcome, length of stay, the three intervention groups were also compared graphically using cumulative probability plots, i.e. one minus the Kaplan–Meier survivor function. EQ-5D data – collected at baseline, 7 days and 28 days – was initially summarised at each of the three time points and compared using parametric/non-parametric methods as for other continuous outcomes. Further analysis using linear mixed-effect regression models to allow for within-patient correlation enabled an assessment of the change in EQ-5D over time to be made and whether there was evidence of an intervention group interaction with time.

A number of patients were randomised more than once owing to the nature of their age and clinical condition. The primary analyses used their *first admission/randomisation*. However, to assess the impact that this assumption had on the results, two sensitivity analyses were undertaken – the first using all admissions but assuming that they were independent, i.e. ignoring the fact that some patients appeared more than once, and the second, perhaps more appropriately, including a random effect in the analyses to account for the inherent correlation induced by patients being rerandomised.

All statistical tests were reported at the 5% significance level, and 95% CIs or credible intervals (CrIs) were reported throughout as the sample size calculations explicitly made allowance for the fact that there were three rather than two groups and inflated the sample size accordingly to maintain an overall 5% significance level.

Ethical arrangements

This study was sponsored by the University Hospitals of Leicester NHS Trust. It was approved by Leicestershire, Northamptonshire and Rutland Research Ethics Committee on 20 July 2005, reference no. 05/Q2502/76.

Revisions to the protocol

We requested protocol amendments as outlined below. All requests were approved by the Local Research Ethics Committee. Protocol amendments that were implemented are outlined below:

1. On 13 January 2006 we requested the following amendments to the protocol in response to poor recruitment:
 - Approve a one-page 'Synopsis' of the six-page Patient Information Sheet to be used by patients who are not known to be suffering from dementia but were too unwell to read the full Patient Information Sheet.
 - Allow recruitment of subjects with an illness of up to 7 days' duration (i.e. ≤ 168 hours) rather than five days' duration (i.e. ≤ 120 hours).
 - Change from 6 hours to 8 hours the interval between initial assessment by the admitting medical team and recruitment to the trial.
 - Allow trained medical students to recruit patients to the study during out-of-hours periods.
2. On 14 March 2006, we requested the following protocol amendments.
 - Change the timing of the convalescent blood sample from day 10 to 'between day 10 and day 30'.
 - Approve recruitment of *all* 18- to 64-year-old subjects with pneumonia and ILI, rather than just those 18- to 64-year-old subjects with pneumonia and ILI who have underlying chronic heart and lung disease, including asthma.
 - Recruit patients until the end of June, rather than the period 'September to April'.
 - Approve a 20-ml urine collection and amendments to protocol where the volume was stated differently.
 - Change the labelling of the packs to correspond exactly with the trial identification numbers. For patients recruited in the Royal Infirmary, the packs were changed from RI-HTA-0001, RI-HTA-0002, etc., to 1-0001, 1-0002, etc. For patients recruited at Glenfield Hospital, the packs were changed from GH-HTA-0001, GH-HTA-0002, etc., to 2-0001, 2-0002, etc.
3. On 21 December 2006 we requested an amendment to aid recruitment:
 - Change, from 8 hours (originally 6 hours) to 16 hours the interval between initial assessment by the admitting medical team and recruitment to the trial.
4. On 20 March 2007 we requested an amendment to aid collection of convalescent sera:
 - Extend from day 10 to day 90 (i.e. 90 days after admission) the period when we could collect convalescent blood.
5. On 5 November 2007 we requested an amendment to aid recruitment of incapacitated adults:
 - Allow personal and professional representatives to provide consent for incapacitated adults to take part in the study.

Chapter 3 Study population

Recruitment and compliance

Between 14 December 2005 and 23 May 2008, 1253 admissions were enrolled and randomised to the rapid near-patient test group ($n = 418$), the molecular diagnostic group ($n = 415$) and the conventional diagnosis group ($n = 420$). One individual withdrew from the study. Altogether a total of 1252 admissions were randomised as shown in *Figure 4*, and participated in the study.

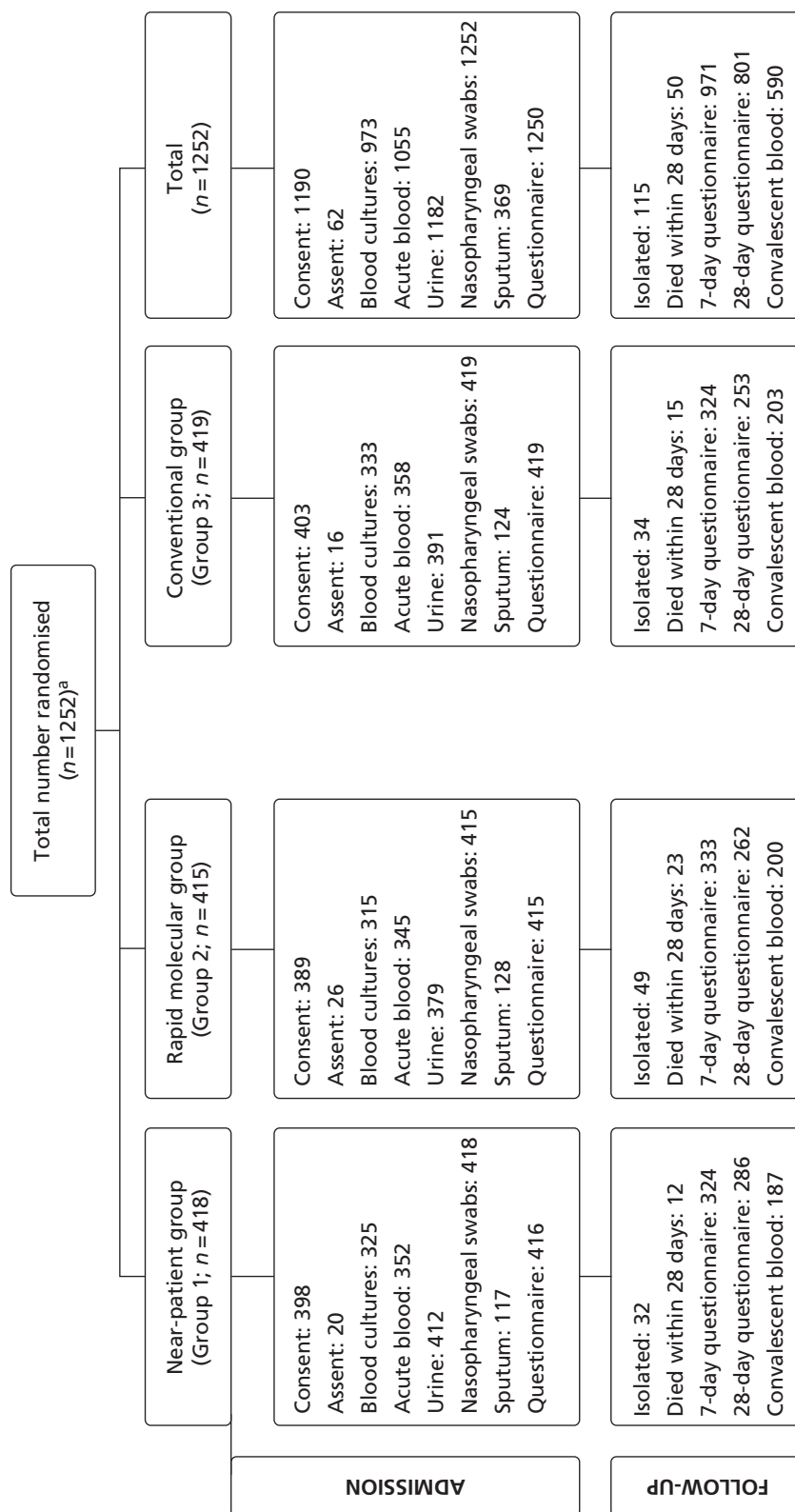


FIGURE 4 Randomisation of admissions, according to diagnostic group. a, The figure 1252 refers to admissions or patient admissions (and not unique patients) – there were 1172 patients of whom 67 were admitted/randomised at least twice.

Demography

The data set comprised data relating to 1252 separate hospital inpatient episodes. There were 1172 unique patients in the study, with 67 individuals having up to four separate inpatient episodes each. The main analyses and results use the first admission for the 1172 patients (see *Chapter 2* for other sensitivity analysis details). The number of admissions per patient is shown in *Table 1*, together with the frequencies of inpatient episodes by patient numbers. The 1172 first admissions were randomised as shown in *Figure 5*.

The demographic variables are described for first admissions only (1172 patients) and are set out in *Table 2*, as well as other patient background information deemed of interest. The baseline demographics are intended to describe the characteristics of the patients participating in the trial and to assess whether the randomisation process had been applied successfully.

From *Table 2*, the only demographic variable that appears to show weak statistically significant evidence of unbalanced distribution across the three trial arms is body mass index (BMI), with a *p*-value of 0.091. However, the mean values of BMI across the three groups are very similar, and it is unlikely that any difference across the groups is clinically significant.

Regarding hospital admissions in the previous year, out of the 1140 first admission patients with data available, 727 had zero admissions in the previous year. The maximum number of previous admissions was 20 (one patient).

TABLE 1 Number of patients having successive inpatient episodes

Admission	No. of patients (% out of 1252 admissions ^a)
First	1172 (93.6)
Second	67 (5.4)
Third	10 (0.8)
Fourth	3 (0.2)

^a The figure '1252' refers to admissions or patient admissions (and not unique patients) – there were 1172 patients, of whom 67 were admitted/randomised at least twice.

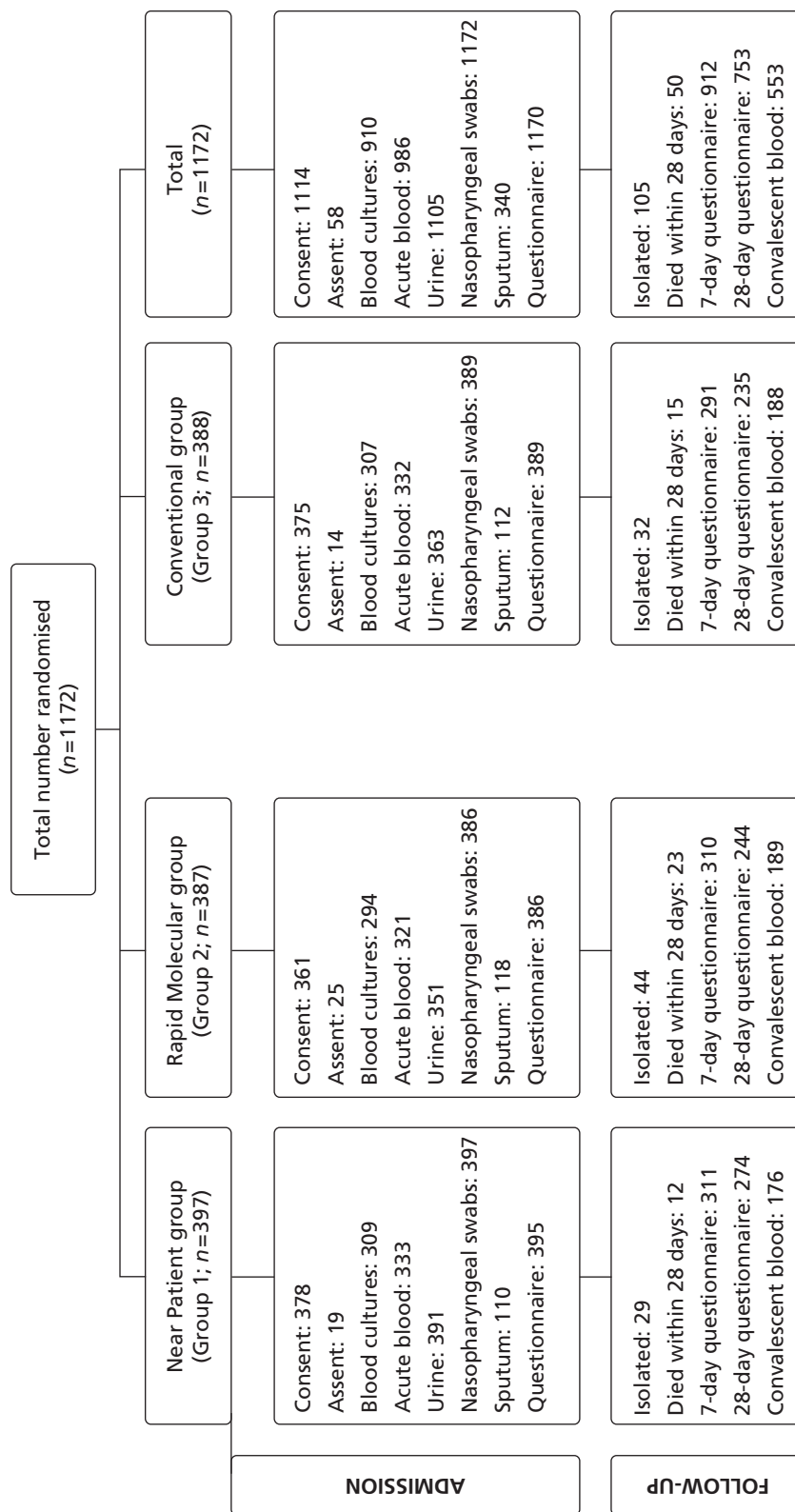


FIGURE 5 Randomisation of first cases, according to diagnostic group.

TABLE 2 Patient demographics at baseline

Covariate	Near patient (n = 397)	Rapid molecular (n = 387)	Traditional (n = 388)	p-value ^a	Missing, n ^b
Gender, n (%)				0.415	0
Male	203 (51.1)	197 (50.9)	182 (46.9)		
Female	194 (48.9)	190 (49.1)	206 (53.1)		
Age (years), n (%)				0.971	0
18–29	23 (5.8)	21 (5.4)	23 (5.9)		
30–49	69 (17.4)	72 (18.6)	76 (19.6)		
50–64	96 (24.2)	83 (21.5)	81 (20.9)		
65–74	89 (22.4)	84 (21.7)	83 (21.4)		
≥ 75	120 (30.3)	127 (32.8)	125 (32.2)		
BMI (kg/m²) (mean, SD)					
	26.6 (6.96)	26.6 (7.49)	25.5 (6.22)	0.091	231 ^b
Ethnicity, n (%)				0.940	0
White	361 (90.9)	347 (89.7)	354 (91.2)		
Indian	25 (6.3)	29 (7.5)	25 (6.4)		
Other	11 (2.8)	11 (2.8)	9 (2.3)		
Smoking status, n (%)				0.123	0
Current	93 (23.4)	90 (23.3)	118 (30.4)		
Previous	184 (46.4)	187 (48.3)	169 (43.6)		
Never	120 (30.2)	110 (28.4)	101 (26.0)		
Flu vaccination this season, n (%)				0.831	0
Yes	235 (59.2)	221 (57.1)	224 (57.7)		
No	162 (40.8)	166 (42.9)	164 (42.3)		
Flu vaccination last season, n (%)				0.435	0
Yes	240 (60.5)	218 (56.3)	233 (60.1)		
No	157 (39.6)	169 (43.7)	155 (40.0)		
Flu vaccination two seasons ago, n (%)				0.856	0
Yes	220 (55.4)	209 (54.0)	217 (55.9)		
No	177 (44.6)	178 (46.0)	171 (44.1)		
Flu vaccination ever, n (%)				0.866	0
Yes	297 (74.8)	283 (73.1)	287 (74.0)		
No (never)	100 (25.2)	104 (26.9)	101 (26.0)		
Hospital admissions in previous year IRR^c (95% CI; p-value)					
	1	1.017 (0.744 to 1.391; 0.915)	1.037 (0.762 to 1.412; 0.816)		132 ^b

BMI, body mass index; IRR, incidence rate ratio.

a The p-values are based on Pearson's chi-squared test, except for BMI, which is based on ANOVA F-statistic.

b Missing values were equally distributed across groups: BMI, 'near patient' 21.6%, 'rapid molecular' 18.6%, traditional 21.9%; hospital admission in previous year, 'near patient' 11.8%, 'rapid molecular' 12.9%, traditional 9.0%.

c Incidence rate ratio based on negative binomial regression.

Comorbidity

Pre-existing medical conditions for the 1172 patients at first admission are set out in *Table 3*. As can be seen from *Table 3*, there is no evidence of any association between trial arm and comorbidity for any disease.

Time to convalescent blood samples

Convalescent blood samples were taken from patients following their admission. Median times to collection of the samples are set out in *Table 4*, for first admissions only, and are similar across trial arms.

TABLE 3 Pre-existing medical conditions for first admissions

Medical condition	Near patient (<i>n</i> = 397)	Rapid molecular (<i>n</i> = 387)	Traditional (<i>n</i> = 388)	<i>p</i> -value ^a	Missing, <i>n</i> ^b
Myocardial infarction, <i>n</i> (%)				0.627	37 ^b
Yes	48 (12.5)	56 (14.9)	51 (13.5)		
No	335 (87.5)	319 (85.1)	326 (86.5)		
Heart failure, <i>n</i> (%)				0.860	37 ^b
Yes	21 (5.5)	21 (5.6)	18 (4.8)		
No	362 (94.5)	354 (94.4)	359 (95.2)		
Angina, <i>n</i> (%)				0.768	37 ^b
Yes	44 (11.5)	37 (9.9)	41 (10.9)		
No	339 (88.5)	338 (90.1)	336 (89.1)		
Stroke, <i>n</i> (%)				0.369	37 ^b
Yes	21 (5.5)	21 (5.6)	29 (7.7)		
No	362 (94.5)	354 (94.4)	348 (92.3)		
Chronic bronchitis, <i>n</i> (%)				0.533	37 ^b
Yes	42 (11.0)	51 (13.6)	45 (11.9)		
No	341 (89.0)	324 (86.4)	332 (88.1)		
Asthma, <i>n</i> (%)				0.999	37 ^b
Yes	162 (42.3)	159 (42.4)	160 (42.4)		
No	221 (57.7)	216 (57.6)	217 (57.6)		

a The *p*-values are based on Pearson's chi-squared test.

b Missing values were equally distributed across groups: 'near patient' 3.5%, 'rapid molecular' 3.1%, traditional 2.8%.

TABLE 4 Time to convalescent samples

Investigation	Near patient (<i>n</i> = 174)	Rapid molecular (<i>n</i> = 185)	Traditional (<i>n</i> = 183)	Total (<i>n</i> = 542)
Median days from admission to collection of convalescent samples (IQR)	28.25 (14.58–59.45)	27.46 (17.95–55.97)	27.72 (19.09–61.59)	28.00 (17.07–59.49)

Chapter 4 Patient outcomes

Introduction

In this section, we report the findings relating to the patient outcomes. The main results reported are based on the first admission for 1172 patients. The following diagnostic tests contributed to the diagnoses made:

1. rapid molecular tests (PCR): influenza and RSV
2. Quidel (NPT for influenza)
3. viral cultures (influenza, RSV)
4. BinaxNOW test (*S. pneumoniae*)
5. sputum cultures (*S. pneumoniae*), and
6. blood cultures (*S. pneumoniae*).

A patient was diagnosed as having any of the three infectious conditions (influenza, RSV or *S. pneumoniae*) if any of the diagnostic tests (not necessarily a test to which the patient had been randomised) showed a positive result, regardless of the results of the other tests. The Gram stain test was not used in determining diagnosis as none of the outcomes were positive for *S. pneumoniae*. In *Chapter 5*, sensitivity to diagnostic test results is further explored using serology data for influenza.

Diagnostic test results for first admissions

The results of the diagnostic tests for 1172 first admissions are set out in *Table 5*. Note that an outcome of 'Not diagnosed' does not indicate a definite negative diagnosis, as for the influenza tests, a diagnostic result was not available for two patients (e.g. due to lack of a suitable sample). From the first admissions, four patients were diagnosed with both RSV and *S. pneumoniae*; also four patients were diagnosed with both influenza and *S. pneumoniae*. No patients were diagnosed with both RSV and influenza.

Overall, the diagnoses appeared to be relatively evenly spread across the three trial arms, with no evidence of an association between trial arm and diagnoses. No attempt is made in these analyses to distinguish patients with multiple diagnoses (e.g. if a patient has a diagnosis of both RSV and *S. pneumoniae*, this patient will be counted in both groups).

Prescribing outcomes

Time from admission to first narrow-spectrum antibiotic

One of the outcomes of interest in this trial is the potential impact of the investigation on the time from admission to the time of prescription of the first narrow-spectrum antibiotic. Of the 1252 admissions, a narrow-spectrum antibiotic was prescribed during 555 admissions. For 161 of these admissions, the duration of time until the prescription was ≤ 0 hours, indicating that the time of prescription of the narrow-spectrum antibiotic was prior to the recorded time of hospital admission, for example in the accident and emergency (A&E) department. For these patients, duration of 0.01 hours was substituted to facilitate the analysis. Of the 1172 first admissions, a narrow-spectrum antibiotic was prescribed during 527 admissions.

TABLE 5 Diagnostic results for first admissions

Diagnosis	Near patient (n = 397)	Rapid molecular (n = 387)	Traditional (n = 388)	p-value ^a	n missing
Influenza, n (%)				0.590	0
Diagnosed	27 (6.8)	30 (7.8)	34 (8.8)		
Not diagnosed	370 (93.2)	357 (92.3)	354 (91.2)		
RSV, n (%)				0.160	0
Diagnosed	11 (2.8)	13 (3.4)	5 (1.3)		
Not diagnosed	386 (97.2)	374 (96.6)	383 (98.7)		
S. pneumoniae, n (%)				0.099	0
Diagnosed	24 (6.1)	36 (9.3)	39 (10.1)		
Not diagnosed	373 (94.0)	351 (90.7)	349 (90.0)		

^a The p-values are based on Pearson's chi-squared test.

For first admissions only, the time to prescription of the first narrow-spectrum antibiotic is shown in Table 6, which includes the HR with 95% CI based on a Cox proportional hazards model (with the 'traditional' group as the reference group) and median survival times for all three diagnostic groups.

Based on Table 6, there is weak evidence (p-value 0.082 for the Cox HR model) for an association between diagnostic group and time to first narrow-spectrum antibiotic comparing the 'rapid molecular' group to the 'traditional' group. However, in the light of the width of the 95% CI for the HR (0.976 to 1.487) and wide IQRs for both groups, the association does not appear to be strong. There is no evidence for an association between diagnostic groups comparing the 'near-patient' group with the 'traditional' group.

Time from admission to first oral antibiotic

All patients who received antibiotics were analysed for time until first oral antibiotic (if prescribed oral antibiotics at all), regardless of whether the patient received antibiotics by another route (e.g. i.v.) prior to receiving oral antibiotics. In total, of the 1252 admissions, 851 received at least one oral antibiotic during the hospital inpatient episode. Of these, 216 admissions had a time to first oral antibiotic that was zero or negative, and duration of 0.01 hours was substituted to facilitate the analysis. Of the 1172 patients with a first admission, 800 received at least one oral antibiotic. The analysis of time to first oral antibiotic, for first admissions only, by diagnostic group, is set out in Table 7. Table 7 shows no evidence for any association between diagnostic group and time to first oral antibiotic.

TABLE 6 Time to prescription of first narrow-spectrum antibiotic: median hours until prescription of first narrow-spectrum antibiotics to 527 patients (among 1172 first admissions), and Cox proportional hazards model by diagnostic group

Investigation	Traditional (n = 199)	Near patient (n = 170)	Rapid molecular (n = 158)	Total (n = 527)
Median hours to first narrow-spectrum antibiotic (IQR)	3 (0.01–8.17)	3.5 (0.01–9.83)	2.67 (0.01–6.75)	3 (0.01–8.08)
Cox HR (95% CI; p-value)	1	1.023 (0.833 to 1.257; 0.829)	1.205 (0.976 to 1.487; 0.082)	

TABLE 7 Time to prescription of first oral antibiotic: median hours until prescription of first oral antibiotic to 800 patients and Cox proportional hazards model by diagnostic group, for all 1172 first admissions

Investigation	Traditional (n = 283)	Near patient (n = 265)	Rapid molecular (n = 252)	Total (n = 800)
Median hours to first oral antibiotic (IQR)	4 (0.1–10.5)	3.75 (0.25–11.33)	4 (0.01–11.5)	4 (0.1–11)
Cox HR (95% CI; p-value)	1	0.957 (0.809 to 1.132; 0.605)	0.905 (0.763 to 1.074; 0.253)	

Time from admission to cessation of antibiotics

For patients with RSV or influenza only, the time to cessation of antibiotics (by all routes of administration) was analysed. For patients with RSV or influenza, 96 received at least one antibiotic during the hospital admission (across all 1252 admissions). Among the 1172 first admissions, 93 of the 120 patients diagnosed with influenza or RSV received at least one antibiotic during their admission. Six of these patients had a time to cessation of antibiotics that was negative, and was replaced by a duration of 0.01 hours. The results of the Cox proportional hazards model, comparing diagnostic groups, and median times to cessation of antibiotics, are shown in *Table 8*.

Table 8 shows no evidence for an association between time from initial hospital admission to final dose of antibiotics among patients with influenza or RSV. However, the numbers of eligible patients in each diagnostics group are relatively small, leading to wide 95% CIs and IQRs.

A corresponding analysis was also performed for all patients with a first admission (regardless of diagnostic outcomes). Across all 1252 admissions, 911 patient episodes were associated with administration of at least one antibiotic (in 44 cases the duration to cessation of antibiotics was negative and replaced by 0.01 hours). Of the 1172 patients admitted for the first time within the study, 857 received at least one antibiotic (42 of whom had a negative duration to cessation of antibiotics, which was replaced by 0.01 hours). The results are shown in *Table 8*. Again, there is no evidence to support an association between diagnostic group and time to cessation of antibiotics.

Neuraminidase prescriptions in patients with influenza

One patient was treated with a NI. This patient was a first admission, in the traditional diagnostic group, and was not diagnosed with *S. pneumoniae*, influenza or RSV.

TABLE 8 Time to cessation of antibiotics: median hours cessation of antibiotics and Cox proportional hazards model by diagnostic group, for first admissions with RSV or influenza, and all first admissions

Investigation	Traditional	Near patient	Rapid molecular	Total
All first admissions with RSV or influenza (n = 120)				
Median hours to cessation of antibiotics (IQR; n)	79.5 (34–116.75; 32)	56.42 (22.5–118; 24)	58.17 (18.98–152.75; 37)	77 (25.83–131.83; 93)
Cox HR (95% CI; p-value)	1	0.887 (0.512 to 1.537; 0.669)	1.014 (0.628 to 1.637; 0.955)	
All first admissions (n = 1172)				
Median hours to cessation of antibiotics (IQR; n)	78.5 (27–116.75; 296)	60.75 (20.25–151; 286)	77.5 (17–152.75; 275)	77 (20.33–146.62; 857)
Cox HR (95% CI; p-value)	1	1.066 (0.906 to 1.255; 0.440)	1.030 (0.873 to 1.214; 0.726)	

Clinical outcomes

Length of hospital stay

Length of hospital stay among survivors was calculated as the time between admission to hospital and discharge for patients who were discharged only (excluding patients who died while in hospital). For the first admissions, only 46 patients died in hospital (39 within 28 days), with the remaining 1126 being discharged.

Using a Cox proportional hazards model to investigate any associations between the duration of hospital stay and diagnostic group, the results are set out in *Table 9*, which shows the Cox HR and median hospital stay (days). Two further analyses were performed on the full cohort of all discharged patients (1205), including discharges resulting from admissions subsequent to the first. These analyses used a Cox proportional hazards model, one of which included a frailty (random effect on individual patient across multiple admissions for those patients who had more than one admission, effectively treating patient as a cluster variable).

TABLE 9 Duration of hospital stay among survivors: median hospital stay (days) until discharge and Cox proportional hazards model (for both survivors and those who died in hospital) by diagnostic group, for all first admissions, and first admissions with RSV, influenza and *S. pneumoniae* only

Investigation	Traditional	Near patient	Rapid molecular	Total
All first admissions discharged (n = 1126)				
Median days hospital stay (IQR; n)	3.23 (1.21–7.86; 374)	2.44 (0.90–7.56; 388)	2.81 (0.76–7.58; 364)	2.98 (0.95–7.75; 1126)
Cox HR (95% CI; p-value)	1	1.041 (0.903 to 1.201; 0.577)	1.109 (0.960 to 1.282; 0.160)	
All first admissions discharged who were diagnosed with influenza (n = 90)				
Median days hospital stay (IQR; n)	3.59 (1.40–7.28; 34)	2.08 (0.37–4.43; 26)	1.96 (0.74–6.82; 30)	2.52 (0.90–6.56; 90)
Cox HR (95% CI; p-value)	1	1.274 (0.758 to 2.143; 0.361)	1.248 (0.762 to 2.043; 0.380)	
All first admissions discharged who were diagnosed with RSV (n = 27)				
Median days hospital stay (IQR; n)	2.99 (2.98–3.16; 5)	2.56 (2.05–8.60; 11)	6.18 (1.27–11.75; 11)	3.10 (1.32–8.84; 27)
Cox HR (95% CI; p-value)	1	0.625 (0.203 to 1.920; 0.412)	0.559 (0.183 to 1.709; 0.308)	
All first admissions discharged who were diagnosed with <i>S. pneumoniae</i> (n = 90)				
Median days hospital stay (IQR; n)	4.21 (2.78–8.75; 37)	3.10 (1.60–6.19; 22)	4.02 (1.10–8.30; 31)	4.13 (1.82–8.50; 90)
Cox HR (95% CI; p-value)	1	1.131 (0.665 to 1.924; 0.651)	1.033 (0.637 to 1.676; 0.896)	
All patients discharged (all admissions, 1205 discharges; no adjustment for multiple admissions)				
Median days hospital stay (IQR; n)	3.23 (1.17–7.63; 404)	2.43 (0.90–7.48; 409)	2.81 (0.79–7.58; 392)	2.99 (0.97–7.52; 1205)
Cox HR (95% CI; p-value)	1	1.035 (0.902 to 1.188; 0.622)	1.098 (0.955 to 1.262; 0.190)	
All patients who died or who were discharged (all admissions, 1205 discharges; frailty^a on individual patient to adjust for multiple admissions in same patient)				
Cox HR (95% CI; p-value)	1	1.055 (0.904 to 1.230; 0.499)	1.118 (0.957 to 1.306; 0.159)	

^a Frailty (random effect) on individual patient (theta): 0.129, p-value for theta = 0 0.166.

As shown in *Table 9*, there was little difference in the HR whether including first admissions only or all admissions. Also, there was little difference in the HR when including frailty in the Cox proportional hazards model. Frailty itself did not appear to be significant (p -value = 0.166), indicating no evidence of an effect on hospital stay, independent of diagnostic group.

Comparing the three diagnostic groups, there did not appear to be any evidence to support any association between duration of hospital stay and diagnostic group. *Figure 6* shows a Kaplan–Meier estimated cumulative probability plot of time to discharge or death by randomised group. It shows the overall similarity in length of stay by randomisation group.

Fever duration

Patients were considered to have been pyrexial from admission if any of the following were indicated:

1. temperature on admission ($> 37.2^{\circ}\text{C}$),
2. pyrexial ($> 37.2^{\circ}\text{C}$) within 48 hours of admission, *and*
3. end date of pyrexia present.

The time/date of the end of fever (or total duration of fever) was derived as follows (in order of precedence):

1. stated end time/date of fever if present (460 admissions out of 1252), *or*
2. discharge/death date if patient discharged/died within 10 days of admission (note: there were 148 patient admissions who were pyrexial on admission but with no stated end time/date of fever out of 1252*).

[*1252 refers to admissions or patient admissions (and not unique patients) – there were 1172 patients, of whom 67 were admitted/randomised at least twice.]

Also, there were two admissions with an unknown date of end of pyrexia (and hence substituted with date of discharge or death) who were recorded as being pyrexial within 10 days, but who had a fever duration of more than 10 days when using the substituted date of end of pyrexia. For these patients, a fever duration of 240 hours was used. There were 26 patients with duration of fever calculated as ≤ 0 hours, and for these patients fever duration of 0.01 hours was substituted to facilitate the analysis. Only patients who became apyrexial within ≤ 240 hours of admission to hospital were included in the analyses (583 admissions out of 1252, and 549 patients out of 1172 first admissions).

The results of a Cox proportional hazards model for median fever duration (hours) comparing the 'near-patient' and 'rapid molecular' diagnostic groups against the 'traditional' group are shown in *Table 10*.

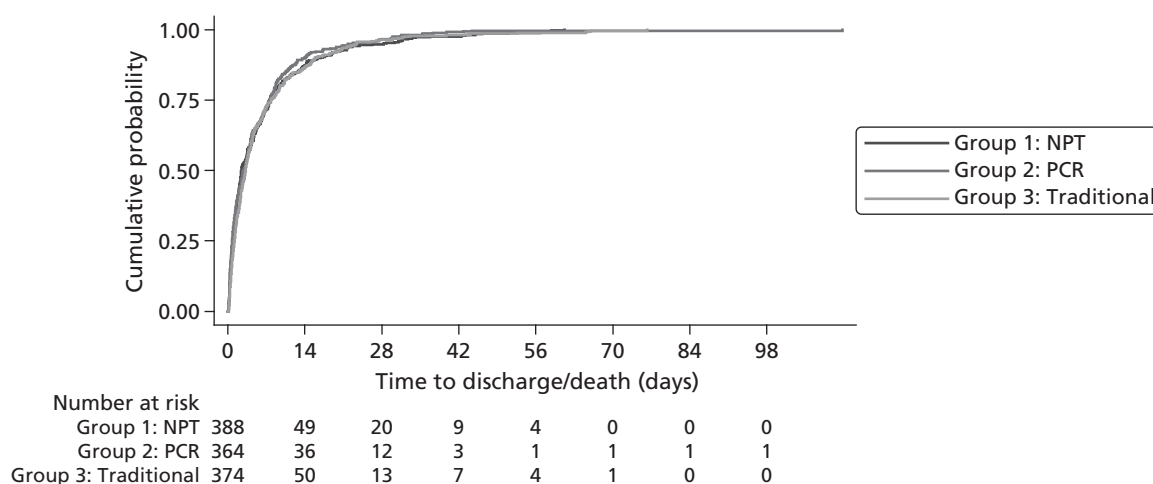


FIGURE 6 Kaplan–Meier estimated cumulative probability of time to discharge (all first admissions discharged $n = 1126$) by randomised group.

TABLE 10 Fever duration: median duration, in hours, of fever, and Cox proportional hazards model by diagnostic group, for all first admissions, and first admissions with *S. pneumoniae* only

Investigation	Traditional	Near patient	Rapid molecular	Total
All first admissions (n = 1172)				
Median fever duration, hours (IQR; n)	22.75 (11.25–51.33; 190)	22.5 (8.92–60; 185)	21.75 (8.17–46; 174)	22.5 (9.17–51.33; 549)
Cox HR (95% CI; p-value)	1	1.003 (0.819 to 1.230; 0.974)	1.158 (0.941 to 1.424; 0.165)	
All first admissions diagnosed with <i>S. pneumoniae</i> (n = 99)				
Median fever duration, hours (IQR; n)	28.17 (8.92–71.5; 23)	28.5 (8.42–70.33; 19)	24 (11–46; 13)	28.17 (8.92–66.75; 55)
Cox HR (95% CI; p-value)	1	1.136 (0.608 to 2.122; 0.689)	1.223 (0.610 to 2.450; 0.570)	

Results are shown for all patients at first admission, and first admissions with *S. pneumoniae* only. Based on the results in Table 10, there is no evidence to support an association between fever duration and diagnostic group in all patients (regardless of any diagnosis), or for patients diagnosed with *S. pneumoniae* only, although the small numbers of patients with *S. pneumoniae* should be noted.

Supplemental oxygen dependence

Of all 1252 admissions, 546 were associated with prescription of oxygen during the admission. Of these 546, 28 had no confirmed end date for cessation of oxygen therapy. For these patients, the cessation date for oxygen therapy was considered to be the date of discharge ($n = 25$) or death ($n = 3$). For patients whose duration of oxygen therapy in hours (from admission to cessation of oxygen) was zero or negative (i.e. their time of cessation of oxygen was recorded as being prior to the recorded time of admission to hospital), their duration was replaced by 0.01 hours (41 patients). Patients with duration of oxygen therapy of more than 240 hours (10 days) were excluded from the analyses.

Regarding the 1172 first admissions only, 436 patients received oxygen therapy that ceased within 240 hours. The results of the time-to-event analysis by diagnostic group for the 436 patients, and for 40 out of 99 patients who were with diagnosed *S. pneumoniae* only, are shown in Table 11.

TABLE 11 Time to cessation of oxygen therapy: median duration, in hours, of oxygen therapy and Cox proportional hazards model by diagnostic group for all first admissions, and first admissions with *S. pneumoniae* only

Investigation	Traditional	Near patient	Rapid molecular	Total
All first admissions (n = 1172)				
Median hours from admission to cessation of oxygen therapy (IQR; n)	32.33 (11–75; 146)	23.92 (9.33–74; 146)	26 (9.25–70.08; 144)	26 (10–72.5; 436)
Cox HR (95% CI; p-value)	1	1.004 (0.798 to 1.265; 0.970)	1.043 (0.828 to 1.314; 0.718)	
All first admissions diagnosed with <i>S. pneumoniae</i> (n = 99)				
Median hours from admission to cessation of oxygen therapy (IQR; n)	45.33 (25.75–130; 18)	40 (17.25–74.5; 9)	30.17 (5.5–59.5; 13)	44.17 (12–80.5; 40)
Cox HR (95% CI; p-value)	1	1.401 (0.618 to 3.176; 0.420)	1.791 (0.847 to 3.790; 0.127)	

Based on these results, there is no evidence to indicate an association between diagnostic group and time to cessation of oxygen, in all patients, or in those diagnosed with *S. pneumoniae*.

Continuous positive airway pressure dependence

Of all 1252 admissions, 17 were associated with the use of continuous positive airway pressure (CPAP) during the admission, with 14 patients receiving CPAP during a first admission. There were three patients with no date of cessation of CPAP; for two of these, the date of CPAP cessation was taken as the date of discharge, and for the third patient the time of death was used. There were three patients with a negative duration of CPAP (from admission to cessation of CPAP, indicating that time of commencement of CPAP was recorded as being before the recorded time of admission to hospital), replaced by a duration of 0.01 hours. All 14 patients who received CPAP during a first admission had duration of CPAP of ≤ 240 hours.

The results of the time-to-event analysis by diagnostic group, for all patients with a first admission, are shown in *Table 12*. Owing to the small numbers of patients who received CPAP, the results should be viewed with caution; however, there is no evidence to support any association between diagnostic group and time to cessation of CPAP. Only two patients diagnosed with *S. pneumoniae* received CPAP during a first admission, one in the 'near-patient' diagnostic group and one in the 'traditional' group. Owing to the very small numbers of patients, analysis of the data is not feasible.

Admissions requiring intensive care and ventilator support

Across the 1252 admissions, six patients were admitted to intensive treatment unit (ITU), of whom five were admitted on a first admission. Of the total of six admissions, three were in the 'near-patient' group, one was in the 'rapid molecular' group and two were in the 'traditional' group. One patient admitted to ITU was diagnosed with *S. pneumoniae* (in the 'near-patient' group and a first admission). None of the patients who were diagnosed with influenza or RSV were admitted to ITU.

All patients who were admitted to ITU required ventilator support (no other patients were ventilated while admitted). Owing to the small numbers of patients requiring ITU admission and ventilation, it is not feasible to make any comparisons across the diagnostic groups for this outcome.

Deaths

A total of 58 deaths were confirmed among the 1252 admissions (57 in first admissions), of which 50 (all in first admissions) occurred within 28 days of admission. Deaths that occurred more than 28 days after admission were not comprehensively recorded, so only deaths that occurred within 28 days are considered in this analysis. All 50 patients who died within 28 days of admission were patients who had been admitted for the first time (of the 1172 patients with first admissions, 50 died within 28 days, 4.3%). Of the 50 deaths, 39 died in hospital and 11 died after discharge. Deaths occurred within 28 days in three (3.3%) admissions with influenza, two (6.9%) with RSV, and ten (10.1%) with *S. pneumoniae*. *Table 13* shows the distribution of deaths within 28 days of admission in each diagnostic group, overall and by diagnosis, for first admissions only. Despite the small number of deaths in the study, we found no

TABLE 12 Time to cessation of CPAP therapy: median duration, in hours, of CPAP therapy and Cox proportional hazards model by diagnostic group, for 14 of all 1172 first admissions

Investigation	Traditional	Near patient	Rapid molecular	Total
All first admissions (n = 1172)				
Median hours from admission to cessation of CPAP (IQR; n)	19.75 (8.5–26; 5)	15.5 (6.42–22.5; 4)	43.92 (0.01–48.83; 5)	19.75 (6.42–3.4; 14)
Cox HR (95% CI; p-value)	1	0.849 (0.220 to 3.276; 0.812)	0.254 (0.045 to 1.440; 0.122)	

TABLE 13 Deaths within 28 days of admission, for first admissions only

Death within 28 days	Near patient (n = 397)	Rapid molecular (n = 387)	Traditional (n = 388)	p-value ^a
Total cohort (N = 1172), n (%)				0.115
Yes	12 (3.0)	23 (5.9)	15 (3.9)	
No	385 (97.0)	364 (94.1)	373 (96.1)	
Influenza (N = 91), n (%)				0.635 ^b
Yes	1 (3.7)	0 (0)	2 (5.9)	
No	26 (96.3)	30 (100)	32 (94.1)	
RSV (N = 29), n (%)				0.648 ^b
Yes	0 (0)	2 (15.4)	0 (0)	
No	11 (100)	11 (84.6)	5 (100)	
S. pneumoniae (N = 99), n (%)				0.241 ^b
Yes	2 (8.3)	6 (16.7)	2 (5.1)	
No	22 (91.7)	30 (83.3)	37 (94.9)	

a The p-values based on Pearson's chi-squared test, unless marked with 'b' (see footnote 'b', below).

b Indicates Fisher's exact test.

evidence to associate any diagnostic group with increased mortality for all patients, or for patients with any specific diagnosis.

Use of isolation facilities

Across the 1252 admissions, 112 patients were admitted to isolation, and, of the 1172 first admissions, 102 patients were admitted to isolation. Of the 1172 patients at a first admission, 120 were diagnosed with influenza or RSV of whom 14 were admitted to isolation at some time during their admission. In five cases, their time from admission to hospital to admission to isolation was zero or negative, and was replaced by duration of 0.01 hours. Owing to the small numbers of patients with RSV or influenza who were admitted to isolation, a time-to-event analysis is difficult, but the results are set out in *Table 14*.

The numbers of patients with influenza or RSV who were admitted to isolation within 120 hours of admission in each group are shown in *Table 15*. Owing to the small number of admissions to isolation within 120 hours of the admission, comparisons between the diagnostic groups are considered inappropriate.

TABLE 14 Time of isolation: median time, in hours, from admission to hospital to admission to isolation and Cox proportional hazards model by diagnostic group, for 14 of all 1172 first admissions with influenza or RSV

Investigation	Traditional	Near patient	Rapid molecular
All first admissions (n = 1172), of whom 14 with influenza or RSV were isolated			
Median hours from admission to 'isolation' (IQR; n)	0.01 (0.01–27.37; 2)	0.01 (0.01–0.01; 4)	23.33 (5.50–55.08; 8)
Cox HR (95% CI; p-value)	1	0.65 (0.10 to 4.20; 0.655)	0.69 (0.14 to 3.39; 0.650)

TABLE 15 Admissions within 120 hours to single-room accommodation by patients with RSV or influenza (first admissions)

Patients	Near patient (n = 397)	Rapid molecular (n = 387)	Traditional (n = 388)
All patients with influenza or RSV, n (%)	38 (9.6)	43 (11.1)	39 (10.1)
No. 'isolated' with influenza or RSV, n (%)	3 (7.9)	7 (16.3)	2 (5.1)

Eight patients who experienced a first admission and were diagnosed with *S. pneumoniae* (but not concomitant influenza or RSV) were admitted to single-room accommodation. Seven were isolated for > 12 hours, including two of 22 (who were diagnosed with streptococcal infection by any means but did not have concomitant influenza or RSV) in the 'near-patient' group (9.1%), four of 34 in the 'rapid molecular' group (11.8%) and one of 35 in the 'traditional' group (2.9%). Overall, taking data relating to RSV, influenza and *S. pneumoniae* infections into consideration, we found no evidence to indicate that diagnostic group has any association with use of isolation facilities, or that patients with RSV and influenza, who pose a higher threat of nosocomial transmission than *S. pneumoniae*, are isolated more often.

Quality of life

Data regarding QoL (EuroQoL EQ-5D scores) are available at three time points in the trial: admission, 7 days and 28 days following admission, and was self-completed by participants. At first admission, all 1172 patients were available for EQ-5D assessment, whereas at day 7, 16 patients (with a first admission) were deceased, and at day 28, 50 patients (with a first admission) were deceased. The numbers of patients alive, by diagnostic group, and with EQ-5D data available at different times, is shown in *Table 16*. Numbers of patients across the diagnostic groups (first admissions only) with full EQ-5D data available at different times during the study period are shown in *Table 17*, which also provides descriptive analyses of EQ-5D scores as combined into one overall score.^{66,67}

TABLE 16 Numbers of patients alive, by diagnostic group, with EQ-5D data available at different times

Days	Near patient (n = 397)	Rapid molecular (n = 387)	Traditional (n = 388)	Total (n = 1172)
Availability of all five EQ-5D scores n (%)				
Admission only	57 (14.4)	64 (16.5)	78 (20.1)	199 (17.0)
Day 7 only	1 (0.3)	3 (0.8)	1 (0.3)	5 (0.4)
Day 28 only	1 (0.3)	0 (0)	0 (0)	1 (0.1)
Admission and day 7	72 (18.1)	91 (23.5)	90 (23.2)	253 (21.6)
Admission and day 28	29 (7.3)	22 (5.7)	26 (6.7)	77 (6.6)
Days 7 and 28	5 (1.3)	4 (1.0)	4 (1.0)	13 (1.1)
Admission, days 7 and 28	228 (57.4)	202 (52.2)	188 (48.5)	618 (52.7)
No EQ-5D at any time	4 (1.0)	1 (0.3)	1 (0.3)	6 (0.5)

For consistency, percentages have as denominator the total number of patients in each group, despite the fact that not all patients remained alive at days 7 and 28.

TABLE 17 Quality of life analyses, at admission to hospital, days 7 and 28 following admission, for patients alive and with a first admission only

Analysis	Near patient (n = 397)	Rapid molecular (n = 387)	Traditional (n = 388)
Quality-of-life data on admission			
All five EQ-5D scores, no. (%)	386 (97.2)	379 (97.9)	382 (98.5)
EuroQoL score:			
Mean (SD)	0.463 (0.330)	0.459 (0.352)	0.469 (0.330)
Median (IQR)	0.487 (0.201–0.743)	0.487 (0.189–0.760)	0.516 (0.260–0.714)
Quality-of-life data on day 7			
All five EQ-5D scores, no. (%)	306/394 (77.7)	300/378 (79.4)	283/384 (73.7)
EuroQoL score:			
Mean (SD)	0.563 (0.332)	0.593 (0.322)	0.591 (0.287)
Median (IQR)	0.639 (0.378–0.796)	0.689 (0.325–0.840)	0.620 (0.433–0.796)
Quality-of-life data on day 28			
All five EQ-5D scores, no. (%)	263/385 (68.3)	228/364 (62.6)	218/373 (58.4)
EuroQoL score:			
Mean (SD)	0.634 (0.308)	0.636 (0.288)	0.588 (0.310)
Median (IQR)	0.691 (0.516–0.814)	0.691 (0.516–0.814)	0.656 (0.516–0.796)

There were no statistically significant differences between the three intervention groups in terms of median EQ-5D score at admission ($p = 0.931$), 7 days ($p = 0.466$) or 28 days ($p = 0.117$).

Repeated measures analyses, with the aim of investigating an interaction between diagnostic group and time of EQ-5D measurement on EQ-5D scores, using a linear mixed-effects model with a random effect for individual patient, are reported in *Table 18*, for first admissions only. These analyses were performed initially on all data available at each time point, and subsequently on data from patients with EQ-5D scores available at admission, days 7 and 28.

The analysis of all available data indicated that there was a significant interaction between 'near-patient' diagnostic group and time of measurement at day 28 (p -value 0.033) and a borderline significant interaction between 'rapid molecular' diagnostic group and time of measurement at day 28 (p -value 0.074). In both cases the coefficient of the interaction was positive, indicating that the EQ-5D scores for day 28 were greater for the 'near-patient' and 'rapid molecular' groups compared with the traditional group. Under both sets of analyses, the effect of changing EQ-5D levels over time was also highly statistically significant ($p < 0.001$), with increases in EQ-5D at both day 7 (0.123; 95% CI 0.076 to 0.169), and day 28 (0.096; 95% CI 0.050 to 0.143) compared with admission.

TABLE 18 Repeated measures/linear mixed-effects model for EQ-5D score at admission, days 7 and 28, with random effect on individual patient (first admissions only)

Covariate	Coefficient (95% CI)	p-value
All patients included with data available at each individual time (no. observations = 2745; no. patients = 1166)		
<i>Diagnostic group</i>		
Near patient	-0.007 (-0.052 to 0.038)	0.763
Rapid molecular	-0.008 (-0.054 to 0.037)	0.723
<i>Time</i>		
Day 7	0.124 (0.086 to 0.162)	< 0.001
Day 28	0.106 (0.064 to 0.148)	< 0.001
<i>Interactions</i>		
Day 7 × near patient	-0.012 (-0.065 to 0.041)	0.665
Day 7 × rapid molecular	0.011 (-0.043 to 0.064)	0.696
Day 28 × near patient	0.062 (0.005 to 0.120)	0.033
Day 28 × rapid molecular	0.054 (-0.005 to 0.112)	0.074
Only patients with data at all three time points included (no. observations = 1854; no. patients = 618)		
<i>Diagnostic group</i>		
Near patient	-0.038 (-0.099 to 0.022)	0.211
Rapid molecular	-0.015 (-0.077 to 0.047)	0.639
<i>Time</i>		
Day 7	0.123 (0.076 to 0.169)	< 0.001
Day 28	0.096 (0.050 to 0.143)	< 0.001
<i>Interactions</i>		
Day 7 × near patient	-0.007 (-0.069 to 0.056)	0.837
Day 7 × rapid molecular	0.004 (-0.060 to 0.069)	0.897
Day 28 × near patient	0.078 (0.015 to 0.141)	0.015
Day 28 × rapid molecular	0.057 (-0.008 to 0.122)	0.084

Case reviews

Altogether eight patients in the 'near-patient' study group had a positive Quidel QuickVue Influenza A + B result. We examined the CRFs of these eight patients to examine at a patient level whether their medical management could have been influenced by the result of diagnostic testing. We also reviewed the CRFs of the 21 patients in the 'near-patient' study group whose urine on admission was positive for pneumococcal antigen using the BinaxNOW test to see if there was a temporal association between the test result and changes to case management and isolation.

QuickVUE influenza A + B test

The following results should be treated with caution given the small number of admissions in the 'near-patient' study group that tested positive in the QuickVUE Influenza A + B test.

A summary of the findings is shown in *Table 19*. None of the patients was admitted within 48 hours of onset of symptoms and none was given NI. All seven patients with data on comorbidity had comorbidities that made them eligible for treatment if their symptoms were of ≤ 48 hours' duration. Two patients were already 'isolated' when tested. Of the remaining six, one was discharged after the test and none of the

TABLE 19 Basic characteristics and NI and antibiotic treatment of eight patients in the 'near-patient' group with a positive POCT for influenza

Observation	Patient							
	1	2	3	4	5	6	7	8
Temperature on admission, °C	37.3	37.2	36.3	36.8	36.7	38.0	37.5	37.6
Age, years	22	30	39	71	74	75	83	86
Eligible for NIs, based on								
Symptom duration	No	No	No	No	No	No	No	No
Comorbidity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unknown ^a
NI prescribed	No	No	No	No	No	No	No	No
Isolated								
At time of diagnostic test	No	Yes	Yes	No	No	No	No	No
Within 24 hours of test	Discharged	Discharged	Discharged	No	No	No	No	No
Antibiotics during the admission:	Unknown ^a	No	Yes	Yes	No	Yes	No	Yes
Oral, narrow spectrum	Unknown ^a	–	Yes	–	–	–	–	–
Oral, broad spectrum	Unknown ^a	–	–	Yes	–	Yes	–	–
Intravenous, broad spectrum	Unknown ^a	–	–	Yes	–	Yes	–	Yes
Changed within 24 hours of testing	Unknown ^a	–	Yes, stopped	Yes, stepped up from oral to i.v.	–	Yes, from i.v. to oral	–	No
Discharged within 24 hours of test	Yes	Yes	Yes	No	No	No	No	No ^b
Provisional diagnosis at admission	Exacerbation of asthma, chest infection	Influenza/ILI	Exacerbation of asthma	Exacerbation of airways disease, heart failure	Heart failure	LRTI	Exacerbation of airways disease	LRTI

a Notes missing.

b Patient died.

remainder was isolated subsequently. Three of the eight patients were discharged within 24 hours of the test without antibiotics – two had a provisional diagnosis of asthma, one had influenza/ILI; they were the youngest of all of the eight patients.

There was no consistent pattern of treatment after diagnostic testing for the four patients who are known to have received antimicrobials. One patient (No. 3), who had an exacerbation of asthma and was afebrile on admission, had treatment with a narrow-spectrum oral antibiotic stopped and was discharged within 24 hours of testing. A 71-year-old patient (No. 4), who was pyrexial (38.8 °C) and was diagnosed with heart failure and an exacerbation of chronic airways disease on admission, had broad-spectrum oral antibiotics switched to the i.v. route for a presumed bacterial co-infection. Conversely, a 75-year-old patient (No. 6) with LRTI had broad-spectrum oral antibiotics switched from the i.v. to the oral route. Finally, an 86-year-old patient (No. 8) with LRTI was kept on broad-spectrum i.v. antibiotics but died from methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia about 48 hours after admission.

BinaxNOW *Streptococcus pneumoniae* test

Twenty-one admissions that were randomised to the 'near-patient' group had a positive BinaxNOW *S. pneumoniae* test result. Characteristics of these patients are shown in Box 3. Details of the spectrum and route of delivery of the antibiotics they received in hospital before and after the urinary antigen test are shown in Table 20.

Table 20 shows the spectrum and route of delivery of antibiotics before and after the results of urinary antigen tests for 20 patients in the 'near-patient' group. Antibiotics were given to everyone except four patients before the test and one person afterwards. All but five patients received broad-spectrum antibiotics before or after the test. Table 20 shows that four patients had a 'step-up' in treatment within 24 hours of the test result. Although it is unclear from the CRFs whether these changes in treatment occurred in response to the test or slow clinical recovery, Table 20 shows that none of the patients had a

BOX 3 Characteristics of 21 admissions in the 'near-patient' group that tested positive in the BinaxNOW *S. pneumoniae* test

Median age (IQR), years: 59 (43–76.5).

Febrile on admission (≥ 37.3 °C), numerator/denominator (%), median (IQR) °C: 8/20^a (40%), 37.1 °C (36.5–37.65 °C).

Symptom duration on admission, median (IQR) hours: 120 (48–168).

Received pre-admission antibiotics from GP, numerator/denominator (%; 95% CI): 3/20^a (15%, 95% CI 3.2% to 37.9%).

Provisional diagnoses on admission:

- CAP ($n = 7$).
- AE airways disease: COPD ($n = 3$), asthma ($n = 2$).
- ARI ($n = 4$).
- Cardiac: heart failure ($n = 3$), arrhythmia ($n = 1$).
- None entered ($n = 1$).

^a Case notes missing for one patient.

TABLE 20 Spectrum and route of delivery of antibiotics used from admission to hospital to the availability of the BinaxNOW *S. pneumoniae* test, and during the first 24 hours afterwards^{a,b}

Subject	None	Narrow spectrum		Broad spectrum		Summary of changes after result
		Oral	i.v.	Oral	i.v.	
1 ^c					✓	None
2	✓				[✓] ^d	Step-up
3		✓				None
4					✓	None
5			✓		[✓]	Step-up
6	✓				[✓]	Step-up
7 ^e			✓			None
8	✓					None
9				✓		None
10					✓	None
11				✓		None
12				✓		None
13		✓				None
14				✓		None
15					✓	None
16					✓	None
17						
18			✓			None
19 ^f					✓	None
20	✓				[✓]	Step-up
21					✓	None

a Patients receiving broad-spectrum i.v. therapy may also have received broad-spectrum oral antibiotics or i.v. and oral narrow-spectrum antibiotics. Similarly, those receiving broad-spectrum oral antibiotics may also have received i.v. or oral narrow-spectrum antibiotics, and those receiving narrow-spectrum i.v. antibiotics may also have received oral narrow-spectrum antibiotics.

b A 'step-down' of antibiotic treatment may have occurred between admission and when the urinary antigen test was reported. This chart shows whether a step-down of antibiotic treatment occurred from the treatment given immediately before the test and 24 hours later.

c Patient died despite broad-spectrum i.v. antibiotics and admission to the ITU. Certified cause of death: pneumonia, COPD, and pulmonary fibrosis.

d '[✓]' refers to the spectrum and route of delivery of antibiotics that were given to patients within 24 hours of results of the BinaxNOW *S. pneumoniae* test.

e The sample was analysed in error in the laboratory, not at the point of care.

f Patient died. Certified cause of death: colonic carcinoma and intra-abdominal sepsis.

'step-down' in treatment within 24 hours of the result, i.e. there was no evidence from this small number of patients that the test led to a 'step-down' in treatment.

All but two of the 21 patients had comorbidities placing them at risks from the consequences of influenza and could reasonably be expected to be considered for treatment with NIs on admission, assuming that their symptoms were of < 48 hours' duration. We examined the data of all 21 patients to see whether any were eligible for treatment, and whether it had been administered and stopped within 24 hours of the urinary antigen test result. Only 4 of the 21 patients had symptoms of < 48 hours' duration when admitted (all four had symptoms of 24 hours' duration) – two were pyrexial (temperature $\geq 37.3^{\circ}\text{C}$). All four patients had symptoms compatible with influenza, three had underlying respiratory comorbidity, and all four had oxygen saturations of 89–95% on admission, the latter on treatment with 5 l of oxygen. None of the 21 patients received treatment with a NI.

We examined data on 'isolation' for all 21 patients before and within 24 hours of the urinary antigen test result. One of the 21 patients was nursed in single-room accommodation between admission and the urinary pneumococcal antigen test result. This patient had a fever of 40.3°C on admission and remained in single-room accommodation after the test result. One other patient was isolated within 24 hours of the urinary antigen test result – for diarrhoea. Overall, there was no evidence that the BinaxNOW *S. pneumoniae* test influenced decisions on 'isolation'.

We examined data regarding the time of discharge in relation to the urinary pneumococcal antigen test result. Four patients were discharged within 24 hours of the urinary antigen test result. It is unknown whether any of these discharges occurred as a consequence of the test.

Discussion

In this chapter we explored the relationship between the diagnostic group and clinical measures, notably antiviral and antibacterial prescribing, the duration of fever and hospitalisation, treatment with oxygen and CPAP, intensive care support and death. We also examined the use of single-room accommodation to see whether the location of care was influenced by different diagnostic tests. Finally, we explored whether the randomisation resulted in any differences in the QoL of survivors across groups. By each measure, we failed to demonstrate any clinical benefit to first admission patients from POCTs for influenza A and B and *S. pneumoniae*, or molecular diagnostic tests for influenza A and B, or RSV A and B. We also found no evidence that the microbiological diagnosis, whether obtained by POCTs or by RT-PCR, had any effect on containment.

This study was carried out in a busy teaching hospital environment that caters for a local population of approximately one million people. The patients who were recruited to our study had a broad range of acute cardiopulmonary conditions that are typically seen in acute care facilities around the country. Our cohort included substantial numbers of patients who were diagnosed with acute exacerbations of asthma, bronchitis, acute exacerbations of COPD, CAP – conditions that are associated with influenza A and B, RSV and *S. pneumoniae*. In our study, influenza A or B occurred in 91 of 1172 first admissions (7.8%, 6.3–9.4%), RSV in 29 (2.5%, 1.7–3.5%), and *S. pneumoniae* in 99 (8.4%, 6.9–10.2), i.e. infection with these pathogens occurred in more than one in six patients.

Two recent studies^{68,69} suggest that rapid influenza testing may influence the management of adults with influenza. Falsey *et al.*⁶⁸ retrospectively evaluated the clinical management of patients with positive rapid antigen tests for influenza upon admission, during a period when the hospital infection control policy mandated such testing. Viral culture tests and/or RT-PCR, or serological testing were performed if the test was negative using the Directigen POCT for influenza. Antibiotic use was cut modestly from 98.7% (79 out of 80) in patients whose antigen test was negative or unknown to 86.0% (74 out of 86) (relative risk reduction 12.8%: 95% CI 5.7 to 21.9%) in those in whom it was positive. This reduction was not

associated with significant differences in either antibiotic days, length of hospital stay among survivors or antibiotic complications; rather, the mean length of stay was 41 hours longer ($p = 0.16$) in those found positive using rapid influenza testing. Although antiviral use was high in the antigen-positive test group (63 out of 86, 73%) compared with patients whose test was negative, or in whom the test was not performed (6 out of 80, 6%), 39% of patients treated in the study presented outside the 48-hour therapeutic window recommended for prescribing antiviral therapy. Regarding infection control, the antigen test was falsely negative in 41.5% out of 147 patients tested; it is unclear whether any of these patients were isolated. It is also uncertain how many antigen-positive cases had false-positive results and were isolated and given antiviral therapy treatment inappropriately.

D'Heilly *et al.*⁶⁹ evaluated the influence on clinical care of different diagnostic tests (an immunoassay and two cell culture assays) that were used to detect influenza in adults with a mean age of 57.4 years who presented to an urgent care or outpatient medical clinic at a Veterans Affairs medical centre in Minneapolis, USA. The rapid antigen test had a sensitivity of 65% (84 patients tested positive overall); 20 of the 55 cases of influenza that were detected by rapid antigen testing had symptoms of < 48 hours and received antiviral medication. Thus, in this study, rapid testing led to treatment of 23.8% of the 84 patients with influenza. Altogether, 91% of patients with a positive rapid antigen test who described symptoms of ≤ 48 hours' duration received antiviral therapy compared with only 8% of patients with a positive rapid cell culture test but a negative rapid antigen test. Individuals with a positive rapid antigen test were significantly less likely to be treated with antibiotics.

Both of the above studies focused on older adults tested under clinical rather than controlled study conditions and illustrate the potential for near-patient influenza tests to influence prescribing practices, with certain provisos.

- First, to meet NICE criteria for treatment of seasonal influenza, it is essential that results are available to clinicians within a period of 48 hours after the onset of symptoms.⁷⁰ Our cohort presented with a median duration of symptoms before admission of 120 hours (IQR 72–168 hours) (see *Chapter 7*), and only 12% of all patients who were studied could potentially benefit from treatment with influenza antiviral drugs (on the basis of symptom duration, the turnaround time of the diagnostic tests and NICE guidance), even if they all had influenza. However, as shown in *Chapter 4*, influenza occurred in 91 out of 1172 (7.7%) first admissions. Thus, with current referral and admission practice, it seems unlikely that detection and treatment of influenza in the small numbers of patients who are eligible (because of underlying ill health and illness duration of < 48 hours) would impact on the outcomes in our study. However, we did not stratify illness severity as part of the study or take into consideration the possibility that late treatment may benefit severely ill patients who are hospitalised with influenza, as such treatment falls outside NICE guidance. Evidence indicates that oseltamivir (Tamiflu®, Roche) treatment of patients hospitalised with seasonal^{71–73} and pandemic 2009 H1N1 influenza^{74–80} is associated with reductions in radiological pneumonia, illness severity and death. Even when administered > 48 hours after symptom onset, oseltamivir showed considerable potential for reducing pneumonia due to 2009 pandemic H1N1 virus.⁷⁹ Survival benefits for H5N1 influenza have also been observed when treatment with oseltamivir was delayed up to 6 days after symptom onset.⁸¹
- Second, the ability to diagnose influenza is dependent on the sensitivity of the test. Many of the studies that have compared rapid tests with RT-PCR and/or cell culture have been carried out in young healthy adults or in children. Children generally present earlier to medical practitioners with ILI and they shed higher titres of virus than older people, who also present later.⁸² In our study, the sensitivity of the POCT in comparison with RT-PCR was low at 24.4% (see *Chapter 5*), indicating that opportunities to identify and treat patients like ours could be reduced considerably. The low sensitivity in our study may reflect the length of illness and age of the patients prior to sample collection. Nilsson *et al.*⁸³ found the sensitivity of the BinaxNOW influenza A/B test against PCR to drop from 71% to 63% and 14% when specimens were collected from adults presenting to the emergency department of Malmö University Hospital on days 1–3, 1–5 and > 5 days, respectively, following onset of symptoms. Similarly, Stripeli *et al.*⁸⁴ observed a fall in sensitivity from 76% to 65% for The QuickVue

Influenza Test when specimens were collected from hospitalised children with disease duration of < 48 hours compared with children with disease duration of longer than 48 hours.

- Third, the sensitivity of near-patient immunoassay tests can also be influenced by virus type, and pandemic 2009 H1N1 virus compared with seasonal influenza.⁸⁵ Heinonen *et al.*⁸⁶ observed a sensitivity of 90% for influenza A viruses but only 25% for influenza B viruses when specimens were collected from young children aged 1–3 years who presented within 24 hours of onset of fever, and tested using the Actim Influenza A&B POCT. Reduced sensitivity for influenza B virus has also been noted by other investigators using other rapid tests.^{87–89} In our study more than one-third of the specimens positive for influenza by RT-PCR were identified as influenza B virus, which may, in part, account for the low sensitivity of the near-patient QuickVue Influenza A + B test in our study (see *Chapter 5*), and the lack of clinical benefit from the POCT in comparison with molecular or conventional diagnostic tests in our study. Our study was carried out before the 2009 H1N1 pandemic.
- Fourth, the quality of the specimen and method of collection can also impact upon test sensitivity. Scansen *et al.*⁹⁰ compared the performance of the Quidel QuickVue Influenza A + B test on secretions from the anterior nares when a polyurethane foam swab was used for collection to that of a nylon flocked swab. The QuickVue test was positive for 40 foam and 30 flocked swabs, for sensitivities of 71% and 54%, respectively, a difference that achieved statistical significance. Agoritsas *et al.*⁹¹ showed that the sensitivity of the QuickVue test was 85% with nasopharyngeal swabs, 78% with nasal swabs and 69% with nasopharyngeal washes, when specimens were collected from children with a mean age of 5 years. Anterior nasal swab collection was performed first with an absorbent foam swab, posterior nasopharyngeal swab collection was performed second with a Dacron swab, and nasopharyngeal washing was performed last with sterile saline. The difference in sensitivity between nasopharyngeal swabs and nasopharyngeal washes was significant. There was no difference in sensitivity between anterior nasal swab collection and the two nasopharyngeal collection methods. Walsh *et al.*⁹² compared nylon flocked swab/universal transport medium collection method (sampling at the mid-turbinate level) with nasal aspirates collected from infants and toddlers in a PCR test – the swab collection method significantly outperformed the use of nasal aspirates. Schmid *et al.*⁹³ evaluated traditional and rapid culture methods for influenza using nasopharyngeal aspirates and throat swabs from adults with symptoms and signs consistent with influenza. Nasopharyngeal aspirates were twice as sensitive as throat swabs. Similarly, Smit *et al.*⁹⁴ tested upper respiratory tract samples in parallel with the BinaxNOW Influenza A&B combination assay, BinaxNOW Flu A and BinaxNOW Flu B assays, the Becton Dickinson Directigen Flu A + B assay and IF, and the results were compared with viral culture. Altogether 521 samples – including 338 nasopharyngeal swabs, 162 throat swabs, 19 nasal washes and two swabs from unspecified sites – were collected from 448 adults and children. There were no significant differences in the performances of all rapid antigen tests, with sensitivities of 53–59% compared with culture and IF but the sensitivities of all the rapid antigen tests were significantly higher for nasopharyngeal samples than for throat swabs. In our study, nasopharyngeal specimen collection was undertaken by trained research staff, and specimens were handled as per the manufacturer's instructions. It is therefore unlikely that specimen quality was responsible for the observed outcomes.

Most antibiotics prescribed in general practice are for respiratory tract infections that represent about 70% of all infections treated in primary care.^{95,96} In the USA, antibiotic prescribing for acute respiratory illness accounts for over 50% of all antibiotics used in primary care.⁹⁷ Antibiotic prescribing has decreased in UK general practices in recent years mainly because there are fewer consultations for common respiratory infections, and partly because GPs are prescribing antibiotics less frequently for conditions that are primarily viral in aetiology.⁹⁸ There is a paucity of evidence showing benefit from antibiotic use in many acute respiratory conditions including acute bronchitis,⁹⁹ acute asthma exacerbations,^{100–102} and in many cases of acute exacerbation of chronic obstructive airways disease.^{103–105} Although overprescription of antibiotics has led to the emergence and proliferation of antibiotic-resistant bacteria,^{106–109} a meta-analysis of 122 reports of CAP showed that approximately 6000 (18%) of 33,148 cases had a bacterial pathogen, with *S. pneumoniae* accounting for 73% of all cases and 66% of fatal cases.^{16,110} Thus, clinicians face the problem of unnecessary use of antibiotics for some respiratory conditions – and the requirement for prompt (empiric) antimicrobial treatment for others.

National and international bodies including the British Thoracic Society (BTS) provide guidance for empiric treatment of CAP due to the risks from delayed treatment and limitations of diagnostic tests.¹⁷ Isolation of *S. pneumoniae* from the blood is specific but lacks sensitivity.^{111–113} Culturing blood before antibiotic therapy is recommended by the BTS (and similar bodies) for all hospitalised patients with moderate and high-severity CAP, but studies have suggested that blood cultures rarely alter antibiotic therapy for patients presenting with pneumonia because of the low overall positive rate of blood cultures.^{112,114–118} Moreover, clinicians did not follow protocols for narrowing an antibiotic spectrum even when appropriate. Sputum culture is often used to help identify aetiological agents and is recommended by BTS to investigate moderate severity CAP and severe CAP that fails to improve.¹⁷ The test lacks specificity, and isolation of *S. pneumoniae* from sputum may represent colonisation.¹¹⁹ In our study, sputum culture had a sensitivity of 100% (2.5–100%) (see *Chapter 5*) when compared with blood culture as the reference standard but the CIs were extremely wide due to the infrequency of a productive cough in our cohort. Musher *et al.*¹²⁰ analysed 105 patients with pneumococcal pneumonia proven by blood culture – sputum culture was positive in only 44% of all cases. These investigators reviewed earlier articles and noted that sensitivity of Gram staining in proven cases of pneumococcal pneumonia ranged from 20% to 69% and that the sensitivity of culture ranged from 29% to 94% (see *Chapter 6*).

Given the limitations of conventional diagnostic tests for *S. pneumoniae* infection, the development of a *S. pneumoniae* urinary antigen test offered several advantages – ease in getting a diagnostic specimen, ability to detect pneumococcal infection after antibiotic treatment has been commenced, its diagnostic yield, and a rapid turnaround time. Among adult patients with CAP, this test has shown sensitivities of 64–87% compared with blood culture,^{111,121} but dropped to 54% when cultures of respiratory tract secretions were included in the reference standard.¹²² In our study, the sensitivity of the urinary antigen test in comparison with blood culture was 57.1% (18.4% to 90.1%) (see *Chapter 5*), which is comparable with previous reports. In our study, the POCT for pneumococcal infection was positive in 92 (7.8%; 6.4 to 9.5) of all 1172 admissions and, together with POCT for influenza, it had no evident effect on clinical outcome.

Only one patient in this study was prescribed a NI. Reasons for the low use these drugs might include the length of illness pre-admission together with unfamiliarity with NIs and the diagnostic test. The number of patients in the ‘near-patient’ group with a positive QuickVue Influenza A+B test was too small to draw definitive conclusions – none of eight patients with a positive result was eligible for treatment based on their duration of symptoms pre-admission and NICE guidance.

Regarding ‘containment’, two of the eight patients in the ‘near-patient’ group with a positive QuickVue Influenza A+B test were already in single-room accommodation when the test was carried out. One patient was discharged shortly afterwards. None of the remaining five patients was isolated, but four had fever and respiratory symptoms and were probably still shedding influenza virus.^{123–125} We may reason that single-room accommodation was either unavailable, or that the nursing and medical carers were unaware of the possible risk of nosocomial transmission. Altogether, 120 of the 1172 patients with a first admission had positive tests for influenza or RSV, of whom only 14 were given single-room accommodation during the admission.

The US Healthcare Infection Control Practices Advisory Committee recommends that patients with influenza are given single-room accommodation, when available, for a period of 5 days, and masked when transported out of the room.¹²⁶ The problem for clinicians is recognising patients with influenza, as exacerbations of asthma,¹²⁷ cystic fibrosis,¹²⁸ COPD,¹²⁹ heart failure,¹³⁰ bouts of pneumonia,¹⁷ acute bronchitis¹³¹ and other acute respiratory conditions are all associated with influenza, and such complications may dominate the features of influenza. Nosocomial influenza is a well-recognised problem in acute care hospital settings.^{132–135} Evidence indicates that nosocomial infection of health-care workers with influenza in acute hospitals is not uncommon¹³⁶ and that influenza acquired within hospitals can be fatal.¹³⁷ In our study, the rate of isolation for patients with influenza or RSV (14/120; 11%, 95% CI 7.1% to 18.6%) was no different to the overall rate of isolation (112/1172; 9.5%, 95% CI 7.9% to 11.4%), suggesting that hospitals like ours have inadequate resources to contain infection.

The extremely low prescription rate for NIs in this study indicates that near-patient testing for *S. pneumoniae* could not reduce NI use, even if considered appropriate. Bacterial pneumonia is a well-recognised complication of influenza and occurred in 29% of ≈ 1200 patients hospitalised during the 2009 H1N1 pandemic. The pneumococcus was by far the most common pathogen,^{138–145} suggesting that withdrawal of NIs from some patients with a positive urinary pneumococcal antigen test may be inappropriate.

Chapter 5 Diagnostic outcomes

Statistical methods

Data on diagnostic performance of the various tests (blood culture, viral culture, sputum culture, PCR, Quidel and Binax POCTs) for the diagnosis of (1) influenza and (2) *S. pneumoniae* infection, are summarised as:

- percentage diagnostic agreement (the percentage of test results, either positive or negative, that are in agreement) (and associated 95% CI), or
- sensitivity (percentage of true-positives correctly identified)
- specificity (percentage of true-negatives correctly identified) (and associated 95% CI)
- positive predictive values (PPVs) (percentage of positive test results that are truly positive) and negative predictive values (NPVs) (percentage of negative test results that are truly negative) (and associated 95% CI), and
- area under receiver operating characteristic (ROC) curve (area under the curve, AUC) (the probability that two patients – one diseased and one not diseased – would be both correctly classified by the test) (and associated 95% CI).

In the case of influenza, uncertainty remains as to what is currently considered to be the reference standard to which all tests should be compared (i.e. 'gold standard'). When the 3WS was designed, standard laboratory testing procedures were anticipated to be the then current 'gold standard'. However, during the course of the 3WS, PCR techniques have been developed and now may be considered to be the 'gold standard' – for example in the meta-analysis reported in *Chapter 6* of influenza diagnoses, 13 out of 64 (20%) studies used PCR as the 'gold standard' and only 24 of 64 (37%) studies considered laboratory culture alone to be the 'gold standard'. Hence a number of analyses using different 'gold standards' have been undertaken to enable comparison between the results from 3WS and those found in the literature.

In the case of influenza, test performance could also be assessed by serology. The primary analysis uses only definite positive serology results and does not allow for month and time between blood samples. However, due to the nature of the 3WS, patients could be discharged from hospital and subsequently have had an influenza vaccination prior to a second (convalescent) blood sample being taken. In order to allow for this, and the fact that positive serology results were graded as definite, probable and possible, two sensitivity analyses were undertaken: (1) excluding those who had their *first* blood taken between September and December and had > 30 days between samples and (2) including both definite and probable positive serology results.

All analyses were undertaken in Stata version 11.

Results

Influenza

Comparison between tests themselves

Table 21 summarises the diagnostic performance of the tests in terms of influenza using either PCR or viral culture as the 'gold standard'. Although there is a relatively high level of overall agreement between the tests, the Quidel POCT has relatively low sensitivity compared with either PCR (24.4%, 95% CI 16% to

TABLE 21 Comparison of test performance for the diagnosis of influenza

'Gold standard'	Comparator	Measure	Estimate	95% CI
PCR	Quidel POCT	Agreement	94.3%	92.8% to 95.5%
		Sensitivity	24.4%	16% to 34.6%
		Specificity	99.7%	99.2% to 99.9%
		PPV	88.0%	68.8% to 97.5%
		NPV	94.4%	93.0% to 95.7%
		ROC AUC	0.62	0.58 to 0.67
	Viral culture	Agreement	94.1%	92.6% to 95.4%
		Sensitivity	21.6%	13.5% to 31.6%
		Specificity	99.8%	99.4% to 100%
		PPV	90.5%	69.6% to 98.8%
		NPV	94.2%	92.7% to 95.4%
		ROC AUC	0.61	0.56 to 0.65
Viral culture	Quidel POCT	Agreement	97.4%	96.4% to 98.2%
		Sensitivity	33.3%	14.6% to 57.0%
		Specificity	98.6%	97.7% to 99.2%
		PPV	29.2%	12.6% to 51.1%
		NPV	98.8%	98.0% to 99.3%
		ROC AUC	0.66	0.56 to 0.76
	PCR	Agreement	94.1%	92.6% to 95.4%
		Sensitivity	90.5%	69.6% to 98.8%
		Specificity	94.2%	92.7% to 95.4%
		PPV	21.6%	13.5% to 31.6%
		NPV	99.8%	99.4% to 100.0%
		ROC AUC	0.92	0.86 to 0.99

34.6%) or viral culture (33.3%, 95% CI 14.6% to 57.0%), although the corresponding specificity is always over 90%. Thus, although the Quidel POCT appears to perform acceptably at classifying truly negative patients, in terms of influenza, less than one-third of those with influenza appear to be detected with the test. In terms of sensitivity, this is considerably lower than values reported in the literature. Overall, in the meta-analysis reported in *Chapter 6*, the 64 studies included yielded a pooled sensitivity of 74%, although those using PCR and viral culture as 'gold standards' produced sensitivities of 51% and 86%, respectively. However, subgroup and sensitivity analyses suggest that comparable estimates to 3WS based on the meta-analysis are lower than these overall headline figures (see *Chapter 6* for further details).

Comparison with serology

Table 22 summarises the diagnostic performance of the tests in terms of influenza using serology as the 'gold standard'. Of the three approaches to testing for influenza, all have relatively high specificities, although PCR has the highest sensitivity (42.6%, 95% CI 28.3% to 57.8%), those of viral culture and

TABLE 22 Comparison of test performance with serology in the diagnosis of influenza

Comparator	Measure	Estimate	95% CI
PCR			
<i>Primary analysis</i>			
	Agreement	92.3%	90.6% to 93.7%
	Sensitivity	42.6%	28.3% to 57.8%
	Specificity	94.2%	92.7% to 95.4%
	PPV	22.2%	14.1% to 32.2%
	NPV	97.7%	96.6% to 98.5%
	ROC AUC	0.68	0.61 to 0.76
<i>Sensitivity analyses^a</i>			
(i)	Agreement	91.8%	90.0% to 93.3%
	Sensitivity	48.8%	32.9% to 64.9%
	Specificity	93.3%	91.5% to 94.7%
	PPV	22.7%	14.5% to 32.9%
	NPV	97.7%	96.6% to 98.5%
	ROC AUC	0.71	0.63 to 0.79
(ii)	Agreement	92.3%	90.7% to 93.7%
	Sensitivity	43.8%	29.5% to 58.8%
	Specificity	94.3%	92.8% to 95.5%
	PPV	23.3%	15.1% to 33.4%
	NPV	97.7%	96.6% to 98.5%
	ROC AUC	0.69	0.62 to 0.76
Viral culture			
<i>Primary analysis</i>			
	Agreement	95.4%	94.1% to 96.5%
	Sensitivity	13.3%	5.05% to 26.8%
	Specificity	98.7%	97.9% to 99.3%
	PPV	28.6%	11.3% to 52.2%
	NPV	96.7%	95.5% to 97.7%
	ROC AUC	0.56	0.51 to 0.61
<i>Sensitivity analyses^a</i>			
(i)	Agreement	95.1%	93.7% to 96.4%
	Sensitivity	15.4%	5.8% to 30.5%
	Specificity	98.5%	97.5% to 99.1%
	PPV	28.6%	11.3% to 52.2%
	NPV	96.6%	95.3% to 97.6%
	ROC AUC	0.57	0.51 to 0.63

continued

TABLE 22 Comparison of test performance with serology in the diagnosis of influenza (*continued*)

Comparator	Measure	Estimate	95% CI
(ii)	Agreement	95.1%	94.1% to 96.5%
	Sensitivity	13.0%	4.9% to 26.3%
	Specificity	98.7%	97.9% to 99.3%
	PPV	28.6%	11.3% to 52.2%
	NPV	96.6%	95.4% to 97.6%
	ROC AUC	0.56	0.51 to 0.61
Quidel POCT			
<i>Primary analysis</i>			
	Agreement	95.3%	93.9% to 96.4%
	Sensitivity	14.9%	6.2% to 28.3%
	Specificity	98.5%	97.6% to 99.1%
	PPV	28.0%	12.1% to 49.4%
	NPV	96.7%	95.6% to 97.7%
	ROC AUC	0.57	0.52 to 0.62
Sensitivity analyses^a			
(i)	Agreement	95.1%	93.6% to 96.3%
	Sensitivity	17.1%	7.15% to 32.1%
	Specificity	98.3%	97.3% to 99.0%
	PPV	29.2%	12.6% to 51.1%
	NPV	96.6%	95.4% to 97.6%
	ROC AUC	0.58	0.52 to 0.64
(ii)	Agreement	95.3%	93.9% to 96.4%
	Sensitivity	14.6%	6.1% to 27.8%
	Specificity	98.5%	97.6% to 99.1%
	PPV	28.0%	12.1% to 49.4%
	NPV	96.7%	95.5% to 97.6%
	ROC AUC	0.57	0.52 to 0.62

a Sensitivity analyses: (i) excluding those who had their *first* blood taken between September and December and had > 30 days between samples; (ii) including both definite and probable positive serology results.

Quidel POCT are relatively low, at 13.3% and 14.9%, respectively. Both sensitivity analyses indicate that these estimates of sensitivity could increase, although only very slightly.

Streptococcus pneumoniae infection

Table 23 summarises the diagnostic performance of the tests in terms of identifying *S. pneumoniae* infection using either blood culture or sputum culture as the 'Gold standard'. In all cases specificity is > 90%, whereas the Binax POCT produces a sensitivity of 57.1% (95% CI 18.4% to 90.1%) compared with blood culture and 30.0% (95% CI 6.7% to 65.2%) compared with sputum culture.

TABLE 23 Comparison of test performance for the diagnosis of *S. pneumoniae* infection

'Gold Standard'	Comparator	Measure	Estimate	95% CI
Blood culture	Binax	Agreement	92.3%	90.3% to 93.9%
		Sensitivity	57.1%	18.4% to 90.1%
		Specificity	92.5%	90.6% to 94.1%
		PPV	5.5%	1.5% to 13.4%
		NPV	99.6%	99.0% to 99.9%
		ROC AUC	0.75	0.55 to 0.95
	Sputum culture	Agreement	97.2%	94.4% to 98.9%
		Sensitivity	100%	2.5% to 100.0%
		Specificity	97.2%	94.3% to 98.9%
		PPV	12.5%	0.3% to 52.7%
		NPV	100%	98.5% to 100%
		ROC AUC	0.99	0.48 to 1.00
Sputum culture	Binax	Agreement	90.0%	85.6% to 93.1%
		Sensitivity	30.0%	6.7% to 65.2%
		Specificity	92.0%	88.1% to 95.0%
		PPV	12.5%	2.7% to 32.4%
		NPV	97.2%	94.3% to 98.9%
		ROC AUC	0.61	0.46 to 0.76

Discussion

We compared the diagnostic performances of viral culture, Quidel QuickVue Influenza A + B test and RT-PCR, using either PCR or viral culture as the 'gold standard'. With PCR as the gold standard, viral culture carried out at the UHL NHS Trust laboratory had a sensitivity of just 21.6% (95% CI 13.5% to 31.6%), which, although similar to the sensitivity reported by the Portuguese national surveillance network, during the 7-year period 1992–93 to 1998–99,¹⁴⁶ is suboptimal in comparison with sensitivities of 61–96% reported in nine studies^{90,91,147–153} (Table 24) that were identified for the systematic review and meta-analysis of POCTs for influenza (see Chapter 6). However, the sensitivity of viral culture was similar to that of the Quidel POCT (24.4%, 95% CI 16% to 34.6%). Although the performance of both the viral culture and the Quidel POCT appears relatively low in terms of identifying truly positive cases, especially in comparison with the headline estimates of the meta-analysis of POCTs for influenza (see Chapter 6), any comparisons need to be approached with caution owing to the extremely heterogeneous nature of the studies reported, and because subgroup and sensitivity analyses indicate that 3WS provides comparable estimates of diagnostic performance to appropriate comparator studies (see Chapter 6).

Factors that may contribute to lower rates of influenza virus isolation, include the type of swab collection device, the cell culture system, the passage history of the mammalian cells used, the stability of protease supplement to the media and, possibly, alterations in receptor binding properties of isolates of influenza A H3N2 and H1N1 since the late 1980s.^{146,154} Specimens were collected according to the methods recommended by the HPA, and by the manufacturer of the Quidel POCT (see www.cliawaived.com/web/items/pdf/QDL-20183-Quidel_Influenza_Tests_Insert~619file1.pdf) by research nurses dedicated to the project. Thus, it seems unlikely that the expertise of personnel who collected the specimens or the method

TABLE 24 Sensitivities and specificity of viral culture compared with PCR as the gold standard for the diagnosis of influenza

Author	Location	Children	Adults	No. in study	Culture sensitivity, % (no. positive by culture/no. positive by PCR)	Culture specificity
Agoritsas, 2006 ⁹¹	USA	From 2 weeks to 18 years	None	122	91.5 (54/59)	
Chan, 2002 ¹⁴⁷	Hong Kong	From < 2 years	To > 55 years	250	91.7 (54/57)	
Cheng, 2010 ¹⁴⁸	China	From 5 months	To 70 years	5740	95.7 (551/576)	
Mehlmann, 2007 ¹⁴⁹	USA	From 3 months	To 86 years	102	93.4 (57/61)	
Poehling, 2002 ¹⁵⁰	USA	From 6 months to 18 years	None	233	61.1 (11/18)	99.5 (214/215)
Rahman, 2008 ¹⁵¹	USA	From 6 months	To ≥ 65 years	932	94.9 (93/98)	100
Ruest, 2003 ¹⁵²	Canada	From 1 day	To 98 years	200	83.5 (71/85)	
Scansen, 2010 ⁹⁰	USA	≤ 17	None	100	87.5 (49/56)	
Simmerman, 2007 ¹⁵³	Thailand	From 1 month	To 86 years	1092	81.3 (205/252)	

of specimen collection were important contributory factors to the low sensitivities of culture and the Quidel POCT observed in our study. In our study specimens were received by the laboratory at a median of 3.6 hours after specimen collection, making delayed transportation and inappropriate specimen handling unlikely as contributory factors. A more plausible explanation is the length of illness prior to sampling, which in our study was a median of 120 hours. Lee *et al.*¹²⁵ evaluated secular shedding of seasonal influenza virus from 147 inpatients aged > 16 years (mean age 72 years, ± 16 years) in Hong Kong. The results of virus isolation showed that among untreated (i.e. by NIs) patients, 38.5% and 21.2% remained culture positive by symptom day ≥ 4 and ≥ 5, respectively, and in patients with comorbidities the proportions were somewhat higher, at 41.7% and 33.3%, respectively. Leekha *et al.*¹⁵⁵ examined secular shedding of seasonal influenza virus by 50 hospitalised patients by culture. Results showed that by symptom days 3, 4, 5 and ≥ 7, 91%, 75%, 52% and 20% of patients, respectively, remained culture positive. Although these observations have implications for infection control, they show that by day 5 of symptoms (i.e. the median duration of symptoms upon sampling in our study), approximately 50–80% of patients with influenza were unlikely to be shedding infectious virus. Presence of viral nucleoproteins that are detectable by the Quidel POCT is likely to fall at a similar rate.

Despite being the most common pathogen in CAP, *S. pneumoniae* is underdiagnosed because of the limitations of conventional diagnostic tests. Although blood culture is used as the 'gold standard' for diagnosis of pneumococcal CAP in many studies, it has low sensitivity and premedication with antibiotics reduces it further. The observed sensitivity (57.1%, 95% CI 18.4% to 90.1%) and specificity (92.5%, 95% CI 90.6% to 94.1%) for the BinaxNOW urinary antigen detection test in our study are comparable to sensitivities of 75% to 88%^{49,156–160} compared with blood culture (or culture of blood and pleural aspirate) in previous studies. The BinaxNOW POCT has a high specificity, in excess of 90%, and contributed to a reduction in the spectrum of antibiotic cover of 41 of 474 episodes of CAP in one recent study.¹⁶¹ In comparison with blood and sputum cultures, the pneumococcal urinary antigen test has advantages of being a simple and rapid method with visually detectable results (see *Chapter 7*), providing speedy diagnosis without any additional equipment or reagents in a clinic or triage setting; is non-invasive; positive results persist over a period of days and occur despite treatment with antibiotics; and the test has high sensitivity and specificity. However, a negative result cannot rule out pneumococcal infection.

In our study, sputum culture had a sensitivity of 100% (2.5–100%) when blood culture was used as the gold standard. The CIs are wide due to the small number of patients with a positive blood culture and productive cough. Musher *et al.*¹²⁰ analysed 105 patients with pneumococcal pneumonia proven by blood culture. Sputum culture yielded a pneumococcus in 44% of cases. Sensitivity data for sputum culture from that review and several recent studies are shown in *Table 25*.^{119,120,162–167} Random-effects meta-analysis of the data in *Table 25* reveals sensitivities of 43% (33–53.0%) when cases who received antibiotics are included, and 59% (21–92%) when they are excluded. Specificity data are not available, but the specificity of sputum culture is generally poor due to colonisation of the respiratory tract. The poor sensitivity and specificity of sputum culture therefore question its value in the management of lower respiratory infections. Sputum culture also has downsides of cost and ease and speed of use, but empiric antibiotic recommendations are ultimately dependent upon the accumulated information available from such tests.

TABLE 25 Sensitivities of sputum culture compared with blood culture as the gold standard for the diagnosis of pneumococcal infection

Author	Location	No. in study	Sensitivity: % (95% CI) (no. positive by sputum culture/no. of positive by blood culture)	Patients with prior antibiotics excluded
Davidson, 1976 ¹¹⁹	USA	25	100 (15.8 to 100) (2/2)	No
Kalin, 1982 ¹⁶²	Sweden	89	44.1 (31.1 to 57.6) (26/59)	No
Musher, 2004 ¹²⁰	USA	105	43.8 (34.1 to 53.8) (46/105)	No
Torres, 1998 ¹⁶³	USA	71	48.8 (33.3 to 64.5) (21/43)	No
Watanakunakorn, 2002 ¹⁶⁴	USA	59	28.8 (33.3 to 64.5) (21/43)	No
Drew, 1977 ¹⁶⁵	USA	31	93.5 (78.6 to 99.2) (29/31)	Yes
Fiala, 1969 ¹⁶⁶	USA	25	56.0 (34.9 to 75.6) (14/25)	Yes
Garcia-Vazquez, 2004 ¹⁶⁷	Spain	133	17.3 (11.3 to 24.8) (23/133)	Yes
Kalin, 1982 ¹⁶²	Sweden	89	66.7 (49.8 to 80.9) (26/39)	Yes

Chapter 6 Systematic review and meta-analysis of near-patient tests for influenza A and B

Introduction

Influenza resembles other acute viral respiratory infections with respect to its seasonality, clinical presentation and complications, but it differs from other respiratory viral conditions by being preventable by annual vaccination and ameliorated by antiviral drugs if given within 48 hours of symptom onset. The gold standard for influenza diagnosis is viral culture, which, although specific, had low sensitivity compared with real-time RT-PCR in our study and gave results long after hospital discharge or death (see *Chapters 5 and 7*). In contrast, we were able to correlate the results of PCR and serology (see *Chapter 5*), confirming the accuracy of RT-PCR, and we showed that it gave a diagnosis in a busy clinical setting within a median of 29 hours (IQR 13.5–31.6 hours) (see *Chapter 7*). This turnaround time might facilitate timely antiviral therapy but concerns have been raised that the demands of the test, requiring transportation of specimens to a laboratory with specialised expertise and equipment, and its turnaround time make it too slow for therapeutic or infection control purposes.^{168–170}

Commercial POCTs were used to manage patients with ILI during the 2009 H1N1 pandemic.^{168,169,171,172} However, there have been mixed reports of the diagnostic accuracy of such tests, perhaps reflecting the test used, patient age, the method of sample collection and transport, the 'gold standard' used, and the type and subtype of influenza (i.e. whether seasonal or pandemic influenza, or influenza B). According to the manufacturer, the QuickVue Influenza A + B test detected all 24 influenza A viruses, subtypes H1–H15, which were isolated from birds and mammals, although performance characteristics were not established (see www.cliawaived.com/web/items/pdf/QDL-20183-Quidel_Influenza_Tests_Insert~619file1.pdf).

We used the QuickVue (Quidel, USA) POCT in our study and found that it had a sensitivity of 33.3% and a specificity of 98.6% when compared with culture and 24.4% and 99.7%, respectively, when compared with RT-PCR (see *Chapter 5*). To compare our findings with other studies, we systematically reviewed published articles on the diagnostic accuracies of commercially available influenza POCTs. To assess the quality of the methodology and the completeness of the reporting of each manuscript, we 'scored' each publication using the QUADAS (quality assessment tool for diagnostic accuracy studies) tool and the Standards for Reporting of Diagnostic Accuracy (STARD) initiative.^{173–176}

Methods

Literature searches

On-line searches were made on MEDLINE/PubMed on 28 April 2011 and on the Bioscience Information Service (BIOSIS) and The Cochrane library on 27 May 2011 for publications on influenza POCT diagnostic accuracy studies between 1991 and 2011 (inclusive) that met the following five criteria:

1. Articles written in English.
2. Commercially available test kits.
3. Testing done in human seasonal and pandemic influenza.
4. Sensitivity results with specific numerators and denominators.
5. We had authorised journal access.

Medical subject heading (MeSH) search phrases included:

1. "QuickVue test influenza".
2. "Rapid influenza test".
3. "Rapid antigen test influenza".
4. "POCT influenza".
5. "Immunochromatographic test influenza".
6. "Bedside test influenza".

Figure 7 shows a flow diagram of the manuscript screening process, taken from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline on systematic reviews.¹⁷⁷

Manuscript scoring

The QUADAS tool is an evidence-based scheme for the determination of the quality of both the methodology and the reporting of findings when doing systematic reviews. It consists of 14 questions called 'items' about the study patients, selection criteria, testing standards, results and clinical data that were answered with a 'yes,' 'no' or 'unclear.'

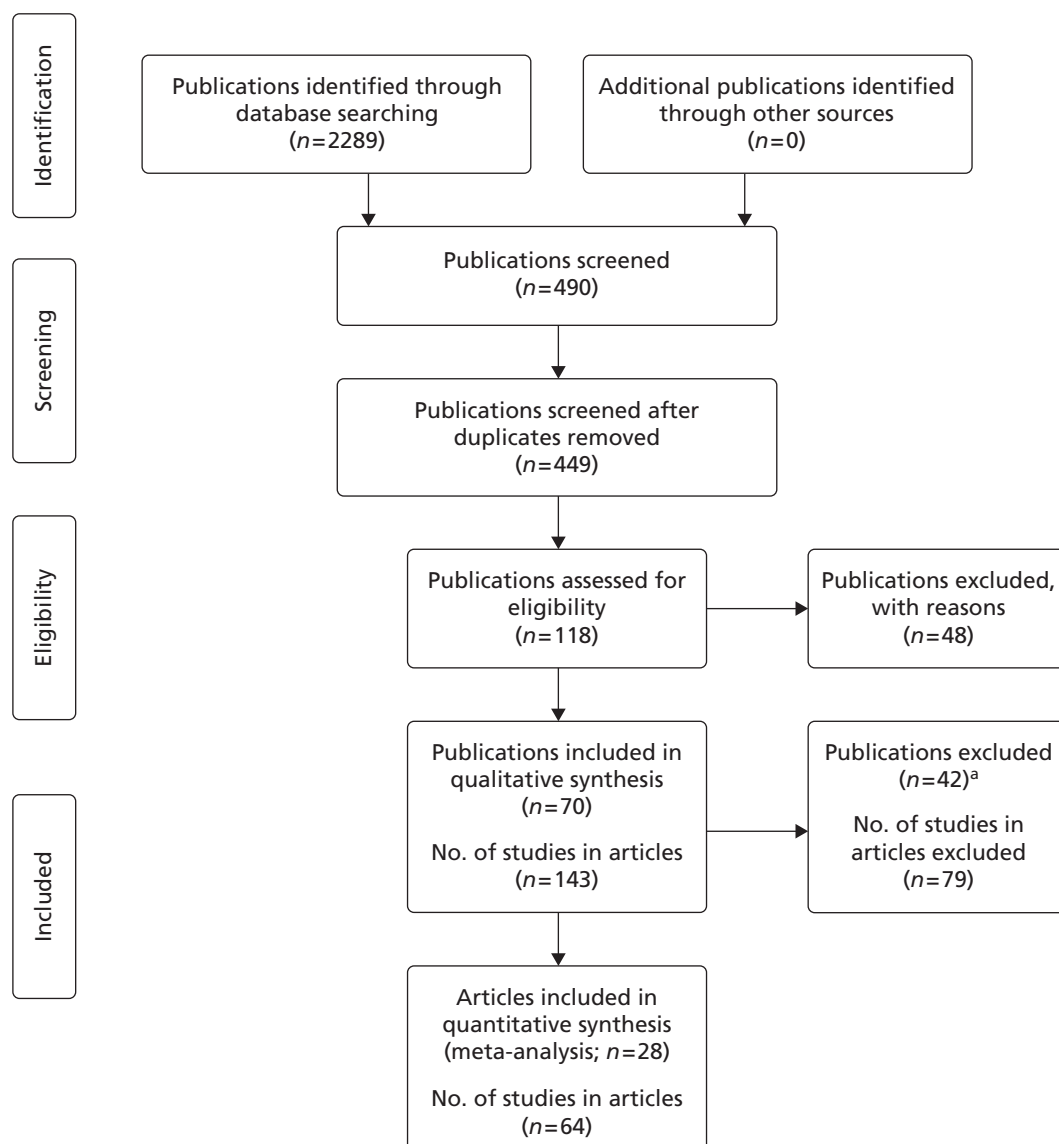


FIGURE 7 The manuscript screening process. a. Partial data from three publications.

The STARD initiative was another evidence-based tool used to assess the accuracy, completeness, and risk of bias in the systematic review of diagnostic accuracy studies. The STARD checklist consists of 25 questions pertaining to a study's title, introduction, methodology, results and discussion sections; the more of the 25 items that are identified or described in the report, the more favourable the outcome.

Data analysis

For those studies that reported a full 2×2 table, i.e. numbers of true-positives, false-positives, false-negatives and true-negatives, or for which these could be calculated, pooled sensitivity and specificities were estimated using a bivariate mixed-effects meta-analysis model.¹⁷⁸ As well as summarising the overall diagnostic measures a hierarchical summary ROC curve was also estimated using the derived logit estimates of sensitivity, specificity and their respective variances.¹⁷⁹ Heterogeneity was assessed using the I^2 measure and explored using subgroup analyses using study-level covariates.¹⁸⁰ A number of studies reported only estimates of sensitivity, and in order to explore whether there was a selection effect between those studies that reported both sensitivity and specificity, and those that reported only sensitivity, a sensitivity analysis was undertaken in which the sensitivities were pooled separately for the two groups of studies using a standard random-effects meta-analysis model on the logit scale, and the pooled estimates compared.

Results

More than 2000 publications were found using the MeSH terms and 490 of these were relevant. In total, 70 out of the 490 publications met all five criteria and were selected for the systematic review. Some of the 70 had more than one finding, which we called 'studies'. There were 143 studies altogether. Twenty-eight of the 70 publications reported full 2×2 data and were used for meta-analysis. There were a total of 68 studies in the 28 publications but four studies from three publications were excluded.^{88,172,181} Thus 64 studies from 28 publications were included in the meta-analysis. *Figure 7* shows a flow diagram of the manuscript screening process, taken from the PRISMA guidance on systematic reviews.¹⁷⁸

Appendix 6 summarises the publications that were screened and *Table 26* summarises the sensitivities and specificities of the 64 POC studies that were included in the qualitative synthesis. *Table 27* presents the QUADAS results and *Table 28* the STARD results. *Figure 8* shows the percentage of studies satisfying each of the QUADAS items and *Figure 9* displays the distribution of the overall QUADAS score. As can be seen from *Figure 9*, 40 of the 64 (62.5%) studies that were included in the meta-analysis scored > 10 indicating that the studies were of a reasonably high quality overall.

TABLE 26 Studies included in the meta-analysis of POCT for influenza using PCR as the gold standard

Author	Location	Children, age	Adults, age	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Agoritsas, 2006 ⁹¹	USA	2 weeks to 18 years	None	Seasonal	PCR and culture (R-mix, Diagnostics Hybrids, Athens, OH, USA)	QuickVue Influenza A+B	NPS: 85 (50/59) NPW: 69 (41/59) NS: 78 (46/59)	NPS: 98 (62/63) NPW: 98 (62/63) NS: 97 (61/63)	NPS: 98 (50/51) NPW: 98 (41/42) NS: 96 (46/48)	NPS: 87 (62/71) NPW: 78 (62/80) NS: 82 (61/74)
Bellei, 2003 ¹⁸⁹	Brazil	None	18–56 years	Seasonal	Culture on MDCK cells	QuickVue Influenza A+B	74 (29/39)	83 (48/58)	–	–
Booth, 2006 ¹⁹⁰	Australia	1–16 years	Included, age not specified	Seasonal, influenza A	Culture on MDCK cells and IFA	ImmunoCard Stat! Flu A&B (Meridian Bioscience, Cincinnati, OH, USA)	80 (28/35)	98 (185/189)	88 (28/32)	96 (185/192)
Cazacu 2004 ²⁰⁰	USA	1–16 years	Included, age not specified	Seasonal, influenza B	Culture on MDCK cells and IFA	ImmunoCard Stat! Flu A&B	47 (7/15)	100 (209/209)	100 (7/7)	96 (209/217)
		1–16 years	Included, age not specified	Seasonal, influenza A	Culture on MDCK cells and IFA	NOW Flu A+B (Binax, Portland, ME, USA)	80 (28/35)	99 (188/189)	97 (28/29)	96 (188/195)
		1–16 years	Included, age not specified	Seasonal, influenza B	Culture on MDCK cells and IFA	NOW Flu A+B	47 (7/15)	100 (208/209)	88 (7/8)	96 (208/216)
Cazacu 2004 ²⁰⁰	USA	From 3 days	To 55.8 years	Seasonal	Culture on RMK cells	Directigen Flu A+B	43.8 (96/219)	99.7 (3863/3873)	90.5 (96/106)	96.9 (3863/3986)
Cazacu 2004 ²⁰¹	USA	Included, age not specified	Included, age not specified	Seasonal	Culture on RMK cells	XPECT® Flu A+B (Remel, Lenexa, KS, USA)	94.4 (118/125)	100 (275/275)	100 (118/118)	97.5 (275/282)

Author	Location	Children, age	Adults, age	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Chan, 2002 ¹⁴⁷	Hong Kong	From < 2 years	To > 55 years	Seasonal, influenza A	Culture on MDCK cells	Directigen EZ Flu A+B	100 (22/22)	99 (225/228)	88 (22/25)	100 (225/225)
Chen, 2002 ¹⁹¹	China	From < 2 years	To > 55 years	Seasonal, influenza B	Culture on MDCK cells	Directigen EZ Flu A+B	88 (28/32)	97 (211/218)	80 (28/35)	98 (211/215)
		Included, age not specified	Included, age not specified	Influenza A	Culture on MDCK cells	FluA Dot (Creative Diagnostics, Shirley, NY, USA)	88.5 (69/78)	99 (146/147)	99 (69/70)	94 (146/155)
Chomel, 1992 ¹⁸¹	France	Included, age not specified	Included, age not specified	Seasonal, influenza A	ELISA	Directigen Flu A	87.9 (87/99)	97 (59/61)	83 (59/71)	97 (87/89)
Covalciuc, 1999 ¹⁹³	USA	From 2 months	To 76 years	Seasonal	Culture on RMK cells	BioStar FLU OIA (Biostar, Boulder CO, USA)	80.1 (121/151)	73 (185/253)		
Diederer, 2010 ¹⁹⁵	Netherlands	From birth	To 81 years	Pandemic	PCR	NOW Flu A+B	47 (18/38)	95 (92/97)		
Hamilton, 2002 ¹⁹²	USA	12 days to 19 years	None	Seasonal	Culture on RMK cells	Directigen Flu A+B	75 (49/65)	93 (218/235)	74 (49/66)	93 (218/234)
		12 days to 19 years	None	Seasonal	Culture on RMK cells	Zstat Flu-II (Zyme Tx, Oklahoma City, OK, USA)	88 (57/65)	92 (216/235)	75 (57/76)	96 (216/224)
continued										

TABLE 26 Studies included in the meta-analysis of POCT for influenza using PCR as the gold standard (continued)

Author	Location	Children, age	Adults, age	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Hara, 2008 ¹⁸⁷	Japan	4 months to 19 years	None	Seasonal, influenza A	Culture on MDCK cells	Directigen EZ Flu A + B	100 (53/53)	99 (438/441)	100 (53/53)	100% (441/441)
			None	Seasonal, influenza B	Culture on MDCK cells	Directigen EZ Flu A + B	76 (206/270)	99 (221/224)	99 (206/209)	78 (221/285)
			None	Seasonal, influenza A	Culture on MDCK cells	Fujirebio Espline® Influenza A&B-N (Fujirebio Diagnostics, Malvern, PA, USA)	100 (53/53)	100 (441/441)	100% (53/53)	100 (441/441)
Hawkes, 2010 ¹⁸⁴	Canada	4 months to 19 years	None	Seasonal, influenza B	Culture on MDCK cells	Fujirebio Espline Influenza A&B-N	86 (232/270)	100 (224/224)	100 (232/232)	85% (224/262)
		4 months to 19 years	None	Seasonal, influenza A	Culture on MDCK cells	NOW Flu A + B	100 (53/53)	98 (430/441)	100 (531/531)	100 (441/441)
		4 months to 19 years	None	Seasonal, influenza A	Culture on MDCK cells	NOW Flu A + B	78 (211/270)	99 (221/224)	99 (211/214)	79 (221/280)
		1 month to 17 years	None	Pandemic	PCR	NOW Flu A + B	62 (66/107)	99 (70/71)	99 (66/67)	63% (70/111)
		1 month to 17 years	None	Influenza A	DFA	NOW Flu A + B	69 (72/104)	99 (567/575)	90 (72/80)	95 (567/599)
		1 month to 17 years	None	Influenza A	Culture and DFA	NOW Flu A + B	68 (75/111)	99 (590/596)	93 (75/81)	94 (590/626)
		1 month to 17 years	None	Influenza B	DFA	NOW Flu A + B	72 (51/71)	100 (605/608)	93 (75/81)	97 (605/625)
		1 month to 17 years	None	Influenza B	Culture and DFA	NOW Flu A + B	68 (52/77)	100 (628/630)	96 (52/54)	96 (628/653)

Author	Location	Children, age	Adults, age	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Hurt 2007 ⁸⁸	Australia	From 4 days	To 64 years	Influenza A	RETClF	Directigen EZ Flu A+B	69 (34/49)	100 (128/128)	100 (34/34)	90 (128/143)
		From 4 days	To 64 years	Influenza B	RETClF	Directigen EZ Flu A+B	30 (3/10)	100 (167/167)	100 (3/3)	96 (167/174)
		From 4 days	To 64 years	Influenza A	RETClF	Denka Seiken Quick Ex-Flu (Denka Seiken, Tokyo, Japan)	71 (35/49)	100 (128/128)	100 (35/35)	90 (128/142)
		From 4 days	To 64 years	Influenza B	RETClF	Denka Seiken Quick Ex-Flu	30 (3/10)	100 (167/167)	100 (3/3)	96 (167/174)
		From 4 days	To 64 years	Influenza A	RETClF	Fujirebio Espline Influenza A&B-N	67 (33/49)	100 (128/128)	100 (5/5)	89 (128/144)
		From 4 days	To 64 years	Influenza B	RETClF	Fujirebio Espline Influenza A&B-N	30 (3/10)	100 (167/167)	100 (3/3)	96 (167/174)
		From 4 days	To 64 years	Influenza B	RETClF	Influenza Antigen test (Rockeby BioMed, Singapore)	10 (5/49)	100 (128/128)	100 (5/5)	74 (128/172)
		From 4 days	To 64 years	Influenza A	RETClF	NOW Flu A+B	73 (36/49)	99 (127/128)	97 (36/37)	91 (127/140)
		From 4 days	To 64 years	Influenza B	RETClF	NOW Flu A+B	30 (3/10)	100 (167/167)	100 (3/3)	96 (167/174)

continued

TABLE 26 Studies included in the meta-analysis of POCT for influenza using PCR as the gold standard (continued)

Author	Location	Children, age	Adults, age	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Kim, 2010 ²⁰²	Korea	From 2 months	To 78 years	Pandemic	PCR	SD Bioline influenza A/B/A H1N1 pandemic rapid test	70 (182/260)	98 (677/688)	94 (182/193)	90 (677/755)
Lucas, 2011 ¹⁹⁸	USA	From < 5 years	To < 60 years	Influenza A	PCR	QuickVue Influenza A+B	15 (2/13)	99 (1464/1479)	12 (2/17)	99 (1464/1475)
		From < 5 years	To < 60 years	Influenza B	PCR	QuickVue Influenza A+B	31 (4/13)	99 (610/615)	44 (4/9)	98 (610/619)
		From < 5 years	To < 60 years	Pandemic	PCR	QuickVue Influenza A+B	20 (6/30)	99 (1464/1479)	29 (6/21)	98 (1076/1096)
		Included, age not specified	Included, age not specified	Pandemic	PCR	Directigen EZ Flu A+B	57.7 (64/111)	100 (1910/1910)	100 (64/64)	97.5 (1910/1957)
Nougairède, 2010 ¹⁸³	France	Included, age not specified	Included, age not specified	Pandemic	PCR	Directigen EZ Flu A+B	57.7 (64/111)	100 (1910/1910)	100 (64/64)	97.5 (1910/1957)
Quach, 2002 ¹⁹⁹	Canada	Included, age not specified	None	Seasonal	Culture on RMK and MDCK cells	QuickVue Influenza A+B	79.2 (42/53)	82.6 (204/247)	49.4 (42/85)	94.9 (204/215)
Rahman, 2007 ¹⁹⁶	USA	From 6 months	To ≥ 65 years	Seasonal	Culture on RMK cells	Directigen EZ Flu A+B	42 (18/43)	96 (72/75)	86 (18/21)	74 (72/97)
Rahman, 2008 ¹⁵¹	USA	From 6 months	To ≥ 65 years	Seasonal	PCR and culture on RMK cells	NOW Flu A+B	61 (11/18)	100 (55/55)	100 (11/11)	89 (55/62)

Author	Location	Children, age	Adults, age	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Rashid, 2007 ¹⁸²	UK and Saudi Arabia	From 1 year	To 85 years	Seasonal	PCR	QuickVue Influenza A+B	22 (13/58)	99 (492/497)	72 (13/18)	92 (492/537)
Rodriguez, 2002 ¹⁸⁵	USA	From < 3 years	To > 21 years	Seasonal	Culture and DFA	BioStar OIA Flu A/B	93 (54/58)	82 (47/57)	84% (54/64)	92% (47/51)
		From < 3 years	To > 21 years	Seasonal	Culture and DFA	Directigen EZ Flu A+B	95 (55/58)	84 (49/58)	86 (55/64)	94% (49/52)
		From < 3 years	To > 21 years	Seasonal	Culture and DFA	QuickVue Influenza A+B	95 (54/57)	76 (42/55)	81 (54/67)	93 (42/45)
		From < 3 years	To > 21 years	Seasonal	Culture and DFA	Zstat Flu AB	72 (41/57)	83 (48/58)	80 (41/51)	75 (48/64)
Ruest, 2003 ¹⁵²	Canada	From 1 day	To 98 years	Seasonal	Culture on MDCK cells	Directigen Flu A+B	86 (57/66)	94 (115/122)	89% (57/64)	92 (115/124)
		From 1 day	To 98 years	Seasonal	PCR	Directigen Flu A+B	80 (63/79)	98 (121/123)	97 (63/65)	88 (121/137)
		From 1 day	To 98 years	Seasonal	Culture on MDCK cells	QuickVue Influenza A+B	91 (64/70)	86 (105/122)	79 (64/81)	95 (105/111)
		From 1 day	To 98 years	Seasonal	PCR	QuickVue Influenza A+B	86 (72/84)	92 (127/138)	87 (72/83)	90 (114/127)
Sabetta, 2009 ¹⁸⁶	USA	Included, age not specified	Included, age not specified	Pandemic	PCR	XPECT Flu A+B	47 (23/49)	86 (12/14)	92 (23/25)	32 (12/38)

continued

TABLE 26 Studies included in the meta-analysis of POCT for influenza using PCR as the gold standard (continued)

Author	Location	Children, age	Adults, age	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Scansen, 2010 ⁹⁰	USA	≤ 17 years	None	Influenza A	PCR	QuickVue Influenza A+B	Swabs:	Swabs:	Swabs:	Swabs:
							Foam 81 (30/37)	Foam 98 (62/63)	Foam 97 (30/31)	Foam 90 (81/90)
							Flocked 59 (22/37)	Flocked 98 (62/63)	Flocked 96 (22/23)	Flocked 81 (62/77)
		≤ 17 years	None	Influenza B	PCR	QuickVue Influenza A+B	Swabs:	Swabs:	Swabs:	Swabs:
							Foam 53 (10/19)	Foam 100 (81/81)	Foam 100 (10/10)	Foam 90 (81/90)
							Flocked 42 (8/19)	Flocked 100 (81/81)	Flocked 100 (8/8)	Flocked 88 (81/92)
		≤ 17 years	None	Influenza A	Culture: R-Mix and DFA	QuickVue Influenza A+B	Swabs:	Swabs:	Swabs:	Swabs:
							Foam 85 (29/34)	Foam 97 (64/66)	Foam 94 (29/31)	Foam 93 (64/69)
							Flocked 65% (22/34)	Flocked 97 (64/66)	Flocked 92 (22/24)	Flocked 84 (64/76)
		≤ 17 years	None	Influenza B	Culture: R-Mix and DFA	QuickVue Influenza A+B	Swabs:	Swabs:	Swabs:	Swabs:
							Foam 60 (9/15)	Foam 99 (84/85)	Foam 90 (9/10)	Foam 93 (84/90)
							Flocked 53 (8/15)	Flocked 100 (85/85)	Flocked 100 (8/8)	Flocked 92 (85/9)

Author	Location	Children, age	Adults, age	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Shoji, 2009 ¹⁸⁸	Japan	From 1 year	To 88 years	Seasonal	Culture	QuickVue Influenza A+B	87.8 (72/82)	Flu A: 90.2 (322/357)		
Waner, 1991 ¹⁹⁴	USA	From < 2 months	None	Seasonal	Culture on RMK cells	Directigen Flu A	100 (23/23)	91.6 (153/167)	62 (23/37)	100 (153/153)
		From < 2 months	None	Seasonal	IFA	Directigen Flu A	100 (24/24)	95 (152/160)	75 (24/32)	100 (152/152)
Yoo, 2007 ¹⁹⁷	Korea	3 months to 15 years	18.5–81.9 years	Seasonal	Culture (R-mix)	QuickVue Influenza A+B	46.7% (35/75)	94.5% (208/220)	74.5% (35/47)	83.9% (208/248)
		3 months to 15 years	18.5–81.9 years	Influenza A	Culture (R-mix)	SD Bioline Influenza A/B/A(H1N1) Pandemic rapid test	61.9 (26/42)	96.8 (245/253)	76.5 (26/34)	93.9 (245/261)
		3 months to 15 years	18.5–81.9 years	Influenza B	Culture (R-mix)	SD Bioline Influenza A/B/A(H1N1) Pandemic rapid test	54.5 (18/33)	100 (262/262)	100 (18/18)	94.6 (262/277)

DFA, direct fluorescent antibody; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; MDCK, Madin–Darby Canine Kidney; NPS, nasopharyngeal swab; NPW, nasopharyngeal wash; NS, nose swab; RETCIF, rapid enhanced tissue culture immunofluorescence; RMK, Rhesus monkey kidney.

a LLCMK2 cells: a continuous rhesus monkey kidney cell line.

TABLE 27 The QUADAS results for the 27 publications in the meta-analysis of POCTs for influenza (PCR as gold standard)

Methodology checklist	Agoritsas, 2006 ⁹¹	Bellei, 2003 ¹⁸⁹	Booth, 2006 ¹⁹⁰	Cazacu, 2004 ²⁰¹	Cazacu, 2004 ²⁰⁰	Chan, 2002 ¹⁴⁷	Chen, 2010 ¹⁹¹	Chomel, 1992 ¹⁸¹	Covalciuc, 1993 ¹⁹³	Diederer, 2010 ¹⁹⁵	Hamilton, 2002 ¹⁹²	Hara, 2008 ¹⁸⁷	Hawkes, 2010 ¹⁸⁴
Patients representative of who will receive test in practice?	N	N	Y	U	Y	Y	U	U	Y	Y	N	N	N
Selection criteria clearly described?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
Reference standard likely to correctly classify target condition?	Y	N	N	N	N	Y	N	N	N	Y	Y	Y	Y
Short time period between index and standard tests?	U	N	N	N	N	N	N	N	N	U	N	U	U
Verification with reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Samples received same reference standard?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Reference standard independent of index test?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Execution of index test described in detail?	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y
Execution of reference standard described in detail?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Index test results interpreted without knowledge of reference test result?	Y	N	N	Y	Y	Y	U	N	U	U	Y	Y	Y
Reference test results interpreted without knowledge of index test result?	U	Y	Y	U	U	U	U	Y	U	U	U	U	U
Routine clinical data available?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Uninterpretable/intermediate results reported?	N	Y	Y	N	N	Y	N	N	N	N	Y	N	N
Study withdrawals explained?	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y

N, no; U, unclear; Y, yes.

Hurt, 2007 ⁸⁸	Kim, 2010 ²⁰²	Lucas, 2011 ¹⁹⁸	Nougairede, 2010 ¹⁸³	Quach, 2002 ¹⁹⁹	Rahman, 2007 ¹⁹⁶	Rahman, 2008 ¹⁵¹	Rashid, 2007 ¹⁸²	Rodriguez, 2002 ¹⁸⁵	Ruest, 2003 ¹⁵²	Sabetta, 2009 ¹⁸⁶	Scansen, 2010 ⁹⁰	Shoji, 2009 ¹⁸⁸	Waner, 1991 ¹⁹⁴	Yoo, 2007 ¹⁹⁷
Y	Y	Y	Y	N	Y	Y	Y	N	Y	N	N	U	N	Y
Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
N	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	N	N
U	Y	U	Y	U	N	U	N	Y	N	U	Y	U	N	U
Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	U	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	U	Y	Y
Y	Y	U	U	Y	Y	Y	Y	U	U	N	U	U	U	Y
U	U	U	U	Y	U	U	U	U	U	N	U	U	U	U
Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
N	N	N	N	Y	N	N	N	N	Y	N	N	U	Y	N
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N

TABLE 28 The STARD results for the 27 publications in the meta-analysis of POCTs for influenza (PCR as the gold standard)

STARD checklist	Agoritsas, 2006 ⁹¹	Bellei, 2003 ¹⁸⁹	Booth, 2006 ¹⁹⁰	Cazacu, 2004 ²⁰¹	Cazacu, 2004 ²⁰⁰	Chan, 2002 ¹⁴⁷	Chen, 2010 ¹⁹¹	Chomel, 1992 ¹⁸¹	Covalciuc, 1993 ¹⁹³	Diederer, 2010 ¹⁹⁵	Hamilton, 2002 ¹⁹²	Hara, 2008 ¹⁸⁷	Hawkes, 2010 ¹⁸⁴
Identify the article as diagnostic accuracy study	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Stated study aims	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Specified inclusion and exclusion criteria?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
What was recruitment based upon?	PS	^a	PS	PS	PS	PS	PS	PS	PS	PS	PS	PS	PS
Consecutive series of participants?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
If not, specify further selection process?							U						
Prospective or Retrospective study?	P	R	P	P	P	P	P	P	P	P	P	P	P
Rationale for reference standard?	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y
Technical specification of materials and methods?	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Definition of, and rationale for, units, cut-offs and/or categories of results?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Number, training and expertise of the technicians?	Y	N	N	Y	N	Y	N	N	N	N	N	N	N
Blinding of results?	N	N	Y	N	N	Y	N	N	N	N	N	N	N
Specify data analysis methods?	Y	N	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y
Specify methods for calculating reproducibility, if done?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Include beginning and end dates of recruitment?	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y

Hurt, 2007 ⁸⁸	Kim, 2010 ²⁰²	Lucas, 2011 ¹⁹⁸	Nougaiere, 2010 ¹⁸³	Quach, 2002 ¹⁹⁹	Rahman, 2007 ¹⁹⁶	Rahman, 2008 ¹⁵¹	Rashid, 2007 ¹⁸²	Rodriguez, 2002 ¹⁸⁵	Ruest, 2003 ¹⁵²	Sabetta, 2009 ¹⁸⁶	Scansen, 2010 ⁹⁰	Shoji, 2009 ¹⁸⁸	Waner, 1991 ¹⁹⁴	Yoo, 2007 ¹⁹⁷
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
PS	PS	PS	PS	PS	PS	PS	PS	PS	PS	PS	PS	PS	PS	PS
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
P	P	P	P	P	P	P	P	P	P	P	P	P	P	P
Y	Y	Y	N	Y	Y	Y	N	N	Y	Y	Y	NA	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
N	N	N	Y	N	Y	Y	N	Y	N	Y	N	NA	N	Y
N	N	N	N	Y	N	N	N	Y	Y	N	N	NA	N	N
N	Y	Y	N	N	Y	Y	N	N	Y	N	Y	NA	N	Y
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y

TABLE 28 The STARD results for the 27 publications in the meta-analysis of POCTs for influenza (PCR as the gold standard) (*continued*)

STARD checklist	Agoritsas, 2006 ⁹¹	Bellei, 2003 ¹⁸⁹	Booth, 2006 ¹⁹⁰	Cazacu, 2004 ²⁰¹	Cazacu, 2004 ²⁰⁰	Chan, 2002 ¹⁴⁷	Chen, 2010 ¹⁹¹	Chomel, 1992 ¹⁸¹	Covalciuc, 1993 ¹⁹³	Diederer, 2010 ¹⁹⁵	Hamilton, 2002 ¹⁹²	Hara, 2008 ¹⁸⁷	Hawkes, 2010 ¹⁸⁴
Include participant clinical and demographic data?	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y
Include no. of participants satisfying the inclusion criteria?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Stated time interval between index and reference test?	N	N	Y	Y	Y	Y	N	Y	N	N	Y	N	N
Included distribution of disease severity?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cross-tabulation of index test results with reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Indicated any adverse events from the test procedure?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Provided estimates of diagnostic accuracy and statistical uncertainty (e.g. 95% CI)?	Y	N	N	Y	N	N	N	N	N	Y	N	N	Y
Specify how indeterminate results and outliers were handled?	N	Y	Y	N	N	Y	N	Y	N	N	Y	N	N
Provided estimates of variability of diagnostic accuracy among subgroups, readers or centres?	Y	NA	Y	N	Y	NA	Y	Y	Y	Y	Y	Y	Y
Provided estimates of test reproducibility, if done?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Discuss clinical applicability of findings?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

N, no; NA, not applicable; P, prospective; PS, presenting symptoms; R, retrospective; U, unclear; Y, yes.
 a Recruitment based upon having received a reference standard test.

Hurt, 2007 ⁸⁸	Kim, 2010 ²⁰²	Lucas, 2011 ¹⁹⁸	Nougairede, 2010 ¹⁸³	Quach, 2002 ¹⁹⁹	Rahman, 2007 ¹⁹⁶	Rahman, 2008 ¹⁵¹	Rashid, 2007 ¹⁸²	Rodriguez, 2002 ¹⁸⁵	Ruest, 2003 ¹⁵²	Sabetta, 2009 ¹⁸⁶	Scansen, 2010 ⁹⁰	Shoji, 2009 ¹⁸⁸	Waner, 1991 ¹⁹⁴	Yoo, 2007 ¹⁹⁷
Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	NA	Y	Y
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
N	Y	N	Y	N	Y	N	N	Y	Y	N	N	NA	Y	N
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	N	N	NA	NA	NA
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
N	Y	Y	N	Y	Y	Y	N	N	Y	N	Y	NA	N	N
N	N	N	N	Y	N	N	N	N	Y	N	N	NA	Y	N
Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y

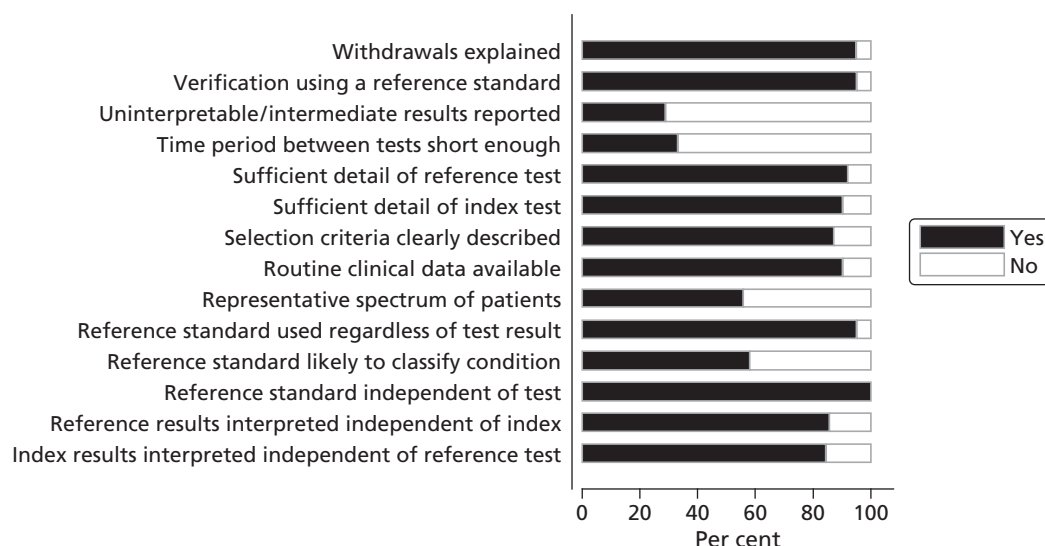


FIGURE 8 Percentage of studies satisfying QUADAS items.

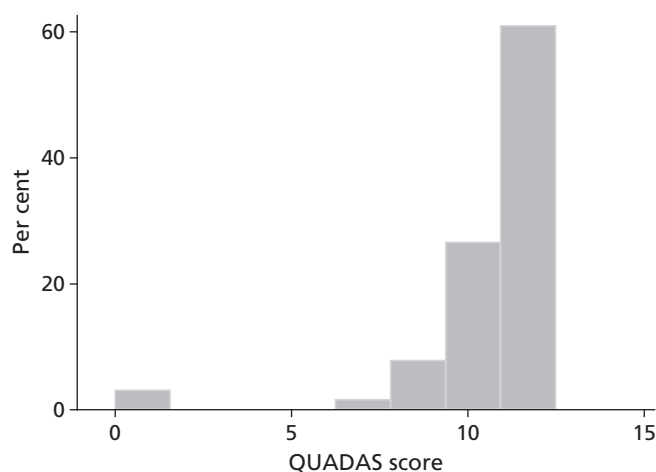


FIGURE 9 Distribution of QUADAS Score.

Of the 143 studies in *Appendix 6* for which data could be extracted, 64 (45%) reported the full 2×2 table, and using a bivariate mixed-effects meta-analysis model produced an overall estimate of sensitivity of 0.73 (95% CI 0.66 to 0.80) and of specificity of 0.99 (95% CI 0.98 to 0.99). However, there was a high level of heterogeneity between the studies for both outcomes (sensitivity: $Q = 777.5$, $p < 0.01$, $I^2 = 91.9\%$, 95% CI 90.5% to 93.3%; specificity: $Q = 2128.9$, $p < 0.01$, $I^2 = 97.0\%$, 95% CI 96.7% to 97.4%), as can be seen from the Forest plots in *Figure 10*. *Figure 11* displays the summary receiver operating characteristic (SROC) curve derived using the estimated overall pooled sensitivity and specificity. Superimposed on the SROC curve are the results from 3WS using (1) PCR (sensitivity 24.4%, specificity 99.7%) and (2) viral culture (sensitivity 33.3%, specificity 98.6%) as the 'Gold standard' tests. As can be seen from *Figure 11*, the 3WS results, although being within the associated prediction region, are nevertheless considerably lower, in terms of sensitivity, than those estimates from other studies in the meta-analysis.

To explore the between-study heterogeneity observed, a number of subgroup-specific models were estimated using study-level covariates (age of participants, 'gold standard' used, geographical region in which study was conducted, type of influenza tested for, type of POCT, and study quality assessed using the QUADAS tool). Owing to the relatively small numbers of studies in some specific subgroups (i.e. < 4) it was not always possible to estimate the associated effects. It can be seen from *Table 29* that the pooled

(a)

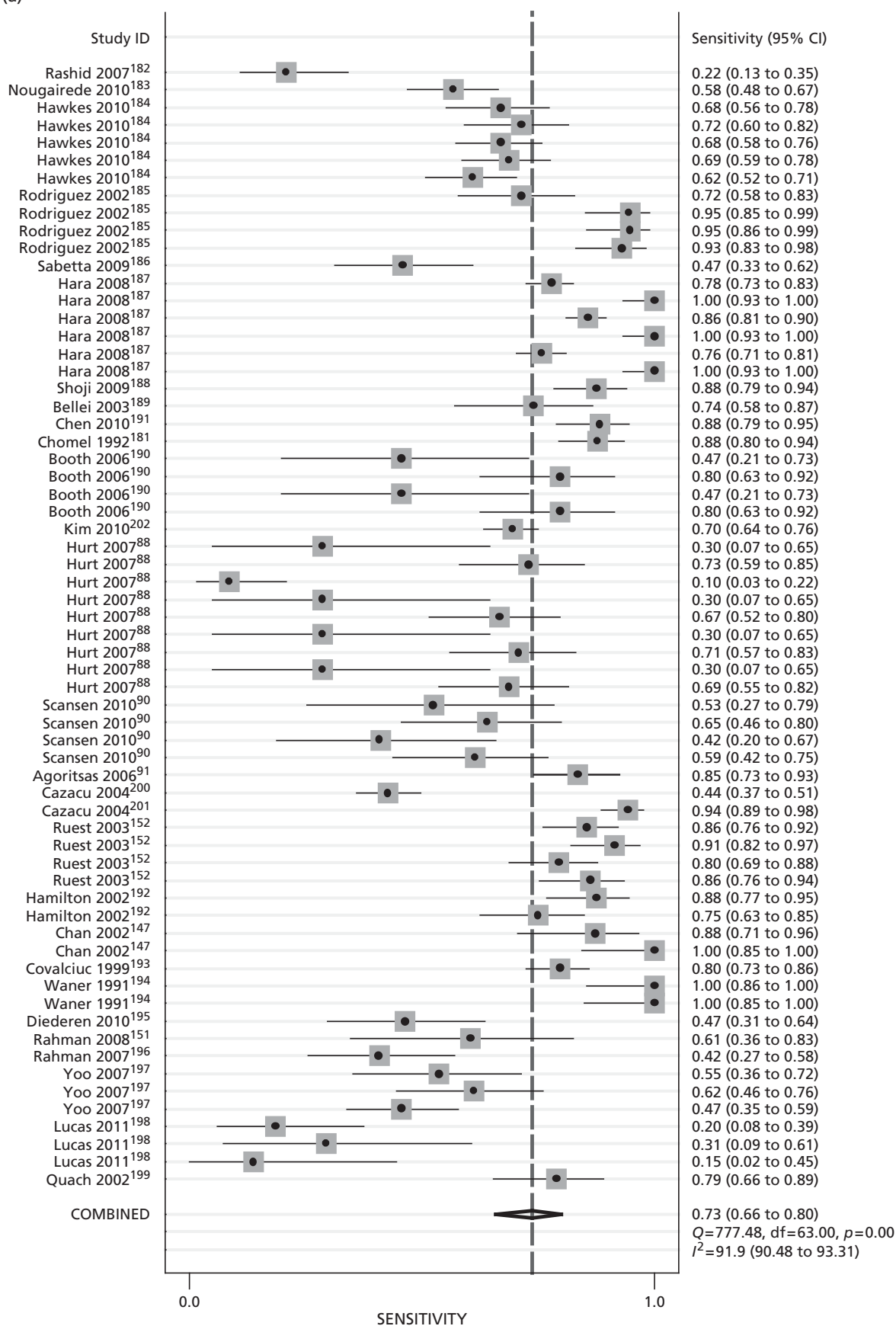


FIGURE 10 Forest plot of sensitivity and specificity for 64 studies reporting full 2×2 data table. (continued)

(b)

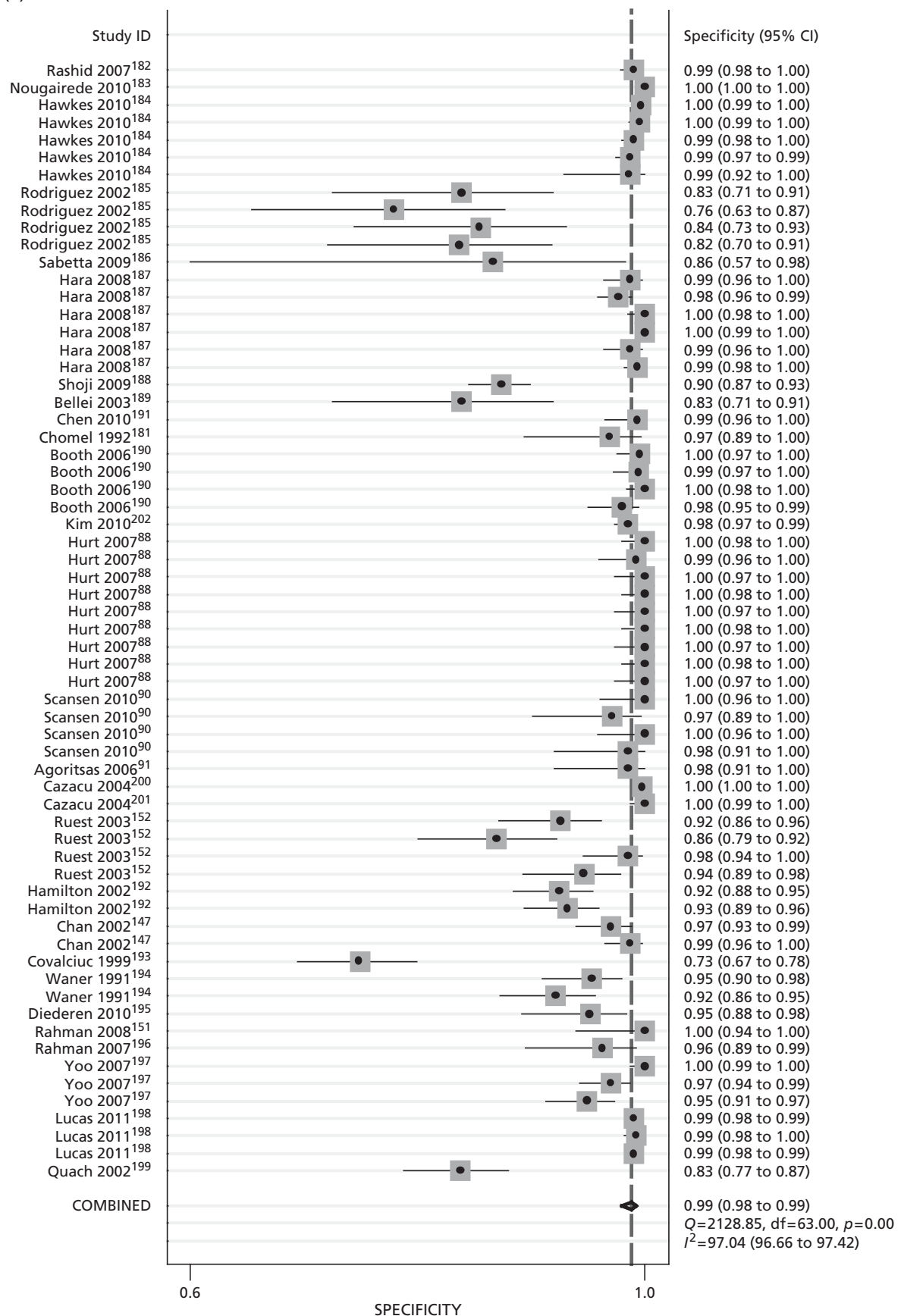


FIGURE 10 Forest plot of sensitivity and specificity for 64 studies reporting full 2 × 2 data table.

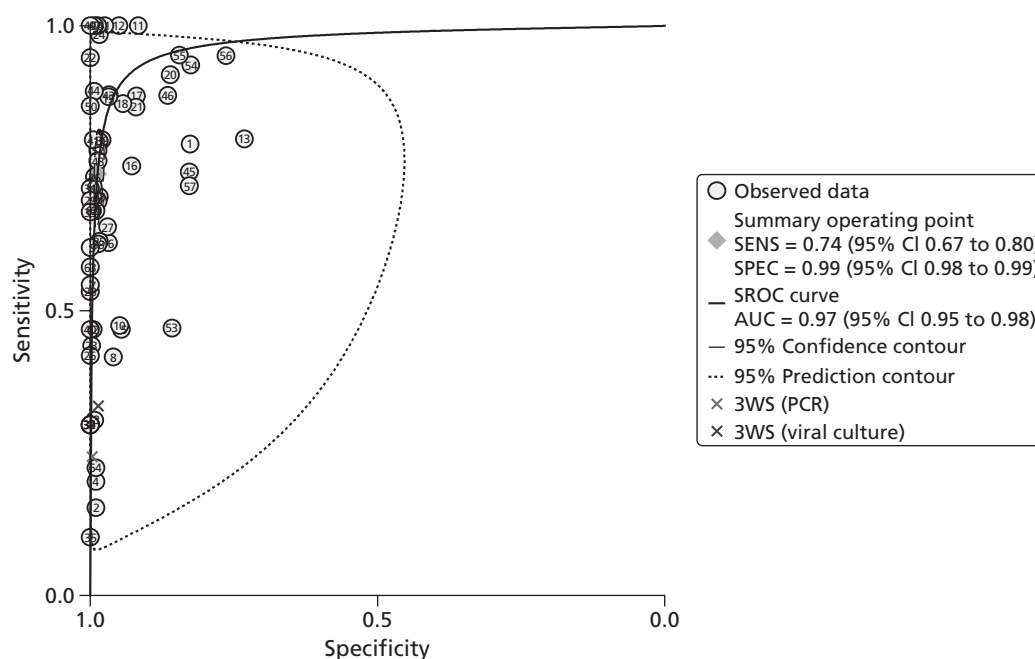


FIGURE 11 Summary receiver operating characteristic estimated using bivariate mixed-effects meta-analysis model with 3WS results using PCR (a) and viral culture (b) as 'gold standard' superimposed.

TABLE 29 Subgroup effects estimated using bivariate mixed-effects meta-analysis model

Covariate/level	No. of studies	Measure	Estimate	95% CI
Age				
Children and adolescents	21	Sensitivity	0.86	0.75 to 0.93
		Specificity	0.99	0.97 to 0.99
Mixed	43	Sensitivity	0.67	0.58 to 0.75
		Specificity	0.99	0.98 to 0.99
'Gold standard'				
PCR	13	Sensitivity	0.51	0.38 to 0.64
		Specificity	0.99	0.97 to 0.99
Culture	24	Sensitivity	0.86	0.77 to 0.92
		Specificity	0.98	0.95 to 0.99
Culture and IF	13	Sensitivity	0.78	0.66 to 0.87
		Specificity	0.98	0.94 to 0.99
IF	11	Sensitivity	0.51	0.35 to 0.66
		Specificity	1.00	0.97 to 1.00

continued

TABLE 29 Subgroup effects estimated using bivariate mixed-effects meta-analysis model (*continued*)

Covariate/level	No. of studies	Measure	Estimate	95% CI
Region				
North America	32	Sensitivity	0.76	0.66 to 0.83
		Specificity	0.97	0.95 to 0.98
Australasia	13	Sensitivity	0.53	0.38 to 0.67
		Specificity	1.00	0.99 to 1.00
Asia	14	Sensitivity	0.89	0.75 to 0.96
		Specificity	0.99	0.97 to 0.99
Europe	4	Sensitivity	0.56	0.29 to 0.80
		Specificity	0.99	0.93 to 1.00
Type of influenza				
Influenza A	19	Sensitivity	0.81	0.64 to 0.91
		Specificity	0.99	0.98 to 0.99
Influenza B	16	Sensitivity	0.59	0.47 to 0.70
		Specificity	1.00	0.99 to 1.00
Seasonal	23	Sensitivity	0.84	0.74 to 0.90
		Specificity	0.94	0.90 to 0.97
Pandemic (swine origin)	6	Sensitivity	0.52	0.39 to 0.65
		Specificity	0.99	0.94 to 1.00
Testing kit				
Directigen EZ	16	Sensitivity	0.85	0.71 to 0.93
		Specificity	0.99	0.97 to 0.99
BinaxNOW	13	Sensitivity	0.69	0.58 to 0.79
		Specificity	0.99	0.99 to 0.99
Quidel QuickVue	16	Sensitivity	0.66	0.48 to 0.80
		Specificity	0.96	0.93 to 0.98
Study quality ^a				
‘Low’ (QUADAS ≤ 10)	24	Sensitivity	0.85	0.72 to 0.93
		Specificity	0.97	0.94 to 0.98
‘High’ (QUADAS > 10)	40	Sensitivity	0.67	0.59 to 0.75
		Specificity	0.99	0.99 to 1.00

^a Assessed using the QUADAS tool and using a cut-point of 10.

estimates of specificity across subgroups were consistently high with relatively little subgroup-to-subgroup variation; however, for sensitivity there was variation in the pooled estimates across subgroups with a mixed age distribution, use of PCR as a 'gold standard', and testing for influenza of swine origin all yielding lower estimates of sensitivity. There was also some variation in sensitivity depending on the geographical region in which the study was conducted, with Europe and Australasia yielding lower estimates; this was also seen for study quality, with 'higher'-quality studies producing a lower pooled sensitivity than those of 'lower' quality.

In terms of the subgroup specific estimates of pooled sensitivity, even the lower estimates were still higher than those found in 3WS – using PCR as the 'gold standard', a Quidel POCT produced a sensitivity of 24.4%, whereas using viral culture as the 'gold standard' it was 33.3%. Although the distribution of studies across the various study-level covariates (and their levels) makes it difficult to obtain an estimate of sensitivity that closely matches the characteristics of 3WS – it is possible to estimate a pooled effect for those studies ($n = 5$), which (1) included both adults and children (as opposed to only children) and (2) compared Quidel with PCR. These produced an overall pooled sensitivity of 34% (95% CI 14% to 62%) and specificity of 99% (95% CI 97% to 100%), which are much more similar to those obtained in 3WS.

As only 64 out of 143 studies (45%) reported sufficient data to permit a formal bivariate analysis to be undertaken, a sensitivity analysis only pooling sensitivities for the 64 and 79 studies separately was undertaken to assess whether there was in fact a selection effect. The 79 studies produced a pooled sensitivity of 60.2% (59.0% to 61.0%), whereas the 64 studies produced an estimate of 69.1% (67.5% to 70.6%) – the latter was slightly lower than that produced by the bivariate model (73%, 95% CI 66% to 80%). A formal test of heterogeneity between the two sets of studies was highly significant ($p < 0.001$) indicating that had the 79 studies reported both sensitivity and specificity the corresponding bivariate model would have produced an estimate of sensitivity lower than that observed.

Discussion

This systematic review concurs with other reviews of diagnostic studies in different disease areas in that there was considerable heterogeneity – both in terms of reporting of data and clinical and methodological characteristics, thus making formal synthesis of study results using appropriate bivariate meta-analysis methods challenging.²⁰³

Overall, the bivariate meta-analysis produced estimates of sensitivity that were considerably higher than that observed in 3WS. However, exploration of the considerable between-study heterogeneity using subgroup analyses showed that for some subgroup combinations the pooled estimate of sensitivity was considerably lower than that estimated for others. In fact, the subgroup combination most closely resembling the characteristics of 3WS (comparing Quidel POCT with PCR in a mixed-age population) produced an estimate of sensitivity in close agreement with 3WS.

Further sensitivity analysis comparing those studies that reported fully data for sensitivity and specificity with those that only reported sensitivity indicated the possibility of a selection effect that would further reduce the *true* estimate of sensitivity of POCT for testing for influenza.

Published evidence on the usefulness of diagnostic tests has been summarised in four systematic reviews including this review. Uyeki²⁰⁴ reviewed published evidence on clinically useful diagnostic tests and antiviral treatment for influenza virus infections in children, which were published in the English language from 1966 to September 2002. The topics covered were wide-ranging, including clinical diagnosis, IF and rapid influenza diagnostic tests, as well as antiviral treatment. Altogether 28 studies of rapid influenza tests were identified. This was a descriptive study with no formal assessment of study quality or meta-analysis of the findings, rather the author presented median sensitivity values for the tests in comparison with cell culture as the gold standard. Overall, the POCTs had sensitivities and specificities of 40.4% to 100% and

65.2% to 100%, respectively. The median sensitivity of the Zstat Flu test (Zyme Tx, Oklahoma City, OK, USA) was 68.8% (range 28.1–96%) and median specificity was 83% (range 62.7–92.4%). The median sensitivity of the Directigen Flu A test was 87.2% (range 39–100%), and the median specificity was 98.1% (range 84–100%). The median sensitivity of the FLU OIA test (Biostar, Boulder, CO, USA) was 71.8% (range 36.7–93%), and the median specificity was 82% (range 65.2–95.7%). In five studies of the QuickVue Influenza Test the median sensitivity was 79.2% (range 74–95%) and the median specificity was 91.9% (range 76–98%). The studies were evidently heterogeneous in terms of age and the author concluded that rapid influenza diagnostic tests were ‘moderately to reasonably’ accurate for detecting influenza virus infections, and that false-negative results appeared more common than false-positive results.

Petrozzino *et al.*²⁰⁵ were supported by the Quidel Corporation, the manufacturer of the QuickVue Influenza A + B test, to undertake a systematic review and meta-analysis of studies reporting sensitivity, specificity, and effects of ‘rapid flu tests’ (RFTs) and clinical diagnosis on decision-making for patients with ILI. Search results were limited to literature published in English between 1984 and 2009. Results from included studies were stratified according to age categories with an approximate cut-off of 15 years of age. It was not possible to stratify results for older people aged > 60 years. No RCTs were found directly comparing RFTs against the clinical diagnostic skills of clinicians. All included studies used an independent gold standard test for confirmatory influenza diagnosis. Separately, these investigators evaluated the clinical diagnosis of influenza.

Among older subjects aged ≥ 15 years, data on the QuickVue test from five studies showed that this POCT had a sensitivity in a fixed-effects model of 57% (52–62%) and specificity of 96% (95–97%). In a random-effects model, the POCT had a sensitivity of 61% (36–81%) and specificity of 96% (94–98%). Data from 11 studies showed the sensitivity of clinical diagnosis in a fixed-effects model to be 64% (51–75%) and much lower specificity of 65% (63–66%). In the random-effects model, clinical diagnosis had a sensitivity of 64% (51–75%) and specificity of 68% (57–77%). Thus clinicians were as able to diagnose influenza clinically as POC testing but wrongly identified other individuals as having influenza, which could be problematic when isolation facilities for adults are scarce, although it is conceivable that these patients also posed an infection risk to others.

Among younger subjects aged < 15 years, data on the QuickVue test from 14 studies showed that this POCT had a sensitivity in a fixed-effects model of 63% (60–67%) and specificity of 94% (92–95%). In a random-effects model, the POCT had a sensitivity of 76% (65–85%) and specificity of 95% (92–98%). Data from five studies showed the sensitivity of clinical diagnosis in a fixed-effects model to be 70% (66–74%), and the specificity of 61% (59–63%) was again lower than that of the POCT. In the random-effects model, clinical diagnosis had a sensitivity of 69% (44–87%) and specificity of 63% (31–87%). For all age groups combined, the sensitivities of the POCT and clinical diagnosis in both the fixed and random-effects models were similar, with sensitivities of 61% (59–64%) and 62% (60–63%) respectively in the fixed-effects model, and 72% (62–81%) and 65% (55–74%) in the random-effects model. The respective specificities were 94% (93–95%) and 63% (62–64%) in the fixed model, and 96% (93–97%) and 67% (57–76%) in the random-effects model.

These authors examined 10 studies reporting outcomes relating to patient management associated with the use of POCT for influenza. This overview led the authors to conclude that in various clinical settings and across a wide age range, RFT use in patients presenting with ILI leads to reduced diagnostic testing, antibiotic use and emergency department length of stay, although increases antiviral prescribing.

Babin *et al.*²⁰⁶ did a review and meta-analysis of published literature on the 2009 novel swine flu outbreak to assess the potential utility of POCTs for initiating infection treatment and control for this pathogen. Although these POCTs were not developed for swine-origin virus, their speed and ease of use (EoU) made them attractive for clinical and public health use. These authors identified 14 reports on sensitivity and/or specificity of seven different POC influenza tests for diagnosis of 2009 pandemic H1N1 virus on clinical specimens. The pooled sensitivity and specificity for all studies were 67.5% (95% CI 66.2% to 68.9%) and

80.7% (95% CI 80.0% to 81.4%). Pooled data were provided for three POCTs from different manufacturers: BinaxNOW Influenza A&B, with a pooled sensitivity of 31.4% (95% CI 26.3% to 36.7%) (no specificity data); Directigen EZ Flu A + B, with a pooled sensitivity of 52.8% (95% CI 45.9% to 59.6%) (no specificity data); and QuickVue A + B, with a pooled sensitivity of 73.6% (95% CI 72.1% to 75.0%), and specificity of 76.6% (95% CI 75.5% to 77.5%). In conclusion, the authors considered that the relatively poor performance of the POCTs affirmed recommendations by the US Centers for Disease Control and Prevention (CDCP) that caution should be applied in the interpretation of negative POCTs.

Our systematic review and meta-analysis confirms and extends the observations in the above reports. In our study, specificity across subgroups was consistently high but sensitivity was higher in studies involving children and adolescents than in 'mixed' populations (i.e. mixed age groups). We may speculate that this might reflect decreased virus shedding in adults than in young children (although virus shedding may be high in very elderly hospitalised patients)¹²⁵ and the effects of vaccination and past infection. We also found that the test sensitivity was a function of the nature of the gold standard used, with PCR setting a higher target than virus culture. The caution issued by the CDCP regarding the sensitivity of POCTs for the detection of the 2009 pandemic 'swine-origin' H1N1 virus was affirmed in our analyses, which also showed better performance of POCTs in the detection of seasonal influenza type A virus than type B virus.

Chapter 7 Ease and speed of use of point-of-care, molecular and traditional test methods for the diagnosis of respiratory infections

Background

The benefits of rapid diagnosis are increasingly appreciated in diverse health-care settings. Besides direct clinical benefits, political and economic imperatives, including the UK NHS 4-hour patient assessment rule in A&E departments, are likely to accelerate demand for rapid diagnostic tests.^{207–209} However, successful adoption of new technology in the health-care sector, and especially in hospitals, depends on its acceptance by end users.^{210,211} The latter is a function of the ease of the required associated procedures, extent of demand on staff time, perceived efficiency, quality and added clinical value of speedy results and the actual reduction in time to a result for the new rapid diagnostic test compared with the method in use. Although there have been various studies comparing one or more of these features of diagnostics tests,^{212–214} to the best of our knowledge only one formal rating system has been described to score the ease and speed of use of diagnostic methods.²¹⁵

In the USA, the Secretary of Health and Human Services has delegated to the Food and Drug Administration (FDA) the authority to determine whether particular tests are ‘simple’ and have ‘an insignificant risk of an erroneous result’. The US Clinical Laboratory Improvement Amendments (CLIA) categorisation criteria grade specific laboratory test system, assay and examination 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 testing materials; (6) test system troubleshooting and equipment maintenance; and (7) interpretation and judgement.²¹⁵ A score of ‘1’ indicates the lowest level of complexity, and the score of ‘3’ indicates the highest level. These scores are totalled to derive a measure of complexity. Here we evaluate the ease and speed of use of selected POCTs, PCR-based rapid molecular assays and traditional culture for the aetiological diagnosis of respiratory infections. As outlined below, we modified the scoring system proposed by CLIA and included additional criteria, specifically: (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 (TtR) of results.

Specimen handling and diagnostic tests

Specimens were collected and transported as described in *Chapter 2*. We evaluated point of care, molecular, and traditional test methods for the diagnosis of respiratory infections as described in *Chapter 2*. These included the following.

POCTs:

- QuickVUE Influenza A&B (Quidel, USA).
- BinaxNOW *S. pneumoniae* test.

Molecular diagnostic tests:

- Semi-nested multiplex conventional PCR for influenza A subtypes H1 and H3, influenza B, and RSV A and B (as used during Year 1).
- HPA Cambridge, one-step, quadriplex, real-time RT-PCR for the detection of influenza (as used during Year 2).
- HPA Colindale, one-step, multiplex, real-time RT-PCR for the detection of influenza (as used during Year 3).
- RSV and hMPV, one-step (Year 2) and two-step (Year 3), multiplex real-time RT-PCR.

Conventional diagnostic tests:

- Virus isolation and culture on continuous cell lines.
- Blood culture.
- Sputum culture.
- Sputum Gram stain and microscopy.

Ease-of-use scores

Each specific test procedure was graded by assigning EoU scores of '1', '2' or '3' for each of the 11 criteria listed below. Like the CLIA system, a low score reflects the lowest levels of complexity of test procedures that can be carried out quickly by personnel with minimal training. A high score reflects high levels of complexity. A score of '2' was assigned to scoring criteria when the characteristics for a particular test are intermediate between those listed for scores of '1' and '3'.

Scoring criteria

1. Test site:
Score 1 Is a POCT.
Score 3 A facility with purpose-built accommodation, ventilation systems and dedicated space is essential.
2. Equipment:
Score 1 (A) No special equipment is required and (B) the test is readily transferred between hospital facilities.
Score 3 Specialised equipment is essential and non-portable.
3. Materials and reagents:
Score 1 (A) Materials and reagents are stable and (B) they are pre-packaged, and/or pre-measured, and require no special handling steps, or storage conditions.
Score 3 Materials and reagents are labile requiring special storage conditions or require special handling steps to ensure reliability and (B) materials and reagents preparation requires manual steps, for example volumetric measurement.
4. Operational steps:
Score 1 (A) Operational steps are either automatically operated (e.g. pipetting, temperature control, mixing of reagents or timing of steps) or (B) are easily controlled.
Score 3 Operational steps require close monitoring and control, and may require special preparation (e.g. for manual nucleic acid extraction), precise temperature control or timing of procedural steps, accurate pipetting or extensive calculations.

5. Training, experience, and knowledge:
Score 1 (A) Minimal scientific and technical knowledge and experience are required to perform the test and (B) knowledge to perform the test may be obtained through on-the-job instruction [i.e. in the UK the test could be done readily by someone at Agenda for Change (AFC) Band 4 or less].
Score 3 Specialised scientific and technical knowledge is essential to perform the testing, and (B) substantial experience is required (i.e. in the UK the test requires skills and knowledge commensurate with someone at AFC Band 7 or higher).
6. Calibration and quality control:
Score 1 (A) Calibration is either automatic or not required or (B) quality control materials are stable and are included in the test, or are readily available.
Score 3 (A) Calibration materials, if available, may be labile, or (B) quality control materials, if available, may be labile, or not available, or (C) technical expertise is required for calibration.
7. Interpretation and judgement:
Score 1 (A) Minimal interpretation and judgement are required to perform the test; and (B) problems require limited interpretation, judgement, and decision-making.
Score 3 (A) Extensive interpretation and judgement are required to perform the test; and (B) resolution of problems requires extensive interpretation, judgement and decision-making.
8. Test system troubleshooting and equipment maintenance:
Score 1 (A) Test system troubleshooting is automatic or self-correcting, or clearly described or requires minimal judgement and (B) equipment maintenance is seldom needed, or can be easily performed.
Score 3 (A) Test system troubleshooting is not automatic or self-correcting and requires decision-making and intervention to resolve most problems and (B) equipment maintenance requires special knowledge, skills, and abilities.
9. TtR of results (included as possible indicator of EoU):
Score 1 Results are reported within 4 hours of collection of almost all specimens.
Score 3 The median TtR of results exceeds the median duration of hospitalisation/time to death.
10. Health and safety:
Score 1 The test is completed using low levels of personal protection, i.e. gloves, and can be conducted outside a laboratory setting.
Score 3 One or more operational steps in the testing process require Biosafety level (BSL) category 3 or higher.
11. Storage and disposal of waste test materials and reagents:
Score 1 Waste materials and reagents from the testing process are stored and disposed using medium duty 'Clinical Waste' plastic bags and Sharps Containers (to BS 7320/UN 3291), or a sluice.
Score 3 Waste materials or reagents from the testing process include hazardous materials (including highly infectious waste, chemical waste, waste with a high content of heavy metals, genotoxic waste or radioactive waste) that require special attention.

Results

As outlined in *Chapter 3*, 1252 admissions were enrolled into the study, of which 418 were randomised to the 'near-patient' group, 415 to the 'molecular' diagnostic group, and 419 to the 'conventional' diagnostic group. The median duration of symptoms before recruitment was 120 hours (IQR 72–168 hours), and the median time to discharge or death was 72 hours (IQR 21–180 hours).

Speed of use of test methods for the diagnosis of respiratory infections

Quidel QuickVUE Influenza A&B

The interval between specimen collection and the results of the near-patient Quidel QuickVue Influenza A + B test was recorded for 327 of the 418 admissions who were randomised to 'near-patient' test group (Group 1). The median interval from specimen collection to the provision of a positive or negative result for the 327 admissions was 15 minutes (IQR 10–23 minutes) (Figure 12). Altogether, 278 results (85%, 95% CI 80.7% to 88.7%) were reported by 30 minutes.

BinaxNOW *S. pneumoniae* test

Urine samples from 412 out of 418 admissions in the 'near-patient' group (Group 1) were available on recruitment for POC testing using the BinaxNOW *S. pneumoniae* test. The interval between specimen collection and the results of the near patient BinaxNOW *S. pneumoniae* test was recorded for 324 admissions. The median interval from specimen collection to the provision of a positive or negative result was 20 minutes (IQR 15–30 minutes) (Figure 13). Altogether, 270 results (83.3%, 95% CI 78.8% to 87.2%) were reported by 30 minutes.

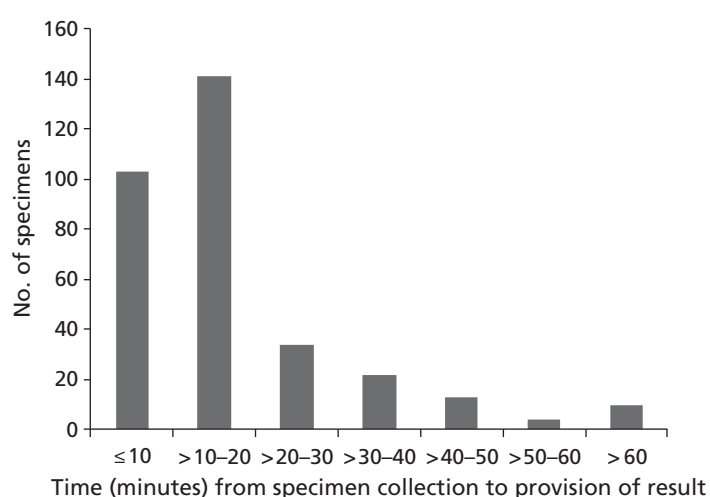


FIGURE 12 Time interval between specimen collection and report (QuickVUE test).

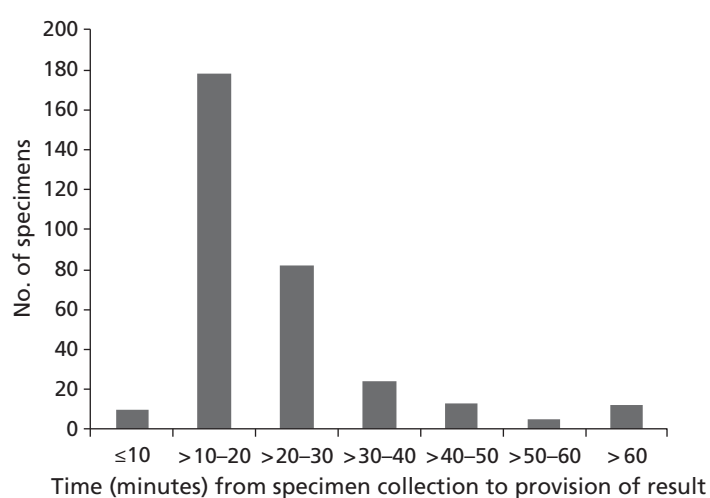


FIGURE 13 Time interval between specimen collection and report (BinaxNOW *S. pneumoniae* test).

Semi-nested multiplex polymerase chain reaction for influenza A subtypes H1 and H3, influenza B and respiratory syncytial virus A and B

The median TtR of results obtained by 'conventional' semi-nested multiplex PCR ($n = 57$, Group 2) was 50.8 hours (IQR 44.3–92.6 hours). *Figure 14* shows a plot of the time interval between specimen collection and the report. Altogether 12 results (21.0%, 95% CI 11.4% to 33.9%) were reported by 36 hours; 18 (31.6%, 95% CI 19.9 to 45.2%) were reported by 48 hours; 36 (63.1%, 95% CI 49.3% to 75.6%) were reported by 72 hours, and 45 (78.9%, 95% CI 66.1% to 88.6%) were reported by 96 hours.

One-step, quadriplex/multiplex, real-time reverse-transcriptase polymerase chain reaction for influenza, and one-step and two-step respiratory syncytial virus and human metapneumovirus multiplex real-time polymerase chain reaction

These real-time PCRs are considered together owing to their similarity. The median TtR of results obtained by 'real-time' RT-PCR ($n = 358$, Group 2) was 29.2 hours (IQR 26–46.9 hours) (*Figure 15*). The difference between the time taken to analyse specimens by the 'conventional' semi-nested multiplex PCR and real-time PCR was 21.9 hours ($p < 0.0001$, Mann–Whitney U -test). *Figure 16* shows the percentage of specimens that are reported as positive or negative by real-time PCR in increments of 12 hours (and at 30 hours) after specimen collection. By 30 hours, results were available for 220 (61.3%, 56.0% to 66.3%) admissions.

Viral culture

Viral culture results were available for 1245 (99.4%, 95% CI 98.8% to 99.8%) of the 1252 nasopharyngeal specimens that were collected from all admissions in Groups 1, 2 and 3. The cumulative percentage of specimens reported by 24-hour time periods for influenza A and B ($n = 21$), other viruses ($n = 49$) and specimens that were culture negative ($n = 1175$) is shown in *Figure 17*. The median time from specimen collection to reporting a positive culture result for admissions with influenza A and B was 629.6 hours (IQR 262.5–846.7), which is approximately nine times greater than the median time to discharge or death (72.08 hours). The median turnaround time of 220.4 hours (IQR 172.1–314.5 hours) for reports of viruses other than influenza was significantly shorter than for the time for influenza ($p < 0.0001$, Kruskal–Wallis test). The time to report the isolation of influenza A or B did not differ from the time to report culture negative results (454.7 hours, IQR 406.0–621.5 hours). Less than 6% (70 of 1245, 5.6%, 95% CI 4.4% to 7.0%) of all virus culture results were reported within 14 days of specimen collection. The results for 17 out of 21 (80%, 95% CI 56.3% to 94.3%) nasopharyngeal specimens that grew influenza virus became available only a median of 459.1 hours (IQR, 290.1–768.2 hours) after death or discharge. For 33 specimens that grew herpes simplex type 1 virus (another virus for which therapy is

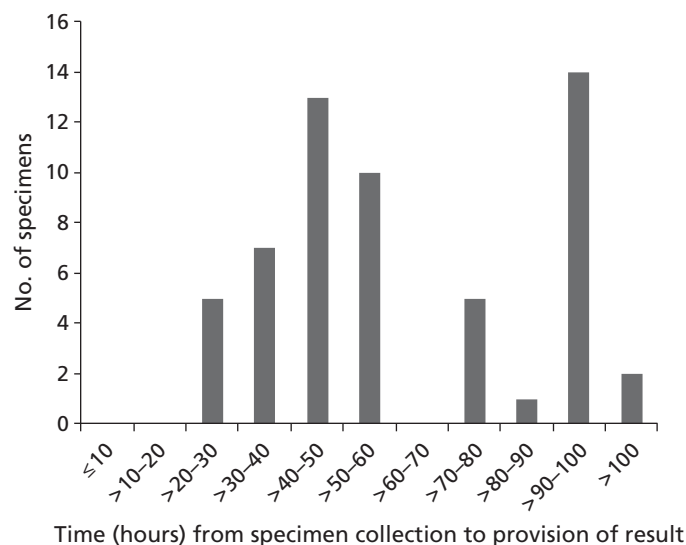


FIGURE 14 Time interval between specimen collection and report (semi-nested multiplex PCR).

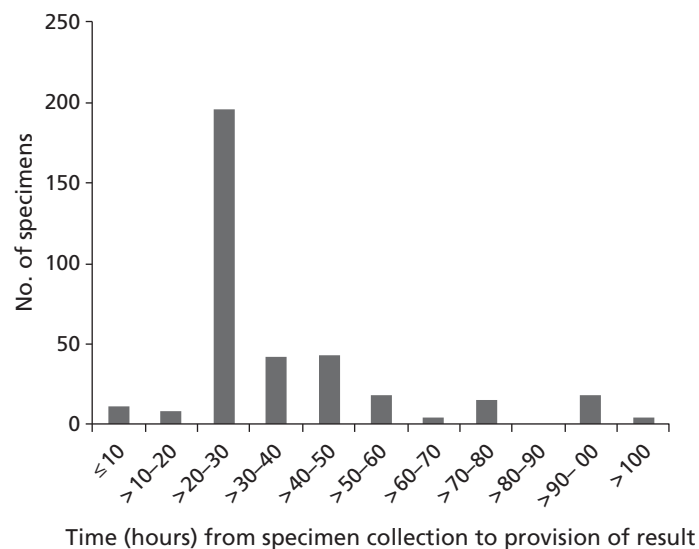


FIGURE 15 Time interval between specimen collection and report (real-time RT-PCR).

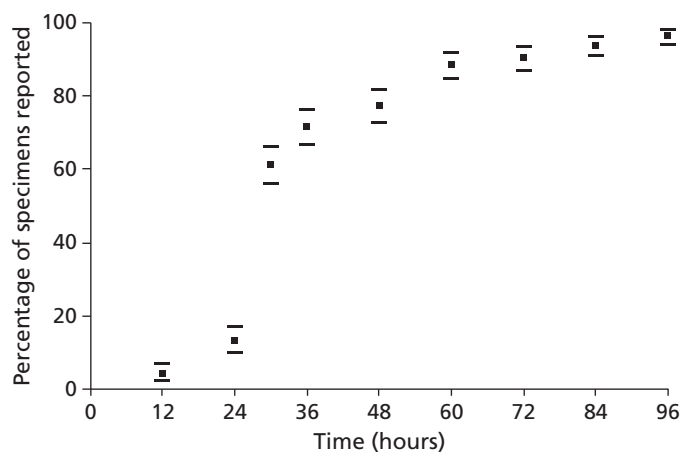


FIGURE 16 Percentage (\pm 95% CIs) of specimens reported as positive or negative by real-time RT-PCR at 12-hour intervals after collection.

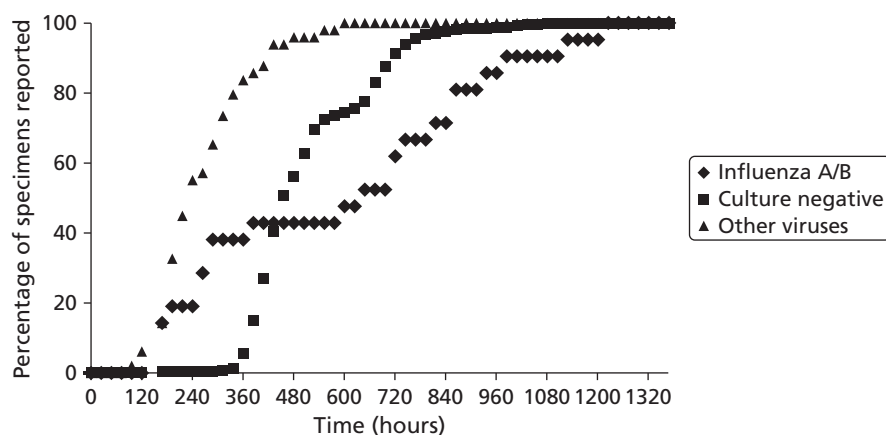


FIGURE 17 Cumulative percentage (\pm 95% CIs) of nasopharyngeal specimens reported as positive or negative by viral culture at 24-hour intervals after collection.

available), the results for 26 (78.8%, 95% CI 61.1% to 91.0%) became available only a median of 298.9 hours (IQR 135.95–552.35 hours) after death or discharge – which is outside the therapeutic window for treatment.

Blood culture

Blood culture results were available for 973 (77.7%, 95% CI 75.3% to 80.0%) patients in Groups 1, 2 and 3. Eighty of the 973 blood cultures grew an organism (including contaminants), and 10 of the 80 grew *S. pneumoniae*. The median TtR *S. pneumoniae* cultures was 84.4 hours (IQR 70.7–137.8 hours), but a provisional report was issued a median of 36.8 hours (IQR 22.7–48.75 hours) after specimen collection. The median TtR bacterial growth for the other 70 specimens was 53.8 hours (IQR 47.7–71.8 hours). The median TtR negative culture results for the remaining 893 specimens was 136.2 hours (IQR 124.4–143.25). Blood culture results for three specimens that grew *S. pneumoniae* were reported a median of 139.2 hours (IQR 27.9–163.4 hours) after death or discharge. The remaining seven pneumococcal culture results were reported a median of 53.2 hours (IQR 30.4–58.1 hours) before discharge. The median interval between specimen collection and reporting all 973 blood culture findings was 130.8 hours (IQR 123.8–142.8 hours). Altogether 619 of the 973 admissions were discharged or died before their blood culture results, i.e. fewer subjects were discharged after the blood culture result was reported than before.

Antimicrobial sensitivity data became available a median of 84.4 hours after specimen collection for the 10 admissions with positive *S. pneumoniae* blood culture results.

Sputum culture

As in previous studies, we found that a substantial number (941) (75.2%, 95% CI 72.7% to 77.5%) of the 1252 admissions with acute cardiopulmonary conditions were unable to produce sputum for analysis. Sputum was collected from 311 (24.8%) admissions. Test results were only available for 296 (23.6%, 95% CI 21.3% to 26.1%) sputa owing to rejection of 15 samples by the laboratory for reasons of poor quality. Of the 296 specimens, sputum culture and Gram stain results were available for 274 specimens and sputum culture results were available for only an additional 22.

A total of 76 of the 296 sputum cultures grew an organism (excluding *Candida* species in five additional specimens); of the 76, 10 grew *S. pneumoniae* after a median interval from specimen collection of 71.4 hours (IQR 69.15–84.0%). The median turnaround time was 60.7 hours (IQR 50.15–71.6 hours) for the remaining 66 culture-positive sputa ($p = 0.0065$, Kruskal–Wallis test) and 50.5 hours (IQR 48.3–66.9 hours) for the 219 of 220 culture-negative sputa with relevant data ($p < 0.0001$). The median interval between specimen collection and reporting sputum culture results for 295 out of 296 admissions was 51.4 hours (IQR 48.75–69.2 hours). Overall, 129 of 294 (43.9%) admissions with relevant data were discharged before their sputum cultures were reported.

The median TtR antimicrobial sensitivity was 133 hours (IQR 123.1–148.1 hours) for 8 of the 10 isolates of *S. pneumoniae*.

Sputum Gram stain

Gram-staining of sputum samples is not routinely performed by the University Hospitals of Leicester NHS Trust, and the median TtR of Gram stain results for 274 sputum samples was 60.7 hours (IQR 50.0–89.4 hours). *Figure 18* shows the cumulative percentage of sputa with Gram stain reports at 12-hour intervals after collection.

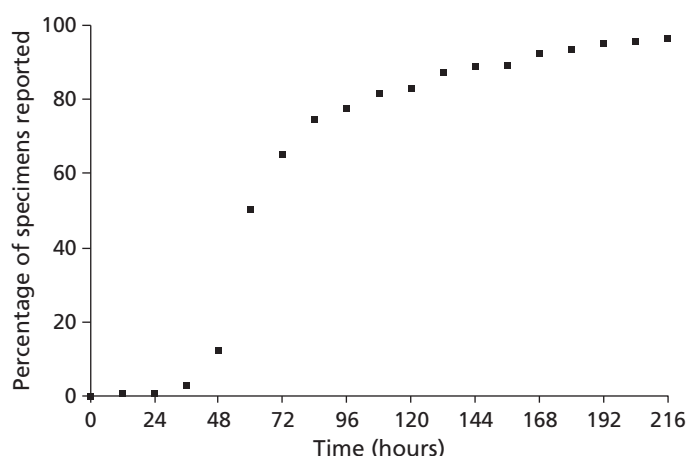


FIGURE 18 Cumulative percentage of 274 sputum samples with Gram stain reports at 12-hour intervals after collection.

Ease of use

Table 30 shows summary EoU scores for the POCT, molecular and conventional diagnostic tests for the diagnosis of respiratory infections. The component scores for each test are shown in Appendix 7. EoU scores of 11 (i.e. component scores of '1' for each of the 11 criteria for categorisation) identified test procedures as being straightforward and undemanding to use, scores of 12–22 identified tests as being of moderate complexity and requirements, and scores of ≥ 23 as being 'complex', requiring particular skills, training and knowledge, specialised equipment and reagents, and/or accommodation, etc.

QuickVUE influenza A&B test

Samples from all 418 patients in the 'near-patient' group (Group 1) were tested using the QuickVUE influenza A&B test at the POC. Unequivocal results were reported for all samples tested. The summary EoU score for the QuickVUE influenza A&B test was 11, indicating that the test was straightforward to use, with component scores of '1' for each of the 11 criteria for categorisation (see Appendix 7, Table 38).

TABLE 30 Summary EoU scores for POCTs, molecular and traditional diagnostic tests for the diagnosis of respiratory infections

Test	Summary EoU score
Point-of-care tests	
QuickVUE Influenza A&B	11
BinaxNOW <i>Streptococcus pneumoniae</i> test	11
Molecular diagnostic tests	
Semi-nested multiplex PCR for influenza A subtypes H1 and H3, influenza B, and RSV A and B	30
One-step, quadruplex/multiplex, real-time RT-PCR for the detection of influenza, RSV and hMPV	25
Two-step multiplex real-time RT-PCR for RSV and hMPV	26
Conventional tests	
Virus culture	26
Blood culture	20
Sputum culture	25
Sputum Gram stain and microscopy	23

BinaxNOW *Streptococcus pneumoniae* test

Urine samples from 412 of the 418 patients in the 'near-patient' group (Group 1) were available on recruitment for POC testing using the BinaxNOW *Streptococcus pneumoniae* test. Unequivocal results were reported for all 412 samples tested. The summary EoU score for the BinaxNOW *Streptococcus pneumoniae* test was '11', indicating that the test was straightforward to use, having component scores of '1' for each of the 11 criteria for categorisation (see *Appendix 7, Table 39*).

Polymerase chain reaction

Samples from 57 (13.7%) of the 415 patients randomised to the 'molecular' diagnostic group (Group 2) were tested using conventional PCR, whereas real-time PCR methods were used to analyse samples from a further 358 patients. All rapid molecular samples were received and tested and unequivocal results were reported for samples from all 415 patients.

Semi-nested multiplex reverse-transcriptase polymerase chain reaction for influenza A subtypes H1 and H3, influenza B, and RSV A and B

The EoU score for the 'conventional' semi-nested multiplex RT-PCR was 30, indicating its complexity and requirements. Inspection of the component scores for the 11 categorisation criteria (see *Appendix 7, Table 40*) reveal scores of '3' for eight categories: 'equipment'; 'operational steps'; 'training, experience and knowledge'; 'calibration and quality control'; 'interpretation and judgement'; 'test system troubleshooting and equipment maintenance'; 'health and safety' and 'storage and disposal of waste test materials and reagents'. Scores of '2' were recorded for the remaining three categories: 'test site', 'materials and reagents' and 'time to reporting (TtR) of results'. None of the categories scored '1'.

One-step, quadriplex/multiplex, real-time reverse-transcriptase polymerase chain reaction for influenza, and one-step and two-step respiratory syncytial virus and human metapneumovirus multiplex real-time polymerase chain reaction

These real-time PCRs are considered together owing to their similarity. The EoU score for real-time PCR was 25 for one-step PCR and 26 for two-step PCR, indicating their complexity and requirements. Component scores for the 11 categorisation criteria are shown in *Appendix 7, Tables 41 and 42*. In contrast with 'conventional' semi-nested multiplex PCR, a score of '1' was allocated to one category – 'materials and reagents'. Besides some minor additional mixing steps, we used real-time PCR kits (Superscript™ III Platinum® One-Step qRT-PCR kit and Platinum® Quantitative PCR Supermix-UDG, Invitrogen, Paisley, UK) that contained ready-to-use reagents, which were optimised and quality-controlled by the manufacturer (Invitrogen). In addition, the test calibration was automatic and all reactions were performed in closed tubes, which reduced the level of risk to the operator and environment. With the one-step method, a score of '3' was allocated to four categories: 'equipment', 'calibration and quality control', 'health and safety' and 'storage and disposal of waste test materials and reagents'. With the two-step method, 'operational steps' also scored '3' (a score of '2' was given with the one-step method) because the reverse transcription step involved precise temperature control and timing. All other steps were scored '2'.

Viral culture

Although swabs in VTM were received from all 1252 patients, viral culture results were available for 1209 (96.6%); contamination of the PLC/PRF5 and MRC-5 tubes prevented the culture of specimens from 41 patients, and two were rejected by the laboratory due to improper storage of samples at room temperature. A further 29 (2.4%) had only partial results due to contamination of PLC/PRF5 or MRC-5 tubes. The EoU score for virus culture was 26, reflecting the complexity and requirements of the method. The component scores for the 11 categorisation criteria (see *Appendix 7, Table 43*) included scores of '3' for five categories: 'equipment', 'materials and reagents', 'operational steps', 'interpretation and judgement' and 'time to reporting (TtR)'. Scores of '2' were recorded for all other categories, except 'Calibration and quality control', which scored '1'.

Blood cultures

Blood cultures from 967 patients were processed using the Bact/ALERT 3D system. The EoU score for blood culture was '20', reflecting moderate complexity and requirements. The component scores for the 11 categorisation criteria (see *Appendix 7, Table 44*) included scores of '3' for one category – 'equipment'. Scores of '2' were given to seven categories: 'test site'; 'training, experience and knowledge'; 'calibration and quality control'; 'interpretation and judgement'; 'time to reporting (TtR) of results'; 'health and safety' and 'storage and disposal of waste test materials and reagents'. The categories 'materials and reagents', 'operational steps' and 'test system troubleshooting and equipment maintenance' all scored '1'.

Sputum culture and Gram stain and microscopy

Sputum culture received an EoU score of 25 (see *Appendix 7, Table 45*), indicating its complexity or requirements. It scored '3' in five categories: 'test site'; 'interpretation and judgement'; 'test system troubleshooting and equipment maintenance'; 'health and safety' and 'storage and waste disposal.' It scored '2' in four categories: 'equipment'; 'materials and reagents'; 'training, experience and knowledge'; and 'time to reporting (TtR) of results'. It scored '1' on 'operational steps' and 'calibration and quality control'.

Sputum Gram staining and microscopy received an EoU score of 23 (see *Appendix 7, Table 46*), primarily reflecting its requirements rather than complexity. It scored '3' in three categories: 'test site'; 'training, experience and knowledge'; and 'health and safety'. It scored '2' in six categories: 'equipment'; 'materials and reagents'; 'operational steps'; 'interpretation and judgement'; 'test system troubleshooting and equipment maintenance'; and 'time to reporting (TtR) of results'. It scored '1' in 'calibration and quality control' and 'storage and disposal of waste test materials and reagents'.

Sensitivity analysis

The EoU score incorporated a score for the time to reporting (TtR) of results as a possible indicator of EoU – the rationale being that tests that provide timely results are easier to use or are less demanding than tests that provide results more slowly. We undertook a sensitivity analysis to examine whether our scoring and ranking of test was unduly influenced by the (TtR) of results or its combination with another measure of EoU and test requirements/complexity. *Table 31* shows total EoU scores and their ranking when (1) all 11 criteria are considered; (2) the total EoU score excluding the component score for the 'time to reporting (TtR) of results'; and (3) the total EoU score excluding the component score for the 'time to reporting (TtR) of results' and each remaining component score in addition. The score relating to the (TtR), when considered alone or with other component scores, has no appreciable effect on ranking of tests in terms of their EoU and/or test requirements (see *Table 31*).

TABLE 31 Sensitivity analysis

Ranking (score)	Easy to use/least demanding				Most difficult to use/most demanding			
	QuickVUE	BinaxNOW	Blood culture	Gram stain	Sputum culture	One-step real-time RT-PCR	Virus culture	Two-step real-time RT-PCR
TS	1=(11)	1=(11)	3 (20)	4 (23)	5=(25)	5=(25)	7=(26)	9 (30)
[TS]–[‘TtR’ score]	1=(10)	1=(10)	3 (18)	4 (21)	5=(23)	5=(23)	5=(23)	9 (28)
[TS]–[‘TtR’ + ‘test site’ scores]	1=(9)	1=(9)	3 (16)	4 (18)	5 (20)	6 (21)	6=(21)	9 (26)
[TS]–[‘TtR’ + ‘equipment’ scores]	1=(9)	1=(9)	3 (15)	4 (19)	7=(21)	5=(20)	5=(20)	9 (25)
[TS]–[‘TtR’ and ‘materials and reagents’ scores]	1=(9)	1=(9)	3 (17)	4 (19)	6=(22)	6=(22)	5 (20)	9 (26)
[TS]–[‘TtR’ + ‘operational steps’ scores]	1=(9)	1=(9)	3 (17)	4 (19)	6=(21)	6=(21)	5 (20)	9 (25)
[TS]–[‘TtR’ + ‘training, experience and knowledge’ scores]	1=(9)	1=(9)	3 (16)	4 (18)	5=(21)	5=(21)	5=(21)	9 (25)
[TS]–[‘TtR’ + ‘calibration and quality control’ scores]	1=(9)	1=(9)	3 (16)	4=(20)	7=(22)	4=(20)	7=(22)	9 (25)
[TS]–[‘TtR’ + ‘interpretation and judgement’ scores]	1=(9)	1=(9)	3 (16)	4 (19)	5=(20)	7 (21)	5=(20)	9 (25)
[TS]–[‘TtR’ + ‘trouble-shooting/maintenance’ scores]	1=(9)	1=(9)	3 (17)	4 (19)	5 (20)	6=(21)	6=(21)	9 (25)
[TS]–[‘TtR’ + ‘health and safety’ scores]	1=(9)	1=(9)	3 (16)	4 (18)	5=(20)	5=(20)	7=(21)	9 (25)
[TS]–[‘TtR’ + ‘storage and disposal of waste’ scores]	1=(9)	1=(9)	3 (16)	4=(20)	4=(20)	4=(20)	7=(21)	9 (25)

TS, total score; TtR, time to reporting.

Sensitivity analysis was carried out initially by deleting the TtR component score from each total score, i.e. for each diagnostic test, and subsequently by deleting each remaining component scores in turn from the total EoU score minus the TtR score.

Discussion

A prime purpose of POCTs and molecular diagnostic tests is to provide information that enables medical and nursing staff to treat patients with optimal medication as soon as possible, and to inform the use of isolation facilities and infection control procedures and equipment. Such measures can potentially cut illness duration, prevent or ameliorate complications, shorten the duration and costs of hospitalisation, improve the cost-effectiveness of health delivery, and also reduce cross-infection. To be of clinical value, such diagnostic tests must have high sensitivity and specificity across all age ranges, be inexpensive and provide test results sufficiently early for a measurable effect. Here we consider the speed and ease of tests rather than their costs, sensitivity and specificity, clinical impact or cost-effectiveness.

The EoU scores used in this study provide a measure of the complexity and requirements of the test procedures that we assessed. We included TtR of results in the scoring system as a possible indicator of EoU. We did a sensitivity analysis and found that exclusion of TtR of results in the scoring system – either alone or with each other component scores – had no appreciable effect on the overall ranking of tests in terms of EoU and/or test requirements.

The patients in our study had a median duration of illness of 120 hours before admission with a lower quartile of 72 hours. Recent systematic reviews and meta-analyses of the therapeutic use of NIs,^{70,216,217} show that a clinically beneficial effect of oseltamivir and zanamivir (Relenza®, GSK) depends on treatment starting within 48 hours of first symptoms when seasonal (inter-pandemic) influenza is circulating. In our study, only the Quidel QuickVUE Influenza A&B test provided results soon enough to influence treatment decisions that might benefit patients – and then only to a small percentage (150/1240, 12.1%) of admissions. In our study, the Quidel QuickVUE Influenza A&B test had a median turnaround time of <30 minutes, and 85% of results were reported within half an hour of specimen collection. The PCR tests were much slower in comparison – the median TtR of results using molecular tests was 50.8 hours for conventional PCR, and 29.2 hours for real-time RT-PCR. For patient cohorts as in our study, these turnaround times preclude RT-PCR from guiding decisions to start antiviral treatment but could influence infection control procedures in hospitals with limited single-room accommodation, as influenza virus can still be detected in nasopharyngeal aspirates by real-time RT-PCR up to 1 week or more among patients who do not receive antiviral therapy.^{125,155} In contrast, conventional virus culture provided results of no clinical or public health relevance to the patient or hospital. In our study, the median TtR of results obtained by virus culture was 452.6 hours (IQR 403.6–620.8 hours) and fewer than 5% of results were available within 14 days of specimen collection – too late to initiate antiviral therapy for influenza or recurrent orolabial herpes simplex virus (HSV) infection. The virus culture results usually became available when the patient had either been discharged or died; this occurred for 80% of the specimens that grew influenza A or B, and 57% of those that grew HSV.

In the EoU evaluation of the diagnostic tests for influenza, the Quidel QuickVUE Influenza A&B POCT was allocated a score of '11' (i.e. component scores of '1' for each of the 11 criteria for categorisation), indicating that it was straightforward and undemanding to use, and can be used with minimum levels of training, knowledge and technical skills. The tests kits can be stored at room temperature and have a 24-month shelf life from date of manufacture, are readily transferable and convenient to use. In contrast, the 'conventional' RT-PCR test for influenza A and B and RSV A and B had the highest of all EoU scores in the analysis ('30'), reflecting its complexity and requirements. In comparison with 'real-time' PCR tests, the 'conventional' RT-PCR test took 20 hours longer when median turnaround times were compared. The EoU scores for the 'real-time PCRs' were '25' and '26', indicating PCRs to be 'complex' in terms of EoU and requirements. Our observations of turnaround times and EoU scores indicate that the 'real-time' RT-PCR method should be used in preference to the 'conventional' RT-PCR test, assuming that both methods are otherwise comparable in terms of sensitivity, specificity and cost. However, it is acknowledged that the technology is evolving rapidly, so what is complex now, with multiple steps, is gradually being automated so as to reduce the skill requirements, and improve turnaround times. The EoU score for the conventional cell culture diagnostic test was '26', which reflects its general complexity and requirements in performance.

and interpretation. As judged by turnaround times, our findings indicate that consideration is given to replacement of conventional virus culture with an alternative test. However, virus culture remains of value in providing specimens for antigenic analysis and antiviral susceptibility, and guiding strain selection for vaccine production.

In the UK, treatment of ILI with NIs is influenced by illness duration and virus activity established through surveillance, rather than POCTs. Similarly, initial therapy of CAP with antibiotics is guided by severity scores – such as CURB-65 – and cannot await ‘early’ microbiology results, although ‘early’ results might subsequently influence the spectrum of antibiotics that are used.

For pneumococcal infection, only the BinaxNOW *S. pneumoniae* test provided results rapidly – the test had a median turnaround time of < 30 minutes, and 85% of results were reported within half-an-hour of specimen collection. The BinaxNOW *S. pneumoniae* POCT had an EoU score of 11 (i.e. component scores of ‘1’ for each of the 11 criteria for categorisation), indicating that it was as equally straightforward and undemanding to use as the Quidel QuickVUE Influenza A&B POCT. Like the QuickVUE Influenza A&B test, the BinaxNOW test can be used with minimum levels of training, knowledge and technical skills, can be stored at room temperature, and is readily transferable and convenient to use. The blood and sputum culture results were much slower in comparison. The median TtR growth of *S. pneumoniae* was 84.4 hours, although a provisional report of the growth of an organism was reported after a median of 36.8 hours. Antimicrobial sensitivity data did not become available for a median of 84.4 hours after specimen collection. Similarly, growth of *S. pneumoniae* from sputum was reported a median of 71.4 hours after collection, and the median TtR antimicrobial sensitivity was 133 hours.

As noted in the review of cases that tested positive in the pneumococcal POCT (see *Chapter 4*), the much shorter turnaround time of the urinary antigen test for pneumococcal antigen compared with blood and sputum culture, did not lead to any step-down in antimicrobial treatment within 24 hours of the test result, nor did a positive test result lead to the release any single-room accommodation. Similarly, the substantially faster turnaround time of the POCT for influenza compared with virus culture had no impact on the use of NIs, antibiotics or single-room accommodation but the number of patients with positive results was very small, and the data should therefore be interpreted with caution.

Chapter 8 Process outcomes and cost-effectiveness

Introduction

This chapter reports the results of a trial-based cost-effectiveness analysis. Resource-use data were collected prospectively during the time patients were in hospital via the CRFs, and retrospectively from discharge until day 28 via the 28-day follow-up. UK unit costs obtained from a variety of sources were then applied to the resource use data to estimate total cost per patient. As well as describing the distribution of total costs for the three diagnostic strategy groups, an incremental cost-effectiveness analysis was undertaken with cost per quality-adjusted life-year (QALY) (estimated using the EQ-5D and mortality data reported in *Chapter 4* via an AUC approach²¹⁸) being estimated when appropriate, together with cost per (correct) case detected (using the diagnostic data reported in *Chapter 5*). To simultaneously allow for the potential for correlation between cost and outcome, as well as their inherent uncertainty, together with the fact that some data were missing for both resource use (and therefore cost) and EQ-5D (see *Chapter 4* for details), a Bayesian approach was adopted^{219–221} using Markov chain Monte Carlo (MCMC) methods, implemented in WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) to estimate the uncertainty surrounding the outcome measures.²²² A series of sensitivity analyses were undertaken, both to assess the sensitivity to the MCMC methods used, and to the prices of the index tests (PCR and POCT), and also the model structure used to estimate cost-effectiveness. The perspective adopted was that of the NHS.

Methods

Resource use data and unit costs

Table 32 displays the unit costs, derived from a variety of sources,^{223–226} for the various major resource use components identified in 3WS. As well as the unit costs in Table 32, all drugs prescribed in the index admission, and subsequently associated with the index admission, were costed using the *British National Formulary* (BNF).²²⁷ The price year adopted was 2007–8, i.e. the final year of the study,²²⁸ and those unit prices that were not in this year were adjusted accordingly using the Hospital and Community Health Services (HCHS) Pay and Price Index.²²⁹ No discounting of either costs or QALYs was applied to the cost-effectiveness analyses, as the time horizon over which patients were followed was 28 days. As well as the average total cost per patient for each of the diagnostic strategies, the main cost components, namely hospital stay (both non-ITU and ITU), index test costs (including staffing and materials), complications [myocardial infarction, stroke, urinary tract infection, wound infection, MRSA/*Clostridium difficile*], post-discharge visits (GP/nurse visits) and A&E attendance], additional investigations (electrocardiography, full blood count, blood gases, blood biochemistry, oxygen levels, ward-based urine analysis and chest radiography) and antibiotic prescribing (both for the index admission and post discharge) were also reported in terms of means and SDs. Owing to the relatively large sample size, both cost components and mean resource were formally compared between the diagnostic strategies using parametric methods – one-way ANOVA or Fisher's exact test as appropriate.²³⁰

TABLE 32 Unit costs for the various resources collected

Cost component/resource	Unit cost (£)	Source
Hospital cost per day		
Ward	276.21	HRG code and DH Reference Costs ²²³
ITU	1410.54	HRG code and DH Reference Costs ²²³
Oxygen therapy	212.00	HRG code and DH Reference Costs ²²³
Ward-based CPAP	219.75	HRG code and DH Reference Costs ²²³
Tests (including staffing and materials)		
Quidel	15.83	UHL NHS Trust
Binax	25.56	UHL NHS Trust
Blood culture	46.00	UHL NHS Trust
Viral culture	48.00	UHL NHS Trust
Sputum culture	38.00	UHL NHS Trust
PCR	48.00	UHL NHS Trust
Complications (average costs for acute phase)		
Myocardial infarction	1138.64	Bravo-Vergel <i>et al.</i> ²²⁴
Stroke	790.03	Bravo-Vergel <i>et al.</i> ²²⁴
Urinary tract infection	32.08	Turner <i>et al.</i> ²²⁵
Wound infection	148.00	DH NHS Reference Costs ²²³
MRSA/ <i>C. difficile</i>	688.00	DH NHS Reference Costs ²²³
Post-discharge visits		
GP: surgery	36.00	PSSRU ²²⁶
GP: home	58.00	PSSRU ²²⁶
Practice nurse	11.00	PSSRU ²²⁶
District nurse	26.00	PSSRU ²²⁶
Home-care worker	39.00	PSSRU ²²⁶
A&E attendance	111.00	PSSRU ²²⁶
Additional investigations		
Electrocardiography	33.45	DH NHS Reference Costs ²²³
Full blood count	2.99	DH NHS Reference Costs ²²³
Blood gases	2.99	DH NHS Reference Costs ²²³
Oxygen levels	2.99	DH NHS Reference Costs ²²³
Blood biochemistry	1.34	DH NHS Reference Costs ²²³
Ward urine analysis	9.15	DH NHS Reference Costs ²²³
Chest radiography	16.00	DH NHS Reference Costs ²²³

DH, Department of Health; HRG, Healthcare Resource Group; PSSRU, Personal Social Services Research Unit; UHL, University Hospitals of Leicester.

Statistical model

Model A

In order to simultaneously allow for the potential for correlation between cost and outcome a bivariate model was assumed for the two outcomes.^{220,231} Thus, if y_{1ij} and y_{2ij} represented the total costs and QALYs for the i th patient in the j th group, respectively, these were then assumed to come from a bivariate normal distribution (model A), such that:

$$\begin{pmatrix} y_{1ij} \\ y_{2ij} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{1j} \\ \mu_{2j} \end{pmatrix}, \Sigma_j\right) \quad (1)$$

where μ_{1j} and μ_{2j} are the mean total costs and mean QALYs for the j th randomisation group respectively, and Σ_j is the associated covariance matrix. Adopting a Bayesian approach to estimating the unknown parameters of model (1), i.e. μ_{1j} , μ_{2j} and Σ_j , prior distributions, representing a priori beliefs, are required for these parameters. To represent vague or non-informative prior beliefs regarding μ_{1j} and μ_{2j} appropriately diffuse normal distributions centred at zero were used, i.e. $N(0, 10^8)$ and $N(0, 10^{-2})$, respectively. For the covariance matrix, a Wishart prior distribution is placed on the precision matrix, i.e. the inverse of the covariance matrix. Thus:

$$\Sigma^{-1} = \begin{bmatrix} \sigma_1^2 & \sigma_{12}^2 \\ \sigma_{12}^2 & \sigma_2^2 \end{bmatrix}^{-1} \sim \text{Wishart}(A, k) \quad (2)$$

where A in (2) represents a priori beliefs regarding the corresponding covariance matrix, and by setting k to be the rank of A , in this case $k = 2$, a non-informative prior distribution is obtained. Initially, A is set such that:

$$A = \begin{bmatrix} 10,000 & 0 \\ 0 & 0.01 \end{bmatrix} \quad (3)$$

Having specified the prior distributions for model A as above, the marginal posterior distributions for μ_{1j} and μ_{2j} are required to assess cost-effectiveness. Owing to the number of unknown parameters in model A (1), MCMC methods are used in which random samples from the conditional posterior distributions are obtained, but which under ergodic theory will converge to the required marginal posterior distributions providing that a sufficient number of samples (iterations) are obtained and that the sampling algorithm has converged to an equilibrium distribution.²³²

Estimation of model parameters and software

The results were reported as posterior means and 95% CrIs, which are analogous to CIs. Primary results are based on a 'burn-in' of 20,000 iterations followed by a further sample of 50,000 iterations. Further sensitivity analyses were conducted to assess both convergence/mixing of the sampling algorithm and influence of prior distributions, which were all chosen to be non-informative. *Appendix 8* displays a sample of the WinBUGS code used for model A. The model parameters were estimated in WinBUGS 1.4.3,²²² and further post-estimation processing of the samples was undertaken in R.²³³

Missing data

There were missing values for both total costs and QALYs for a number of patients (costs – traditional 8.4%, POCT 8.6% and PCR 8.4%; QALYs – traditional 51.1%, POCT 44.0% and PCR 48.1%) and these were treated as unknown parameters in the estimation of model A, and hence at each iteration values were sampled from their corresponding posterior predictive distribution, i.e. conditional upon both the data and the model parameters, in a manner similar to multiple imputation.²³⁴ Thus, appropriate allowance for all uncertainty in the MCMC estimated mean total costs and QALYs has been made.²³⁵

Assessment of cost-effectiveness

Having estimated the mean effects, i.e. QALYs and total costs per patient, and after allowing for the imputation of missing data, the posterior probability of each diagnostic strategy being the least costly and also having the highest gain in QALYs was estimated from the MCMC samples, i.e. at each iteration the strategies were ranked and the probability of each strategy being ranked first (for QALYs) and third (for costs) was calculated as the proportion of iterations for which this was the case. An incremental cost-effectiveness analysis was then undertaken in which the three diagnostic strategies were first ranked in terms of ascending cost, and then any strategies which were dominated, i.e. for which there was another strategy which produced a greater QALY gain at lower cost, or extendedly dominated, i.e. for which there was another combination of strategies which produced the same QALY gain at lower cost, were excluded from the incremental analysis. For the two or three strategies that remain, cost-effectiveness was then assessed by calculating the appropriate incremental cost-effectiveness ratios (ICERs) to obtain an estimate of cost per additional QALY. Thus, for two strategies, j and k , the ICER is obtained by:

$$\text{ICER} = \frac{\bar{\mu}_{1j} - \bar{\mu}_{1k}}{\bar{\mu}_{2j} - \bar{\mu}_{2k}} \quad (4)$$

where $\bar{\mu}_{1j}$ and $\bar{\mu}_{2j}$ are obtained by averaging over the MCMC samples in R outside WinBUGS.²²¹

The probability of cost-effectiveness at willingness-to-pay thresholds, λ , of £20,000 per QALY and £30,000 per QALY, the currently accepted thresholds for NICE,²³⁶ were estimated as the proportion of MCMC samples for which the corresponding monetary net-benefit (NB) function was positive.²²⁰

Thus, for strategy j the NB function is given by

$$\text{NB} = \mu_{2j}\lambda - \mu_{1j} \quad (5)$$

In addition, the probability of error for any strategy deemed to be cost-effective was also estimated, i.e. the probability that by adopting that strategy an incorrect adoption decision had been made. For the incremental cost per confirmed case of influenza analysis, the strategies were again ranked in terms of ascending average total cost per patient, and the mean total cost per case, confirmed using serology (see Chapter 5), estimated.²³⁷

Sensitivity analyses

A series of one-way sensitivity analyses were undertaken to examine whether the MCMC methods (i.e. initial settings of burn-in, sample length and starting values), prior distributions, statistical model or price of PCR or POCT had an impact on the mean costs and QALYs, i.e. μ_{1j} and μ_{2j} , and therefore on the incremental cost-effectiveness analysis.

Markov chain Monte Carlo methods

To assess evidence of non-convergence, the history trace plots, i.e. the sampled values at each iteration plotted against iteration number, were examined for systematic movement in the chain and therefore evidence of non-convergence. In addition, the auto-correlation functions/plots were examined to identify poor mixing of the MCMC sampler, i.e. that successive sampled values were not entirely random, and therefore a longer sample length would be required.

To assess the sensitivity of the cost-effectiveness results to the length of burn-in, length of sample, initial starting values and prior distributions in using MCMC methods to estimate mean costs and QALYs, a number of one-way sensitivity analyses were undertaken. Specifically, two additional sets of length of burn-in/sample were used: 10,000/20,000 and 50,000/100,000 compared with the base-case analysis,

which used 20,000/50,000. Alternative prior distributions for μ_{1j} and μ_{2j} were also used, i.e. $N(0,10^5)$ and $N(0,1)$, respectively, compared with $N(0,10^8)$ and $N(0,10^{-2})$ in the base case, and A was set such that:

$$A = \begin{bmatrix} 1000 & 0.5 \\ 0.5 & 0.1 \end{bmatrix} \quad (6)$$

Finally, two additional chains, i.e. runs of the MCMC sampler, were used with qualitatively very different initial starting values to those used in the base case, and Brooks–Gelman–Rubin plots were explored,²³⁸ as well as the separate summary statistics for μ_{1j} and μ_{2j} , to identify evidence that the chains did not produce qualitatively similar results. The Brooks–Gelman–Rubin plots compare the width of 80% CrIs of the pooled chains with the average width of 80% CrIs across chains – the two should be the same unless there is evidence of non-convergence. This also gives an informal way in which to check whether a longer period of burn-in is required.

Model B

Model A (1) assumes that y_{1ij} and y_{2ij} , representing the total costs and QALYs for the i th patient in the j th group, respectively, are assumed to come from a bivariate normal distribution. This theoretically means that both total costs and QALYs could become negative. To assess the sensitivity of the base-case results to this modelling assumption an alternative statistical model (model B)²²¹ was developed in which y_{1ij} is assumed to follow a gamma distribution, i.e. so that costs can only be positive, and logit of y_{2ij} , i.e. $\log(y_{2ij}/(1 - y_{2ij}))$ is assumed to follow a normal distribution but that these two distributions are interlinked so that correlation between costs and QALYs is allowed. Thus:

$$y_{1ij} \sim \text{Gamma}(\eta_j, \lambda_i) \quad \lambda_i = \frac{\eta_j}{\phi_i} \quad (7)$$

$$\text{logit}(y_{2ij}) \sim N(\mu_{2j}, \sigma_j^2) \quad \text{where } \phi_i = \mu_{1j} + \beta_j(y_{2ij} - \mu_{2j}) \quad (8)$$

The unknown parameters in (7) and (8) are then given plausible yet vague or non-informative prior distributions. The means of the costs and logit QALYs, i.e. μ_{1j} and μ_{2j} , are given uniform(1,50000) and normal(0,1000) distributions, respectively, whereas the shape parameters of the gamma distribution in (5), η_j , are given uniform(1,100) prior distributions, and σ_j , the SD of logit QALYs in each randomisation group, is given a half-normal prior distribution with a mean of zero and a SD of 1 truncated at zero, i.e. $\sigma_j \sim N(0,1)|(0,.)$. Finally, β_j , the regression parameters that represent the degree of correlation between costs and (logit) QALYs, through λ_i – the scale parameter of the gamma distribution in (7) – are given vague normal prior distributions, i.e. $\beta_j \sim N(0,1000)$. Although the mean costs can be estimated directly from the MCMC samples, because the logit transformation is not linear it cannot be directly back transformed to provide estimates of mean QALY gain. However, it is possible to estimate mean QALYs on their natural scale using Monte Carlo integration within R (see *Appendix 8, section C*, for R code used).²²¹

Price reductions for polymerase chain reaction and point-of-care test

To assess the impact of price of the index test in the different diagnostic strategies, further cost-effectiveness analyses were undertaken in which either the price of PCR or POCT, as these are evolving technologies, was reduced by either 20% or 50%.

Results

Table 33 displays the mean/frequency of resource use for the main constituents of the cost components for patients with no missing data, i.e. complete case analysis. As can be seen, the only statistically significant difference between the three strategies was in terms of use of a practice nurse ($p = 0.03$).

TABLE 33 Mean resource use for the elements of the different cost components for each of the diagnostic strategies

Cost component	Traditional (n = 419)	Near patient (n = 418)	Rapid molecular (n = 415)	p-value ^a
Hospital stay	Mean (SD)^b [n]^c	Mean (SD)^b [n]^c	Mean (SD)^b [n]^c	
Non-ITU (days)	7.11 (11.30) [419]	6.70 (10.96) [418]	6.35 (9.56) [415]	0.6
ITU (days)	0.07 (0.84) [3]	0.15 (2.06) [3]	0.03 (0.45) [2]	0.4
Oxygen therapy (hours)	38.75 (108.47) [160]	48.64 (214.14) [177]	51.25 (257.75) [169]	0.6
Ward-based CPAP (hours)	0.59 (11.74) [5]	0.38 (5.63) [5]	0.06 (0.87) [2]	0.6
Complications	n (%)	n (%)	n (%)	
Myocardial infarction	3 (0.72)	1 (0.24)	4 (0.96)	0.4
Stroke	1 (0.24)	0 (0.00)	0 (0.00)	0.9
Urinary tract infection	5 (1.19)	3 (0.72)	6 (1.45)	0.6
Wound infection	1 (0.24)	1 (0.24)	2 (0.48)	0.7
<i>C. difficile</i>	6 (1.43)	2 (0.48)	1 (0.24)	0.1
MRSA	1 (0.24)	3 (0.72)	2 (0.48)	0.6
Additional investigations	Mean (SD)^b [n]^c	Mean (SD)^b [n]^c	Mean (SD)^b [n]^c	
Electrocardiography	1.51 (1.52) [344]	1.47 (1.64) [336]	1.44 (1.74) [322]	0.8
Full blood count	2.71 (3.19) [399]	2.69 (3.35) [397]	2.51 (3.14) [385]	0.6
Blood gases	1.86 (8.13) [249]	2.11 (12.55) [245]	1.39 (4.11) [245]	0.5
Oxygen levels	15.88 (20.16) [397]	16.24 (31.85) [387]	15.57 (21.41) [395]	0.9
Blood biochemistry	3.23 (5.17) [403]	2.99 (3.84) [397]	2.81 (3.68) [387]	0.4
Ward urine analysis	0.40 (0.64) [141]	0.38 (0.61) [140]	0.37 (0.61) [130]	0.7
Chest radiography	1.22 (1.04) [397]	1.22 (1.07) [392]	1.20 (0.98) [385]	0.9
Post-discharge visits	Mean (SD)^b [n]^c	Mean (SD)^b [n]^c	Mean (SD)^b [n]^c	
GP: surgery	0.36 (0.77) [100]	0.40 (0.98) [91]	0.35 (0.84) [91]	0.7
GP: home	0.14 (0.53) [37]	0.11 (0.42) [34]	0.10 (0.38) [33]	0.4
Practice nurse	0.01 (0.15) [1]	0.04 (0.29) [9]	0.06 (0.41) [12]	0.03
District nurse	0.17 (1.54) [22]	0.09 (0.69) [25]	0.09 (0.69)	0.5
Home-care worker	0.28 (2.60) [17]	0.15 (1.12) [18]	0.24 (2.03) [18]	0.6
A&E attendance	0.02 (0.15) [6]	0.03 (0.23) [8]	0.01 (0.11) [2]	0.3

a Calculated using either one-way ANOVA or Fisher's exact test.

b Calculated using all index admissions for each diagnostic strategy regardless whether resource was used.

c Number of admissions in which resource was used.

However, this should be interpreted with caution owing to the number of hypothesis tests undertaken. *Table 34* displays the mean (and SD) cost per patient for the cost components that make up the overall total cost, as well as the mean overall total cost itself, for each of the three diagnostic strategies. It can be seen that the means for each cost component, as well as for the total, are similar across the three strategies, although there is considerable uncertainty surrounding some of these. Formal comparison of the three strategies using one-way ANOVA did not identify any statistically significant differences between them ($p = 0.3$). For the observed QALYs, i.e. based on patients who did not have any missing data, POCT produced a mean QALY gain of 0.008137 (SD 0.007191), PCR 0.007724 (SD 0.005977) and traditional laboratory culture 0.007631 (SD 0.006244), which were not statistically significant from one another ($p = 0.7$).

Figure 19 displays the distribution of observed total costs for the three diagnostic strategy groups. As can be seen, the distributions are skew, but are very similar to one another.

Table 35 displays the MCMC posterior mean estimates for the total costs and QALYs (gained during the 28 day follow-up period of the trial) associated with each of the three strategies, together with associated 95% CrIs, which can also be seen to very similar to one another. More formally, the posterior probabilities that each strategy has the *highest* QALY gain are all less than 50%, ranging from 21.1% for traditional laboratory culture to 48.9% for POCT, whilst the posterior probability that PCR is the *least* costly is only 78.6%. *Figure 20* displays 50,000 samples for the mean total costs and QALYs gained for each of the three diagnostic strategies, and again demonstrates both the level of uncertainty in both costs and QALYs, and broad similarity between the strategies. *Table 35* also shows a formal incremental analysis which indicates that traditional laboratory culture testing is dominated by POCT, in that it has the highest mean total costs but the smallest QALY gain, and is therefore excluded further from the incremental analysis. Although PCR has lower mean total cost than POCT (cost difference: +£181, 95% CrI: -£219 to +£587), POCT also has a larger QALY gain (QALY difference: +0.000256, 95% CrI: -0.001474 to +0.001978), and the associated ICER of POCT compared with PCR is £734,717.

TABLE 34 Mean costs for different resource use components for each of the diagnostic strategies

Cost component	Traditional mean (SD), £	Near-patient mean (SD), £	Rapid molecular mean (SD), £	p-value ^a
Hospital stay:	2004 (3174)	1972 (3753)	1782 (2698)	0.5
Non-ITU	1977 (3121)	1855 (3030)	1759 (2652)	0.6
ITU ^a	27 (485)	117 (1662)	24 (482)	0.3
Index tests ^b	94	41	112	
Complications ^a	22 (139)	11 (94)	16 (120)	0.5
Post-discharge visits ^a	56 (143)	52 (126)	50 (156)	0.8
Additional investigations	137 (116)	138 (151)	130 (118)	0.6
Antibiotics	26 (56)	23 (58)	23 (61)	0.7
Total costs	2326 (3370) [172 ^c]	2158 (3254) [167 ^c]	1980 (2355) [121 ^c]	0.3

a Calculated using one-way ANOVA.

b Index tests were standard within each arm and, therefore, there was no uncertainty around them.

c Standard error.

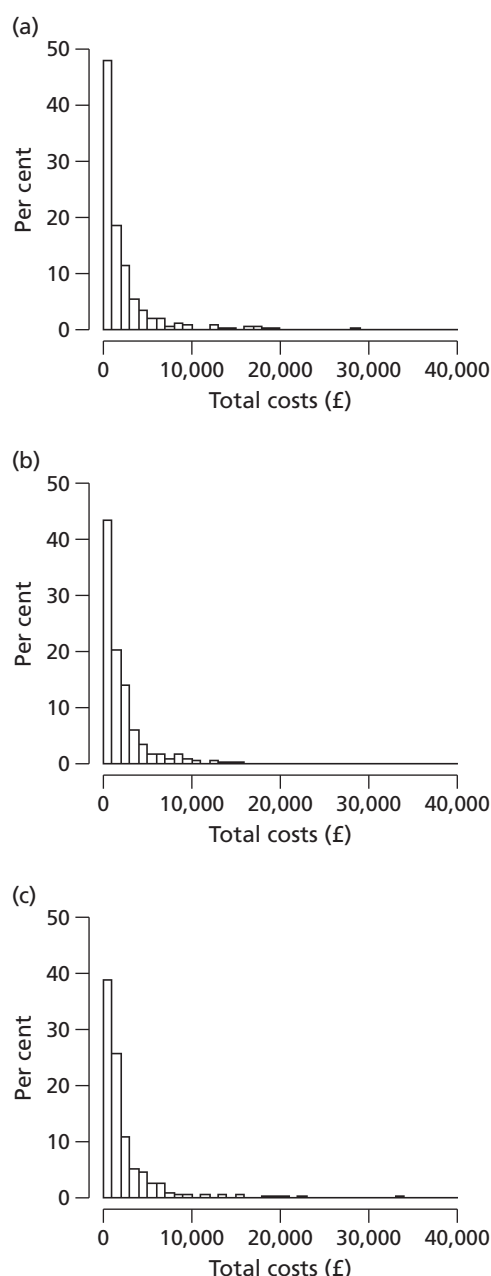


FIGURE 19 Distribution of total costs for each of the diagnostic strategies. (a) POCT; (b) PCR; (c) laboratory culture.

Figure 21 displays the cost-effectiveness plane, i.e. incremental costs plotted against incremental QALYs for POCT compared with PCR, together with a £20,000-per-QALY willingness-to-pay threshold. In fact, the probability of POCT being cost-effective at £20,000 threshold is 18.3%, and at £30,000 is 18.6%, reflecting the considerable uncertainty, whereas the probability of PCR being cost-effective at a £20,000 threshold is 78.3% and at £30,000 is 78.1%. The probability of error for adopting PCR, i.e. the probability of making an incorrect adoption decision, is 21.7% at a £20,000 threshold and 21.9% at £30,000. The corresponding cost-effectiveness acceptability curves (CEACs) for all three diagnostic strategies are displayed in Figure 22.

To assess the impact of price on the overall cost-effectiveness results, Table 36 displays the results of a series of one-way sensitivity analyses exploring the impact of 20% and 50% price reductions for POCT and PCR.

TABLE 35 Cost-effectiveness results estimated using MCMC

Mean total cost per patient, £ (95% CrI)	Mean QALYs gained ^a (95% CrI)	Probability of being <i>least</i> costly	Probability of having <i>highest</i> QALY gain	Incremental mean total cost (95% CrI)	Incremental mean QALY gain, £ (95% CrI)	ICER, £	Probability (of error) of being cost-effective at thresholds of:	
							£20,000 per QALY	£30,000 per QALY
PCR								
1978 (1743 to 2216)	0.007779 (0.006555 to 0.008983)	0.786	0.300	– ^b	– ^b	– ^b	0.783 (0.217)	0.781 (0.219)
POCT								
2159 (1828 to 2485)	0.008035 (0.006772 to 0.009280)	0.178	0.489	+£181 (–£219 to +£587)	+0.000256 (–0.001474 to +0.001978)	734,717	0.183	0.186
Traditional								
2327 (1989 to 2664)	0.007588 (0.006334 to 0.008854)	0.036	0.211	Dominated ^c	Dominated ^c	Dominated ^c	0.034	0.033
<div><div>^a Gained over the 28-day period of follow-up in the 3WS trial.</div><div>^b Not estimated as traditional was dominated, and POCT had higher mean cost but also higher QALY gain than PCR and therefore the ICER was calculated for POCT compared with PCR.</div><div>^c Dominated in that POCT has lower mean total costs per patient and a greater QALY gain over 28 days.</div></div>								

^a Gained over the 28-day period of follow-up in the 3WS trial.

^b Not estimated as traditional was dominated, and POCT had higher mean cost but also higher QALY gain than PCR and therefore the ICER was calculated for POCT compared with PCR.

^c Dominated in that POCT has lower mean total costs per patient and a greater QALY gain over 28 days.

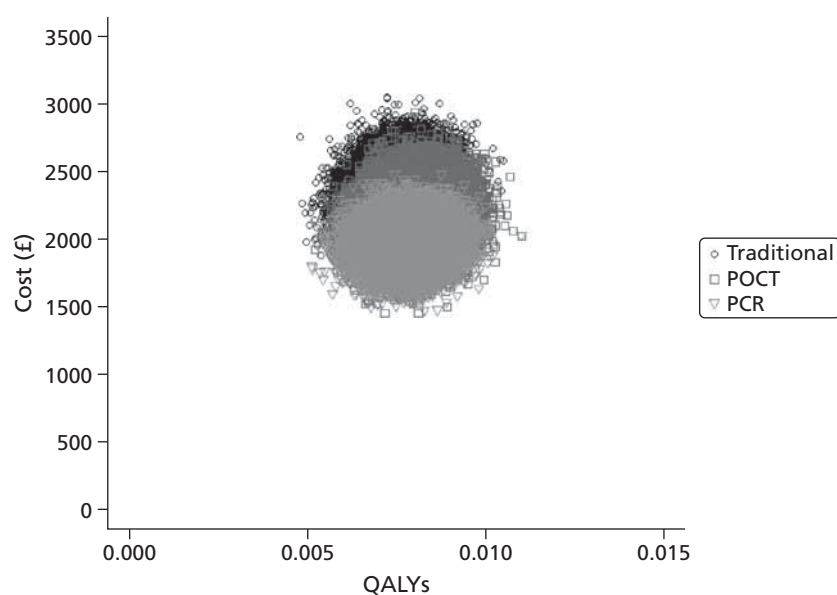


FIGURE 20 Mean costs and QALYs for 'traditional', 'near-patient' and 'molecular' diagnostic tests for 50,000 MCMC samples.

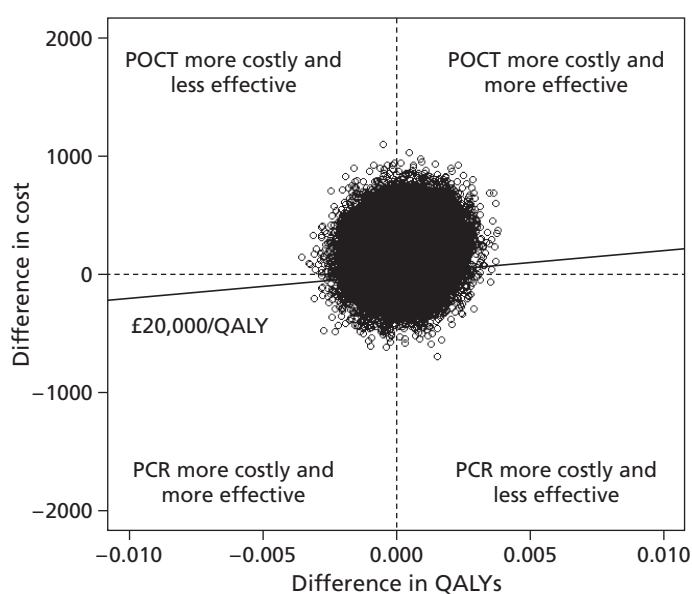


FIGURE 21 Cost-effectiveness plane, i.e. incremental costs plotted against incremental QALYs for POCT compared with PCR, using 50,000 MCMC samples together with a £20,000 per QALY willingness-to-pay threshold. Sampled values below the threshold line indicate that POCT should be adopted as the most cost-effective strategy at a willingness to pay of £20,000 per QALY.

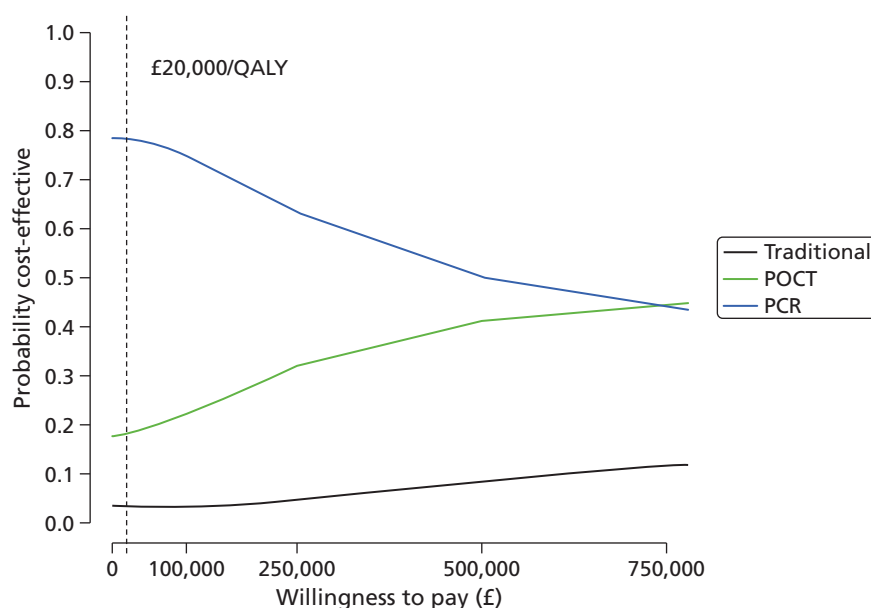


FIGURE 22 Cost-effectiveness acceptability curve for the three diagnostic strategies, based on 50,000 MCMC samples together with a willingness-to-pay threshold of £20,000 per QALY.

It can be seen from *Table 36* that all of the possible price reductions have relatively little impact on the estimated mean total costs and QALY gains for the three diagnostic strategies, for example even with a 50% price reduction for PCR the mean total costs for PCR are £1953 (95% CrI £1719 to £2189) compared with £1978 (95% CrI £1743 to £2165) in the base case, and similarly a 50% reduction in the price of POCT results in estimated mean total costs of £2139 (95% CrI £1813 to £2468) compared with £2159 (95% CrI £1828 to £2485) in the base case. In all cases not only are the estimated mean costs and QALYs very similar to the base case, but also the ranking of the treatments in terms of both costs and QALYs remains the same as in the base case.

Table 36 also presents the results obtained using an alternative statistical model (model B) in which costs are assumed to follow a gamma distribution and logit transformed QALYs a linked normal distribution. As anticipated, given the skewness of the original cost data presented in *Figure 19*, the estimated mean costs for each of three diagnostic strategies are higher than in the base case, although for each diagnostic strategy the 95% CrIs for both mean costs and QALYs overlap, and the ranking of the treatments remains the same, with traditional laboratory culture being dominated by POCT, and the associated ICER for POCT compared with PCR, which still has the lowest estimated mean cost, being £342,750 per QALY, still considerably higher than the normal upper limit of £30,000 adopted by NICE in England and Wales.

Sensitivity analyses to the MCMC methods used are displayed in *Appendix 8*, section B. Here, *Table 47* displays the results of using different combinations of length of burn-in/sample, initial starting values and prior distributions. It can be seen that there appears to be little evidence of non-convergence of the MCMC estimation of model A, with the resulting estimated mean costs and QALYs being very similar across the different sensitivity analyses. This is further supported by *Figures 23–25*, which display the history trace plots, the Brooks–Gelman–Rubin plots, and the autocorrelation function plots, respectively, for the estimated mean costs and QALYs for each diagnostic strategy, i.e. μ_{1j} and μ_{2j} . *Figure 23* shows that the mean of the MCMC samples remains approximately constant over the 50,000 iterations with only random variation present, whereas *Figure 24* shows that the two methods of calculating 80% CrIs (either by pooling the three chains, defined by the different sets of initial starting values, or by averaging over them) give very similar results in terms of the estimated mean costs and QALYs. Finally, *Figure 25* indicates that the MCMC algorithm is efficiently sampling for the joint posterior distribution with relatively little autocorrelation present, i.e. successive samples appear to be virtually random, thus providing further

TABLE 36 One-way sensitivity analyses exploring impact of 20% and 50% price reductions for POCT and PCR and an alternative statistical model

Models	Traditional	Rapid molecular	Near patient
Base case (model A)			
Costs, average total cost (95% CrI)	2327 (1989 to 2664)	1978 (1743 to 2165)	2159 (1828 to 2485)
QALYs	0.007588 (0.006334 to 0.008854)	0.007779 (0.006555 to 0.008983)	0.008035 (0.006772 to 0.009280)
PCR, cost reduction of 20%			
Costs, average total cost, £ (95% CrI)	2327 (1989 to 2667)	1967 (1733 to 2204)	2160 (1834 to 2488)
QALYs	0.007601 (0.006331 to 0.00889)	0.007779 (0.006575 to 0.008985)	0.008029 (0.006776 to 0.009286)
PCR, cost reduction of 50%			
Costs, average total cost, £ (95% CrI)	2327 (1989 to 2667)	1953 (1719 to 2189)	2160 (1834 to 2488)
QALYs	0.007601 (0.006331 to 0.00889)	0.007779 (0.006575 to 0.008985)	0.008029 (0.006776 to 0.009286)
POCT, cost reduction of 20%			
Costs, average total cost, £ (95% CrI)	2327 (1989 to 2667)	1977 (1743 to 2213)	2152 (1825 to 2480)
QALYs	0.007601 (0.006331 to 0.00889)	0.007779 (0.006575 to 0.008985)	0.008029 (0.006776 to 0.009286)
POCT, cost reduction of 50%			
Costs, average total cost, £ (95% CrI)	2327 (1989 to 2667)	1977 (1743 to 2213)	2139 (1813 to 2468)
QALYs	0.007601 (0.006331 to 0.00889)	0.007779 (0.006575 to 0.008985)	0.008029 (0.006776 to 0.009286)
Alternative model (model B)			
Costs, average total cost, £ (95% CrI)	2349 (2131 to 2589)	2007 (1819 to 2210)	2189 (1976 to 2424)
QALYs	0.008392 (0.007033 to 0.009750)	0.008896 (0.007452 to 0.010341)	0.009427 (0.007734 to 0.011120)

evidence that the 20,000/50,000 burn-in/sample length combination used in the base case is sufficiently large.

Finally, *Table 37* presents the results of an incremental cost per confirmed case of influenza analysis. In this analysis, potential cases of influenza identified by the three diagnostic strategies were confirmed by serology (see *Chapter 5*). It can be seen that on the basis of the diagnostic strategies the prevalence of influenza was low but confirmation with serology reduced this even further, with, in fact, no correctly identified cases being identified under the POCT strategy, thus hampering the calculation of a cost-per-case estimate. It should be noted that in *Chapter 5*, as the aim was to estimate diagnostic performance, all 1252 admissions were used as each received all three diagnostic strategies but only those randomised to each strategy had their clinical management based on the strategy to which they randomised, and hence the absolute prevalence was considerably greater. Consequently, the cost per case for PCR was estimated as £164,570 (based on five cases) and for traditional laboratory culture £315,696 (based on three cases), with traditional laboratory culture being dominated by PCR.

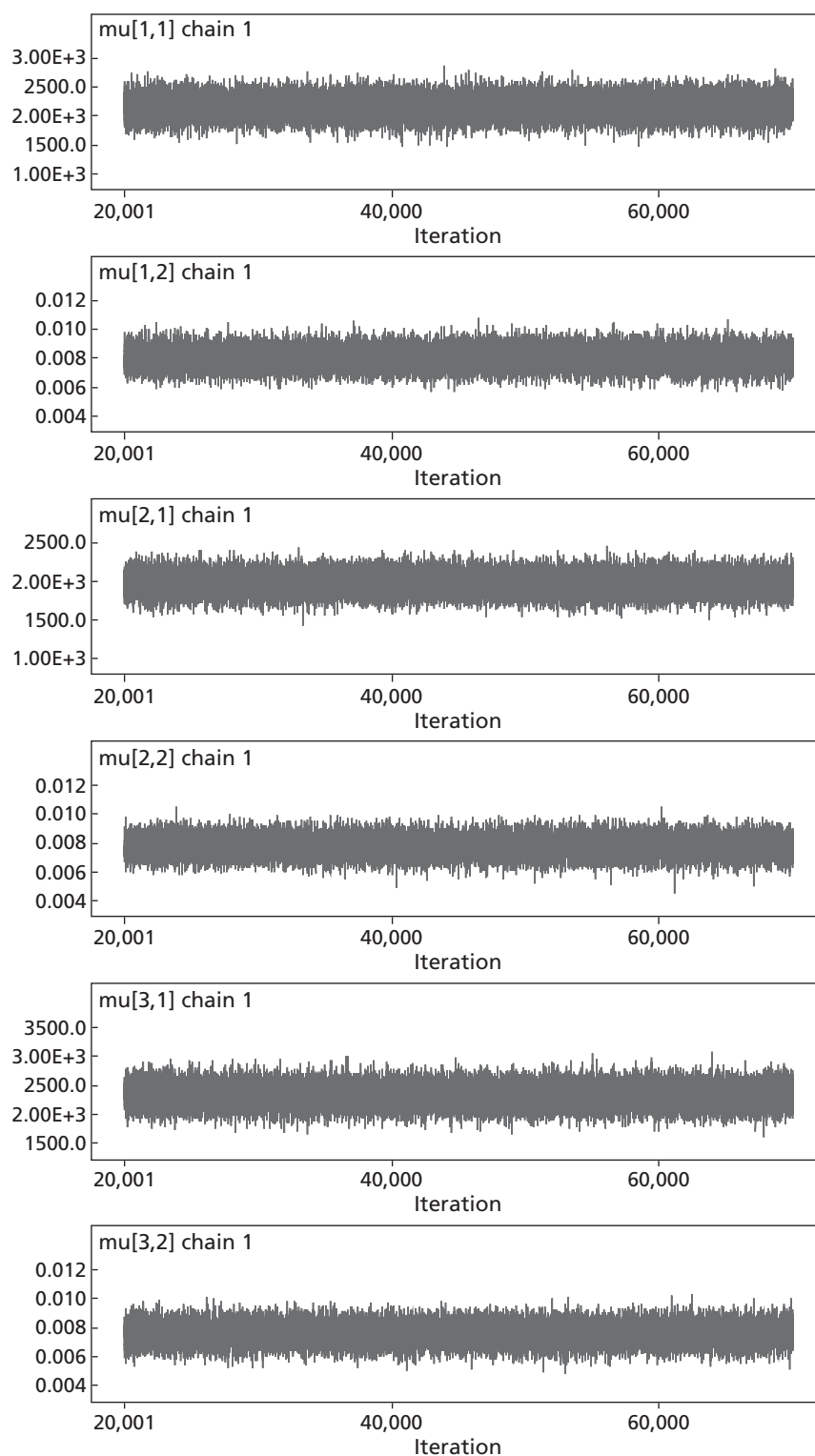


FIGURE 23 Markov chain Monte Carlo history plots for mean costs and QALYs.

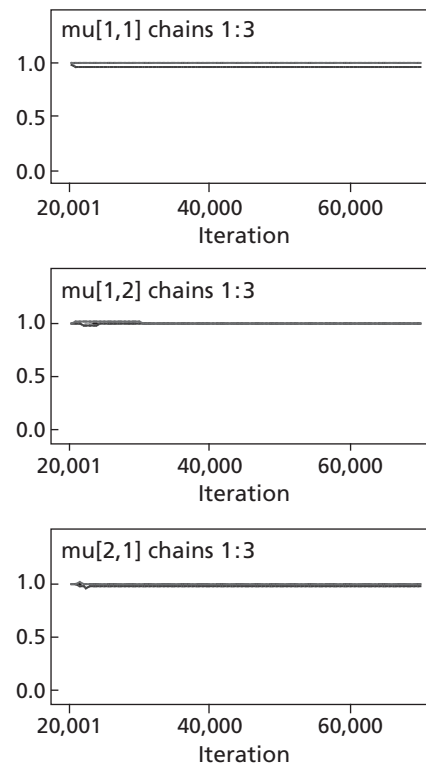


FIGURE 24 Brooks–Gelman–Rubin plots for chains 1, 2 and 3, representing three different sets of starting/initial values.

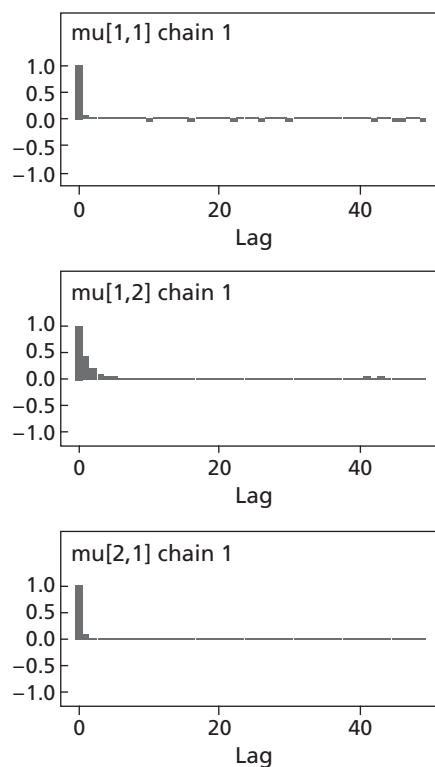


FIGURE 25 Markov chain Monte Carlo autocorrelation plots for mean costs and QALYs.

TABLE 37 Incremental cost per confirmed (using serology) case of influenza analysis

Mean total cost (£)/patient (95% CrI)	No. of patients with eligible serology	No. (%) of patients testing positive for influenza with index test	No. (%) of serology confirmed cases of influenza	Cost per confirmed case of influenza	Incremental cost per additional confirmed case of influenza detected
PCR					
1978 (1743 to 2216)	416	30 (7.2)	5 (1.2)	164,570	— ^a
POCT					
2159 (1828 to 2485)	416	8 (1.9)	0 (0)	— ^b	— ^a
Traditional					
2327 (1989 to 2664)	407	9 (2.2)	3 (0.7)	315,696	Dominated
<p>a Not estimated as traditional was dominated and POCT had zero confirmed cases of influenza.</p> <p>b Cannot be estimated as there are zero confirmed cases of influenza in this group.</p>					

Discussion

There is relatively little difference in the cost distributions or QALYs gained by each of the three diagnostic strategies. A strategy of using traditional laboratory culture led to an overall cost profile that is the most expensive but is also associated with the lowest gain in terms of QALYs, and is therefore dominated. Although POCT has the highest gain in terms of QALYs, this gain over PCR is not offset by its higher cost at current thresholds of willingness to pay.

The cost-per-case analysis is hampered by the relatively low prevalence (within each diagnostic strategy group) of influenza as diagnosed by serology. Indeed, as discussed in *Chapter 5* and *Chapter 6*, there are issues with the manner in which serology was undertaken in 3WS, although sensitivity analyses in *Chapter 5* imply that as far possible this had little impact on the results, and in *Chapter 6* the majority of other studies identified in fact used PCR as the 'gold standard'. Thus, if the 30 cases of influenza identified in the PCR strategy group were in fact 'true' cases of influenza the cost per case detected would fall to £26,042 for that strategy compared with £164,570 when serology was used as a 'gold standard'. If PCR was adopted as a 'gold standard' for the other two strategies, then five of the eight cases identified under the POCT strategy would be confirmed, rather than zero using serology, leading to a cost per case of £179,628, and all 9 cases identified by traditional laboratory culture would be confirmed leading to a cost per case of £105,232. Both POCT and traditional laboratory culture would however be dominated by PCR.

From a purely cost-effectiveness point of view, PCR would appear to be the most cost-effective diagnostic strategy, and, in fact, when viewed in light of the comparison with serology for influenza its superior diagnostic ability would reinforce that. However, set against this is the fact that there are no statistically significant differences between the three groups in terms of the main clinical and process outcomes. The fact that in the systematic review and meta-analysis, reported in *Chapter 6*, the majority of studies identified used PCR as the 'gold standard' perhaps also underlines the fact PCR should be adopted as the de facto standard, but that POCT would appear to offer no clear benefit either in terms of cost or effectiveness.

As described in *Chapter 2*, the 3WS was designed/powered to be able to estimate the diagnostic accuracy of the three strategies to within prespecified limits. In fact if the 3WS was designed with respect to clinical end points, for example length of stay, then the study would have been considerably smaller. However, with respect to cost-effectiveness or rather the differences in cost and effect, in terms of QALYs, a retrospective power analysis was undertaken. Assuming that cost-effectiveness was established using a willingness-to-pay threshold of £20,000 per QALY, the difference in mean costs and the difference in mean QALYs required to achieve such a threshold, providing the other outcome was held constant as

estimated in *Table 35*, the power of the study assuming a sample size of 1252 admissions was calculated. In terms of QALYs, the actual sample size of 3WS ensured over 90% power to detect a QALY difference that would ensure cost-effectiveness of one strategy over another. However, owing to the large variability in costs, as can be seen from *Tables 34* and *35* for both the observed and estimated cost components and total costs, the 3WS as it was designed had < 50% power to be able to detect a minimum cost difference between any two strategies, assuming the QALY difference was as estimated in *Table 35*. Whether 3WS could have ever been undertaken to ensure an appropriate level of power typically required, given the level of variability, is debatable, especially as its already relatively large sample size was driven by diagnostic accuracy rather than *clinical* effectiveness.

A possible major limitation of the cost-effectiveness analysis reported here is the fact that it is a purely trial-based analysis, with follow-up limited to 28 days post admission/randomisation, and that therefore further readmissions, for example, are not captured and costed appropriately. It could be argued that if any differences between the diagnostic strategies did exist then these would be expected to be seen within 28 days, and, in fact, within the index admission, and that if such a scenario did exist the key question would be whether any short-term benefit, for example if reduced length of stay was offset by a higher probability of readmission in the near future. However, as there are few differences, if any, between any of clinical outcomes, and in fact the clinical management of patients overall, then this would appear to be an unlikely scenario. A further limitation of the analyses presented is the level of missing data, approximately 50% for QALYs and 8.5% for costs, necessitating the use of MCMC predictive-based methods to impute missing values, conditional on the model and observed data. Although this approach is recommended for cost-effectiveness analyses,²³⁴ under the assumption that data were missing at random, a further sensitivity analysis using only complete cases was undertaken. The mean costs and QALYs for the three diagnostic strategies were broadly similar to those obtained using MCMC methods, and resulted in traditional laboratory culture remaining dominated, and POCT still having higher mean total cost than PCR, but with a smaller associated gain in QALYs, resulting in an ICER of £4,080,242 per QALY, and the probability of PCR being cost-effective rising to 93%. Finally, the perspective considered was that of the NHS, and it could be argued that there could be wider societal costs borne by patients or their informal carers, for example family members, which are not considered as part of the analyses presented here.

Chapter 9 Discussion

Main findings

Prescribing outcomes

- Antibiotic use was high in our cohort of patients. Altogether, 857 (73.1%) of all 1172 first admissions received at least one antibiotic for a median of 77 hours.
- Overall, 77.5% (96/120) of all first admissions with RSV or influenza received at least one antibiotic for a median of 77 hours – indicating that antibiotics are often prescribed for prolonged periods to patients with viral infections, many of whom are unlikely to derive clinical benefit. We found no evidence for an association between diagnostic group and time to final dose of antibiotics in patients infected with RSV or influenza.
- Regardless of the high level of antibiotic use, we found no evidence for any association between diagnostic group and *three prescribing outcomes*, specifically (1) time from admission to first narrow-spectrum antibiotic; (2) time from admission to first oral antibiotic; and (3) time from admission to cessation of antibiotics.

Clinical outcomes

- Altogether, 48.5% (608/1252) of admissions had a raised temperature ($\geq 37.3^{\circ}\text{C}$) on admission. There was no evidence for any association between *fever duration* and diagnostic group for (1) all first admissions (regardless of any diagnosis) and (2) patients diagnosed with *S. pneumoniae* infection.
- Overall, 43.6% (546/1252) of all admissions and 37.2% (436/1172) of first admissions received *oxygen therapy* during the admission. Time-to-event analysis for the 436 first admissions and for 40 out of 99 first admissions who were diagnosed with *S. pneumoniae* and were prescribed oxygen found no evidence of an association between diagnostic group and time to cessation of oxygen, in all patients, and in those diagnosed with *S. pneumoniae*.
- *CPAP dependence* was infrequent in our patient cohort (1.2%, 14 out of 1172 first admissions). Time-to-event analysis by diagnostic group for all patients with a first admission found no evidence of an association between diagnostic group and time to cessation of CPAP.
- *Admissions to ITU* were infrequent in this cohort (0.4%, 5 of 1172 first admissions). All five patients who were admitted to the ITU were ventilated. The small numbers of patients requiring ITU admission and ventilator support precluded comparison across the diagnostic groups for either end point.
- We found no evidence for any association between *duration of hospital stay* and diagnostic group. Using a Cox proportional hazards model, we found that length of stay was comparable across the following groups (1) all first admissions who were discharged; (2) all first admissions discharged who were diagnosed with influenza; (3) all first admissions discharged who were diagnosed with RSV; and (4) all first admissions discharged who were diagnosed with *S. pneumoniae* infection.
- Fifty *deaths* occurred within 28 days of admission. All 50 deaths occurred in first time admissions. We found no evidence to associate any diagnostic group with any increase or decrease in mortality for (1) 'all' patients, or for first admissions with a specific diagnosis of (2) influenza ($n = 91$); (3) RSV ($n = 29$); and (4) *S. pneumoniae* infection ($n = 99$).
- Only 8.7% of first admissions (102/1172) were given *single-room accommodation* at some time during their admission. Hardly any (11.7%, 14/120) admissions with influenza or RSV received care in single-room accommodation. Owing to the small number of patients with RSV or influenza who were isolated, comparison across diagnostic groups was considered inappropriate. The majority of admissions with influenza and RSV were nursed in open areas of the hospital where they posed some degree of risk of nosocomial infection to vulnerable patients and staff. We found no evidence of any association with 'containment' across groups for infections with RSV, influenza, and *S. pneumoniae*.

- We found no statistically significant differences between the three intervention groups in terms of *EQ-5D* scores on admission and subsequently. However, repeated measures analyses using a linear mixed-effects model revealed greater improvements in scores at both days 7 and 28 for the 'near-patient' and 'rapid molecular' groups compared with the 'traditional' group.
- A review of data for eight patients in the 'near-patient' group with a positive test for influenza showed that none was eligible for treatment with a NI because they had illness duration of > 48 hours. None of the patients who remained in hospital after the result became available were isolated. There was no consistency in their subsequent treatment with antibiotics but the number of patients was too small to draw meaningful conclusions.
- A review of data for 21 patients in the 'near-patient' group with a positive pneumococcal antigen test showed that none of the patients had a step-down in antibiotics within 24 hours of the result. The number eligible for treatment with a NI was small (4 out of 21), as assessed by duration of symptoms at presentation. There was no change in use of single-room accommodation following the diagnosis.
- The median duration of symptoms before admission was 120 hours overall; few admissions were eligible for treatment with an NI as assessed by duration of symptoms.

Diagnostic accuracy

- In comparison with PCR as the 'gold standard', the Quidel POCT had a sensitivity of 24.4% (95% CI 16% to 34.6%), a specificity of 99.7% (95% CI 99.2% to 99.9%), and PPVs and NPVs of 88.0% (95% CI 68.8% to 97.5%) and 94.4% (95% CI 93.0% to 95.7%), respectively.
- In comparison with viral culture as the 'gold standard', the Quidel POCT had a sensitivity of 33.3% (95% CI 14.6% to 57.0%), a specificity of 98.6% (95% CI 97.7% to 99.2%), and PPVs and NPVs of 29.2% (95% CI 12.6% to 51.1%) and 98.8% (95% CI 98.0% to 99.3%), respectively.
- In comparison with PCR as the 'gold standard', viral culture test had a sensitivity of 21.6%, (95% CI 13.5% to 31.6%), a specificity of 99.8% (95% CI 99.4% to 100%), and PPVs and NPVs of 90.5% (95% CI 69.6% to 98.8%) and 94.2% (95% CI 92.7% to 95.4%), respectively.
- In comparison with viral culture as the 'gold standard', PCR had a sensitivity of 90.5%, (95% CI 69.6% to 98.8%), a specificity of 94.2% (95% CI 92.7% to 95.4%), and PPVs and NPVs of 21.6% (95% CI 13.5% to 31.6%) and 99.8% (95% CI 99.4% to 100.0%), respectively.
- In comparison with serology as 'gold standard', PCR had the highest sensitivity (42.6%, 95% CI 28.3% to 57.8%). The sensitivity of viral culture and the Quidel POCT were low in comparison (culture: 13.3%, 95% CI 5.05% to 26.8%; POCT: 14.9%, 95% CI 6.2% to 28.3%).
- In comparison with blood culture as the 'gold standard', the BinaxNOW pneumococcal POCT had a sensitivity of 57.1%, (95% CI 18.4% to 90.1%), a specificity of 92.5% (95% CI 90.6% to 94.1%), and PPVs and NPVs of 5.5% (95% CI 1.5% to 13.4%) and 99.6% (95% CI 99.0% to 99.9%), respectively.
- In comparison with sputum culture as the 'gold standard', the BinaxNOW POCT had a sensitivity of 30.0% (95% CI 6.7% to 65.2%), a specificity of 92.0% (95% CI 88.1% to 95.0%), and PPVs and NPVs of 12.5% (95% CI 2.7% to 32.4%) and 97.2% (95% CI 94.3% to 98.9%), respectively.
- In comparison with blood culture as the 'gold standard', sputum culture had a sensitivity of 100% (95% CI 2.5% to 100%), a specificity of 97.2% (95% CI 94.3% to 98.9%), and PPVs and NPVs of 12.5% (95% CI 0.3% to 52.7%) and 100% (95% CI 98.5% to 100%), respectively.

Systematic review and meta-analysis of point-of-care tests for influenza A and B

- A bivariate mixed-effects meta-analysis model produced an overall estimate of sensitivity of 74% (95% CI 67% to 80%) and specificity of 99% (95% CI 98% to 99%). There was a high level of heterogeneity between the studies for both outcomes.

- Exploration of between-study heterogeneity using bivariate mixed-effects meta-analysis showed that for some subgroup combinations the pooled estimate of sensitivity was considerably lower than that estimated for others:
 - *Age* Sensitivity of POCTs in children and adolescents was 86% (95% CI 75% to 93%) but 67% (95% CI 58% to 75%) in populations of 'mixed' age.
 - *'Gold standard'* Use of PCR as 'gold standard' produced an estimate of sensitivity of 51% (95% CI 38% to 64%), but the estimate of sensitivity was 86% (95% CI 77% to 92%) when virus culture was used as 'gold standard'.
 - *Target virus* Sensitivity of POCTs for diagnosis of seasonal influenza was 84% (95% CI 74% to 90%) but 52% (95% CI 39% to 65%) for diagnosis of infection caused by 2009 pandemic H1N1 virus.
- Comparison of estimates of sensitivity of POCTs produced by different manufacturers indicated that they were broadly similar – Directigen EZ: 85% (95% CI 71% to 93%); BinaxNOW: 69% (95% CI 58% to 79%); Quidel QuickVue: 66% (48–80%).
- Comparison of estimates of sensitivity of POCTs for the detection of influenza A and B suggested that kits may detect influenza A more readily than influenza B – Influenza A: 81% (95% CI 64% to 91%); Influenza B: 59% (95% CI 47% to 70%).
- Analyses of five studies^{152,182,198} that included both adults and children and compared the Quidel POCT with PCR produced an overall pooled sensitivity of 34% (95% CI 14% to 62%) and specificity of 99% (95% CI 97% to 100%), which are much more similar to those obtained in 3WS.

Speed of use

- *Quidel QuickVUE Influenza A&B POCT* The median interval from specimen collection to the provision of a positive or negative result was 15 minutes (IQR 10–23 minutes).
- *BinaxNOW S. pneumoniae test*: The median interval from specimen collection to the provision of a positive or negative result was 20 minutes (IQR 15–30 minutes).
- *Semi-nested multiplex PCR for influenza A subtypes H1 and H3, influenza B, and RSV A and B* The median interval from specimen collection to the provision of a positive or negative result was 50.8 hours (IQR 44.3–92.6 hours).
- *One-step, quadriplex/multiplex, real-time RT-PCR for influenza, and one-step and two-step RSV and hMPV multiplex real-time PCR* The median interval from specimen collection to the provision of a positive or negative result was 29.2 hours (IQR 26–46.9 hours). By 30 hours, results were available for 61.3% of 220 specimens that were tested.
- *Viral culture* The median interval from specimen collection to the provision of a positive result for patients with influenza A or B was 629.6 hours (IQR 262.5–846.7 hours), which is approximately nine times greater than the median time to discharge or death (72.08 hours).
- *Blood culture*: Eighty of the 973 blood cultures grew an organism (including contaminants), and 10 of the 80 grew *S. pneumoniae* with median time of 84.4 hours (IQR 70.7–137.8 hours); a provisional report was issued a median of 36.8 hours (IQR 22.7–48.75 hours) after specimen collection. Seven pneumococcal culture results were reported a median of 53.2 hours (IQR 30.4–58.1 hours) before the patients' discharge. Three others were reported a median of 139.2 hours (IQR 27.9–163.4 hours) after death or discharge. Altogether 619 of 973 (63.6%) admissions were discharged or died before their blood culture results were reported.
- *Sputum culture* The majority (941/1252: 75.2%, 95% CI 72.7% to 77.5%) of admissions with acute cardiopulmonary conditions were unable to produce sputum for culture. In total, 76 of the 296 sputum samples that were of acceptable quality for culture grew an organism; 10 of the 76 grew *S. pneumoniae* after a median interval from specimen collection of 71.4 hours (IQR 69.15–84.0 hours). The median TtR antimicrobial sensitivity was 133 hours (IQR 123.1–148.1 hours) for 8 out of the 10 isolates of *S. pneumoniae*. Altogether 129 of 294 (43.9%) patients were discharged before their sputum cultures were reported.

Ease of use

- A scoring system was devised to compare the EoU of the different tests, based on 11 criteria, each assigned a score of 1, 2 or 3. A high score (maximum possible 33) reflects a high level of complexity, requiring specific expertise, equipment and facilities, etc. A score of '11' identified test procedures as being straightforward and undemanding to use; scores of '12–22' identified tests as being of moderate complexity and requirements; and scores of '23 and higher' as being 'complex'.
- The QuickVUE Influenza A&B POCT and the BinaxNOW *S. pneumoniae* POCT were both rated as straightforward and undemanding to use. Blood culture was rated moderately complex. All other tests were rated as complex, with PCR testing being the most complex.

Process outcomes and cost-effectiveness

- There were no statistically significant differences in the distributions of total costs, or QALYs gained, for the three diagnostic strategy groups, whether based on observed costs and effects, i.e. complete case analysis or after allowing for missing data using MCMC methods.
- Average total NHS costs for the three diagnostic groups are relatively similar to one another (near-patient group, £2159; 'molecular' group £1978; 'traditional' group £2327), with the probability that any one strategy is the least costly not exceeding 79%.
- The overall cost profile of traditional laboratory culture is the most expensive and is associated with the lowest gain in terms of QALYs.
- The 'near-patient' group has the highest gain in terms of QALYs but this gain in QALYs is not offset by its higher cost at current thresholds of willingness to pay, with an ICER of £734,717.
- In terms of cost per correct case of influenza detected, and verified by serology, both PCR and POCTs have lower estimates of cost than traditional laboratory culture but there is considerable uncertainty surrounding each. Overall, the cost per case detected was lowest by PCR.

Conclusions

- The Quidel and BinaxNOW POCTs for influenza A and B and *S. pneumoniae* are straightforward and undemanding, and do not require laboratory facilities.
- The Quidel and BinaxNOW POCTs for influenza A and B and *S. pneumoniae* provide results within minutes. Their speed of use provides opportunities to influence treatment decisions well within the median time to hospital discharge or death.
- As judged by our trial, both the Quidel POCT for influenza A and B and traditional viral culture have low sensitivity when compared with PCR or serology as gold standard.
- Meta-analysis of studies that included both adults and children and compared the Quidel POCT for influenza A and B with PCR produced an overall pooled sensitivity of 34%, which is similar to the observed sensitivity in our clinical trial.
- The PCR tests are considered complex, requiring specialised equipment, reagents and expertise. The median TtR real-time PCR results for influenza A and B (≈ 29 hours) limits the usefulness of PCR in guiding treatment with NIs.
- PCR has greater sensitivity than viral culture or the Quidel POCT for influenza A and B using serology as gold standard.
- Conventional viral culture is demanding, requiring specialist equipment, reagents and skills. The time taken to report positive culture in our study was several-fold longer than the median duration of hospitalisation. Conventional viral culture results cannot provide results soon enough to influence clinical management or control of infection.
- The BinaxNOW pneumococcal POCT has suboptimal sensitivity compared with blood culture. It cannot be used to rule out pneumococcal pneumonia.

- Sputum culture is moderately demanding in terms of test site and expertise. The clinical usefulness of sputum culture is limited by the inability to produce sputum (75% were unable to produce sputum in our study) and TtR positive cultures (median \approx 71 hours for *S. pneumoniae*).
- Blood culture is moderately demanding in terms of equipment, test site and expertise. Blood cultures are often negative when the BinaxNOW pneumococcal POCT is positive. The median times to issuing a provisional report (\approx 37 hours) and identifying the organism as *S. pneumoniae* and its antimicrobial sensitivity (\approx 84 hours) further limit the usefulness of blood culture in guiding antimicrobial therapy.
- All diagnostic tests that we evaluated had limitations, including suboptimal sensitivity, complexity, test requirements, or long turnaround time.
- Few people in our study were admitted within 48 hours of illness onset. Virus shedding declines within days of illness onset, so diagnostic tests for influenza must be done early after illness onset and have very low limits of virus detection.
- Few patients were prescribed NIs. The reason(s) remains speculative but delay between illness onset and admission, the knowledge base of junior doctors (i.e. unfamiliarity with viral diagnostic tests, NIs, and influenza and its complications) and the sensitivity and/or speed of use of the diagnostic tests are likely factors.
- Many patients in this study were febrile on admission suggesting infection as a likely cause. The infrequent use of single-room accommodation across all admissions for acute cardiopulmonary illness (8.9%) and patients with influenza or RSV (11.7%) risks nosocomial transmission of infection.
- We found no evidence that POCTs for influenza or *S. pneumoniae* infection, or PCR tests for influenza A and B and RSV A and B, influenced prescribing of antibiotics or NIs by clinicians providing care, or influenced clinical outcomes (including the duration of fever, requirement for supplemental oxygen, oxygen delivery by CPAP, admissions to ITU, ventilator support, deaths, or duration of hospitalisation) and use of single-room accommodation.
- The total costs and QALYs for each diagnostic strategy were similar, although 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. In terms of cost per correct case of influenza detected, traditional viral culture was the most expensive diagnostic strategy, and PCR was the least expensive.
- Overall, there was a high level of consistency between the different facets of the study. The sensitivity of the Quidel POCT for influenza A and B was low and was in keeping with the results of our meta-analysis when adjustments were made for the 'gold standard', manufacturer and age distribution of those tested. The BinaxNOW pneumococcal test had suboptimal sensitivity that was comparable to sensitivities reported by others. Our study identified other factors that hamper patient care, notably the interval between illness onset and hospital admission, the limited availability of sputum, the infrequency of positive blood and sputum cultures, and the tardiness of individual tests (apart from the POCTs). We found no evidence that diagnostic strategy influenced clinical outcomes, or total costs and QALYs, findings that are consistent with the various limitations outlined above.
- Our studies do not support routine use of POCTs for either influenza or pneumococcal antigen for adults hospitalised with acute cardiopulmonary conditions.
- Our findings support the replacement of traditional viral culture by PCR – for reasons of greater sensitivity, speed, and cost-effectiveness.

Strengths and limitations of the study

Strengths

- Compared with other studies identified in our meta-analysis, the 3WS is one of the largest undertaken on POCTs – only Ruest *et al.*,¹⁵² Nougairède *et al.*¹⁸³ and Lucas *et al.*¹⁴² had larger sample sizes, but clinicians in our study were blind to the nature of tests for clinical management.
- Our study was powered to enable both clinical effectiveness (in terms of length of stay) and diagnostic performance to be evaluated with sufficient power/precision.

- In terms of conduct, the prospective nature of 3WS meant that clinicians were blind to the results of the test strategies to which patients were not randomised. Thus, it enabled an unbiased assessment of the impact of the strategy to which they were randomised on the clinical management of eligible patients.
- The research nurses who carried out the study spent most of their time on the admissions unit of the two hospitals providing care for acute medical admissions. They interacted directly with the teams of doctors and nurses providing initial care for the patient volunteers, particularly when patients were recruited, and also when the results of the POCTs were entered into the case notes and when the patients were followed up. Positive blood culture results were telephoned to the team in the usual manner, and results of microbiological tests were uploaded on to the pathology department results' database when they became available. We ensured that bacteriology and virology results were made available to clinicians as soon as possible. Members of the research team and hospital microbiologists were available to answer any queries regarding the pathogens, the tests and the results of individual tests.

Limitations

- The accuracy study for influenza and pneumococcal infection was limited primarily by the lack of an adequate reference standard. The serological tests for influenza were relatively unhelpful because the period between collection of acute and convalescent sera either coincided with annual vaccination against seasonal influenza or seasonal influenza activity. Blood culture is regarded as the gold standard for pneumococcal infection but cultures are often negative. This impacted on the cost-per-case analysis, and, as such, the findings of this analysis, should be considered exploratory.
- It could be argued that the length of follow-up in 3WS, i.e. 28 days, was insufficient to detect any potential longer term consequences of the diagnostic strategies on the longer-term management and clinical outcomes of these patients. However, given the age distribution and clinical presentation of the patients in 3WS, 28 days should have enabled an appropriate assessment and evaluation of the index admission. The main driver in terms of patient outcome (and in fact of resource use, and therefore cost) was length of stay, and only 53 (4.2%) patient admissions had a length of stay beyond 28 days. The main outcome that further follow-up would have enabled to be assessed was readmission, although as 3WS covered the two acute hospitals in Leicestershire, readmissions pertaining to the index admission would have been identified, and, indeed, of the 1172 unique patients in 3WS, only 67 (5.7%) were readmitted (and rerandomised). Of course, there may have been other patients who were also readmitted but who declined to take any further part in 3WS. It also further brings into question the value of conducting further decision modelling over a longer time horizon, especially given that such an exercise would be dependent upon adequate resource use and outcome beyond that provided by 3WS.
- This study was purposefully carried out during autumn through spring, a period that was specifically selected because it embraced seasonal influenza, RSV activity and the distinct winter seasonality when invasive pneumococcal disease reaches a peak. Clearly, if the study found no benefit from near-patient or molecular diagnostic tests when these pathogens peak (as occurred in this study) then it would be extremely unlikely to be of benefit during the summer months when cases of invasive pneumococcal disease are fewer, and those of RSV and influenza effectively absent. However, had the study shown a clear advantage of either the NPTs, or rapid molecular diagnosis, then there would be uncertainty of the value (both clinical effectiveness and cost-effectiveness) of such a programme when disease activity is much lower.
- The molecular tests that were used in the study evolved during the study and were updated and implemented by a technician with considerable experience in molecular diagnostic tests, with back-up and training from the HPA. Although it could be argued that the time to report the PCR test results could have been shortened with a longer period of embedding the new developments into clinical practice, the complexity and turnaround times of PCR techniques actually decreased throughout the study. It could be argued that the study should have awaited newer developments and reconfiguration of the laboratory, as it is now possible to produce same day results. Indeed, this was implemented

successfully in Leicester during the 2009 H1N1 pandemic; PCR results were available within 6 hours when specimens were delivered to the laboratory by 10 AM.

- Traditional virus culture technology was used as the comparator for PCR and the Quidel Influenza A + B POCT in this study. More rapid cell culture diagnostic techniques have been developed. Their cost, EoU, sensitivity and specificity, and clinical effectiveness and cost-effectiveness were not assessed in this study.
- The cost-effectiveness analysis was subject to a variety of forms of uncertainty. There were a significant number of missing data, which, although allowed for in the MCMC-based analysis, was a concern. However, a series of sensitivity analyses has established that the conclusions of this report are, apparently, robust to both the inherent uncertainty in the data and methodological uncertainty induced by potentially different analytical approaches.

Implications for practice

- Our findings do not support the routine use of POCTs for pneumococcal disease for all acute admissions with acute cardiopulmonary conditions. Indeed, the information provided by the POCT for pneumococcal antigen is considered, on the basis of our results, to be of questionable value even in patients with CAP. We note that at least three investigators have used the results of pneumococcal antigen test (exclusively) prospectively to target narrow-spectrum β -lactam treatment in CAP, with inconsistent results.^{161,239,240} Guchev *et al.*²³⁹ did a non-randomised study that evaluated a targeted approach to antibiotic therapy, based on the results of the pneumococcal urinary antigen test in young military recruits patients with non-severe pneumonia. Twenty-two per cent of patients with CAP had positive urinary tests and all were treated with oral amoxicillin. Treatment failures occurred in 5 out of 48 (10.4%) patients. Falguera *et al.*²⁴⁰ treated 177 patients empirically and then randomised them into two arms when clinically stable; 89 patients were randomised to empiric treatment, and 88 to a target treatment study. Of the 88, 25 had positive urinary antigen tests and 63 had negative tests, i.e. 28.4% of the 88 patients were antigen positive. The 25 patients assigned to targeted treatment showed a statistically significant higher risk of clinical relapse compared with the remaining population (12% vs. 3%, $p = 0.04$). However, Sordé *et al.*¹⁶¹ reduced the spectrum of antibiotics in 41 patients with positive antigen tests; pneumonia was cured in all patients. Factors for further consideration include the proportion of patients with CAP who have *S. pneumoniae* infection, the sensitivity and costs of the test, failure rate of 'optimised' antimicrobial therapy (i.e. step-down treatment) and whether or not the period of hospitalisation is cut by targeted treatment. The BTS, in its 2009 guidelines,¹⁷ recommended pneumococcal antigen testing in all patients with moderate- or high-severity CAP.
- Our findings do not support the routine use of POCTs for influenza A and B throughout winter for adults presenting with acute cardiopulmonary conditions for three main reasons: first, the suboptimal sensitivity of these tests, particularly with the new lineage of H1N1 virus; second, evidence that the majority of patients present with illness duration exceeding 48 hours; and third, the lack of evidence that those identified as influenza positive had any change in treatment or isolation status. However, if further research substantiates preliminary evidence of benefit from NI treatment of patients who begin treatment in hospital > 48 hours after illness onset, there may be a place for using POCTs for influenza A and B in hospitals during periods of heightened influenza activity. The data accrued from our study and the 2009 H1N1 pandemic should facilitate modelling to identify whether this strategy might be cost-effective.
- Our findings on the sensitivity, turnaround times, cost, and EoU of conventional diagnostic virology suggest that this technology should be replaced by PCR. The improved performance of PCR over conventional cell culture technology – in terms of test turnaround times and sensitivity – make PCR the preferred option, but it is acknowledged that PCR technology remains complex and demanding in terms of expertise and resources. We believe that laboratories should invest in developing molecular diagnostic processes and quality systems in preparation for forthcoming automation and molecular 'black box technology'.

- Our research identified as a sizeable problem the number of admissions with febrile acute respiratory illness who are nursed in open wards. This practice is likely to result in nosocomial transmission of influenza and other respiratory viruses that can be life-threatening in people with underlying heart and lung disease. Consideration must be given to one or more of the following: improving the design of future hospitals to include more single-room accommodation; managing single-room accommodation better than now; ensuring that all patients with acute respiratory illness follow 'respiratory etiquette'; and use of quantitative PCR to support the flow of patients between single-roomed accommodation and an open-ward environment.
- We are concerned that current NICE guidance⁷⁰ is based on the results of double-blind RCTs that were designed and powered to establish whether NIs ameliorate symptomatic ILI. These studies were not powered to establish whether NI treatment prevents or ameliorates complications of influenza. Moreover, most RCTs were done in young otherwise healthy people who are not representative of patients who are hospitalised with influenza complications, including acute exacerbations of COPD, asthma, cystic fibrosis or heart failure. Recent publications indicate that (1) NIs may benefit patients when given > 48 hours after illness onset and (2) NIs ameliorate/prevent life-threatening complications. These observations were not generated by RCTs, rather by observational studies and risk being ignored.

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 GP surgeries (or a commercial pharmacy setting) for people at risk of serious complications due to age and chronic ill-health, during declared outbreaks.
4. There is good evidence that influenza virus exacerbates asthma, COPD, cystic fibrosis and is causally associated with CAP 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 include assessments of quantitative viral shedding and biomarkers to evaluate their role in guiding patient management.

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Advice on original proposal:

- Robert George, HPA, Centre for Infections, London.
- Timothy Harrison, HPA, Centre for Infections, London.
- David Turner, Principal Research Fellow in Health Economics, Wessex Institute, University of Southampton, Southampton.

Facilitation of trial recruitment:

- Michael Steiner, University Hospitals of Leicester NHS Trust, Leicester.
- Iain Stephenson, University Hospitals of Leicester NHS Trust, Leicester.

Contribution to laboratory analysis:

- Catherine Thompson, HPA, Centre for Infections, London.

Contribution to the Trial Steering and Data Monitoring Committee:

- Piers Lawford, University Hospitals Coventry and Warwickshire NHS Trust, Respiratory Medicine, Walsgrave Hospital, Coventry.

Design and maintenance of the database:

- Hasnukh Patel, University of Leicester, Leicester.

Help to support the statistical analyses:

- Chris Nelson at the Department of Health Sciences, University of Leicester, Leicester.

Contributions of authors

Karl G Nicholson was jointly responsible for the original proposal. He designed the study, drafted the protocol, contributed to the design of the data collection forms, led the process of integrating the various components into the final draft and drafted the final report.

Keith R Abrams was jointly responsible for the original proposal, for all of the statistical analyses and cost-effectiveness studies, and contributed to the drafting of the final report.

Sally Batham was trial manager and was involved in consent, data collection, patient contact, data entry and management of the research nurses, and contributed to the drafting of the final report.

Marie Jo Medina was responsible for the molecular diagnostics assays, collated data for all laboratory assays and contributed to the drafting of the final report. She also collated the evidence for the systematic review and meta-analysis of the POCTs for influenza.

Fiona C Warren performed statistical analyses regarding patient outcomes and contributed to the drafting of the final report.

Mike Barer was jointly responsible for the original proposal and oversaw the trial accounts.

Alison Bermingham advised on the original proposal and helped establish the multiplex PCR for influenza A and B, and RSV A and B, in Leicester. She also was responsible for the serological tests and interpretation of the results, and contributed to the drafting of the final report.

Tristan W Clark was responsible for coding the spectrum of the antibiotics that were prescribed to patients in this study and calculating the duration of their administration.

Nicholas Latimer advised on the collection/extraction of resource use data, identified unit cost sources and data, and advised on the analysis/reporting of the cost-effectiveness analyses.

Maria Fraser advised on the original proposal and, as consultant virologist at the University Hospitals of Leicester NHS Trust, supervised the virus isolation from clinical samples.

Nelun Perera was responsible for the conventional diagnostic bacteriology and for coordinating medical validation and reporting of laboratory results of conventional diagnostic tests to the clinicians responsible for the care of patients in this study, and contributed to the drafting of the final report.

K Rajakumar helped establish the multiplex PCR for influenza A and B and RSV A and B, in Leicester.

Maria Zambon advised on the original proposal and facilitated the initial transfer of the multiplex PCR to Leicester and the serological tests at the HPA Centre for Infections, Colindale, and contributed to the drafting of the final report.

The report was drafted by Karl Nicholson (principal investigator and Professor of Infectious Diseases), Keith Abrams (Professor of Medical Statistics), Sally Batham (trial manager), Marie Jo Medina, Fiona Warren and Maria Zambon. These authors take responsibility for the content of the report. All authors approved the final draft. Keith Abrams and Karl Nicholson are guarantors for the report.

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Appendix 1 Summary of the protocol for the Three Winters Study

Study protocol

Randomised controlled trial to evaluate 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 18–64-year-olds

Funder ref no. 03/39/18

Principal investigator Professor Karl G Nicholson,
Infectious & Tropical Diseases Unit,
Leicester Royal Infirmary,
Infirmary Square,
Leicester LE1 5WW, England
Telephone – 0116 2586164
Facsimile – 0116 2585067

Date 26/11/2007 Version 6

Protocol synopsis

Title

Randomised controlled trial to evaluate 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 18–64-year-olds.

Sponsor

NHS R&D National Coordinating Centre for Health Technology Assessment.

Study population

Male or female elderly (> 65 years old) patients,

Male or female patients aged > 18 years with underlying heart or lung disease including asthma, or pneumonia/influenza type symptoms.

Study setting

Medical Admissions Units in the University Hospitals of Leicester NHS Trust (Leicester Royal Infirmary, Glenfield Hospital, Leicester General Hospital).

Duration

August 1 2005 – July 31 2008 (36m). Patient enrolment will occur during: September 1 2005 to June 30 2006;

September 1 2006 to June 30 2007; &

September 1 2007 to June 30 2008.

All patients will be followed up for 28 days.

Rationale

The purpose of this study is to determine the diagnostic accuracy and clinical- and cost-effectiveness of rapid molecular and near-patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections in the elderly, and subjects aged > 18 years with chronic cardiopulmonary conditions, or pneumonia/influenza type symptoms, in comparison to traditional laboratory culture.

Objectives and hypotheses

Research objectives

1. To determine the diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) of rapid molecular and near-patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections in comparison to traditional laboratory culture.
2. To assess the potential benefits of ease of use, and speed of rapid molecular and near-patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections, in comparison to traditional laboratory culture.
3. To determine whether rapid molecular and near-patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections have any impact on the prescription of antimicrobials.
4. To determine whether rapid molecular and near-patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections allow more appropriate use of isolation facilities, in comparison to traditional laboratory culture.
5. To compare the costs of performing rapid molecular and near-patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections, in comparison to traditional laboratory culture.
6. To assess cost-savings associated with earlier use of narrow-spectrum antimicrobial therapy (or avoidance or discontinuation of antibiotics) in patients whose influenza, RSV and *S. pneumoniae* infections are diagnosed more rapidly by rapid molecular and near-patient diagnostic tests, in comparison to traditional laboratory culture.
7. To compare the outcome of patients whose influenza, RSV, and *S. pneumoniae* is diagnosed more rapidly by rapid molecular and near-patient diagnostic tests, compared with those who are diagnosed by traditional laboratory culture.
8. To assess the impact that rapid molecular and near-patient diagnostic tests have on the costs associated with an inpatient stay and on costs post-discharge up to a maximum of 28 days after admission.
9. To assess the impact that rapid molecular and near-patient diagnostic tests have on quality-of-life, as measured by the EuroQol, and to use this information to estimate the quality adjusted life years (QALYs) generated during the 28 days after admission.
10. To assess the cost-effectiveness of rapid molecular and near-patient diagnostic tests in comparison to traditional laboratory culture. This will be done on the basis of both cost per case detected and cost per QALY.

Hypotheses

1. The increased diagnostic accuracy of rapid molecular and near-patient tests over traditional laboratory methods improves patient management through better use of antimicrobials and isolation facilities. Rapid molecular and near-patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections are more cost-effective than traditional laboratory diagnostic tests.
2. Rapid molecular and near-patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections provide benefits in terms of (a) ease of use, and (b) more rapid results, in comparison to traditional laboratory culture.
3. Rapid molecular and near-patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections result in earlier use of 'narrow-spectrum' antimicrobial therapy; an earlier switch from intravenous to

oral therapy; and earlier discontinuation of antibiotics in patients infected with influenza and RSV – in comparison to traditional laboratory culture.

4. Rapid detection of influenza and RSV by rapid molecular and near-patient diagnostic tests leads to the appropriate isolation of patients, but only in hospitals/wards having an adequate provision of cubicles.
5. The costs of performing rapid molecular and near-patient diagnostic tests for influenza, RSV and *S. pneumoniae* infections, differ significantly from the cost of traditional laboratory culture.
6. The earlier use of narrow-spectrum antimicrobial therapy (or avoidance or discontinuation of antibiotics) in patients whose influenza, RSV and *S. pneumoniae* infections are diagnosed more rapidly by rapid molecular and near-patient diagnostic tests results in significant cost-savings, in comparison to traditional laboratory culture.
7. A streamlining of antimicrobial prescribing that may arise from more rapid diagnosis of influenza, RSV and *S. pneumoniae* infections by rapid molecular and near-patient diagnostic tests does not adversely affect patient outcome.
8. Any increase in costs incurred by rapid molecular and near-patient diagnostic tests, in comparison to traditional laboratory culture, are more than offset by savings that arise from either rational antimicrobial prescribing or earlier discharge from the hospital.
9. Rapid molecular and near-patient diagnostic tests result in an improvement in quality-of-life, as measured by the EuroQol, which arises from streamlining of antibiotics and earlier discharge into the community.
10. Rapid molecular and near-patient diagnostic tests are more cost-effective than traditional laboratory culture.

Observational objectives

1. To estimate the admission rates for influenza, RSV, and *S. pneumoniae* in the target population.
2. To compare the clinical characteristics and economic burden of influenza A and B and RSV A and B.
3. To review the implications of rapid diagnosis on isolation policy, and review alternate approaches to managing the infection control issues.

Hypotheses (observational)

1. The admission rates in the target population are higher for *S. pneumoniae* than influenza A and B. The admission rates for influenza A and B are similar to those for RSV A and B.
2. The clinical characteristics and economic burden of influenza A and B and RSV A and B are similar.
3. Rapid near-patient and/or molecular diagnostic tests will reveal more cases of influenza and RSV who require isolation than can be isolated. Alternate approaches to managing the infection control issues, such as the use of influenza neuraminidase inhibitors, may be pertinent.

Methodology

Study design

Prospective, randomised controlled trial of the impact of diagnostic testing [(i) Group 1: rapid near-patient diagnostic tests (influenza and pneumococcus), (ii) Group 2: rapid molecular tests (influenza and RSV), plus laboratory pneumococcal antigen testing, and (iii) Group 3: traditional 'laboratory culture' (influenza, RSV, and *S. pneumoniae*)] in elderly (> 65 years) and 'high-risk' patients, who present to Medical Admissions' Units in Leicestershire with an acute cardio-pulmonary illness.

All tests will eventually be done on all patients who enter the study, but patients in Groups 1 and 2 will only be provided with rapid test results relating to their randomisation group.

Number of cases

Elderly Estimated 2752 cases of acute cardio-pulmonary illness in the elderly, of whom 664 will have pneumonia (J12.9-J18.9). An estimated 556 will have unspecified acute lower respiratory tract infections (J22.X). About one third of the pneumonia cases will have *S. pneumoniae* infections ($n = 221$); If ~5% of all acute cardiopulmonary admissions have laboratory-confirmed RSV and ~10% have influenza, then ~138 cases of RSV and ~275 cases of influenza would be studied in the elderly.

High-risk 18- to 64-year-old An estimated 83 cases of pneumonia, with one-third ($n = 28$) having *S. pneumoniae* infections. An estimated 93 cases of unspecified acute lower respiratory tract infections (J22.X); 29 acute unspecified URTI's (J06.9); and 181 cases of COPD. If ~5% of these admissions ($n = 386$) have laboratory-confirmed RSV and ~10% have influenza, then ~19 cases of RSV and ~38 cases of influenza would be studied in 18 to 64 year-old high-risk patients.

Demographic data

- Male or female elderly, aged > 65 years of age.
- Male or female 'high-risk' patients with underlying heart or lung conditions, aged 18 to 64 years of age, or with pneumonia or influenza like symptoms.

Inclusion criteria

- Able and willing to give written informed consent, OR a relative or carer is willing to give written informed assent for patients who are too debilitated to provide consent.
- Age > 65 years, OR age > 18 years with underlying chronic heart or lung disease including asthma; OR with pneumonia or influenza like symptoms.
- Have an acute exacerbation of chronic cardio-pulmonary illness of < 168 hours (7 days) duration, OR an acute cardio-pulmonary illness or influenza-like illness of < 7 days' duration, including:
 - Pneumonia,
 - Influenza/influenza-like illness,
 - Exacerbations of chronic obstructive pulmonary disease (COPD),
 - Bronchitis,
 - Asthma,
 - Congestive heart failure,
 - Cardiac arrhythmia.
- Able and willing to adhere to the procedures stated in the protocol.
- Patients should have access to a telephone.

Exclusion criteria

- Inclusion criteria not met.
- Angina/suspected myocardial infarction.
- Were recruited to this study within 28 days of the current admission.
- Could not be recruited into the study within a **16**-hour period of initial assessment by a doctor on the Medical Admissions Unit or a ward accepting acute medical admissions.
- Enrolment in a study of antimicrobial therapy for the illness for which the patient was admitted.

Randomisation:

Patients in each centre will be randomly allocated to one of three diagnostic policy groups:

- **Group 1:** near-patient tests (Quidel – influenza; BinaxNOW – pneumococcus).
- **Group 2:** rapid molecular tests ('flu & RSV plus laboratory testing of concentrated urine in the BinaxNOW assay); and
- **Group 3:** traditional laboratory culture.

using computer generated randomisation codes stratified by centre.

Assessment methods:**Clinical**

Impact of test result on prescribing, specifically:

- (a) Earlier use of 'narrow-spectrum' anti-microbial therapy.
- (b) Earlier switch from intravenous to oral therapy.
- (c) Avoidance or earlier discontinuation of antibiotics in patients infected with influenza and RSV, and
- (d) Prescriptions of influenza neuraminidase inhibitors.

Will be assessed in rapid near-patient (Group 1) and molecular diagnostic groups (Group 2) and compared with traditional laboratory culture (Group 3).

Clinical outcomes, specifically:

- (a) Length of hospital stay.
- (b) Fever duration.
- (c) Supplemental oxygen dependence and CPAP dependence.
- (d) Admissions to Intensive Care.
- (e) Ventilatory support, and
- (f) Deaths.

Will be assessed in rapid near-patient (Group 1) and molecular diagnostic groups (Group 2) in comparison to traditional laboratory culture (Group 3).

Duration of hospitalisation, until discharge or death, will be obtained from the UHL Leicester hospital activity analysis (i.e. from computerised records).

Fever duration The participants' temperature charts will be monitored during the first 10 days of hospitalisation to identify when they first became afebrile (temperature $< 37.2^{\circ}\text{C}$), and remained so for a period of at least 24 hours.

Supplemental oxygen dependence and CPAP dependence The participants will be monitored during the first 10 days of hospitalisation to identify when they no longer required oxygen for a period of at least 24 hours.

Admission to Intensive care, and Ventilatory support during the first 10 days of hospitalisation will be identified and documented by the study nurse in the Case Report Form.

Deaths that occur within a maximum of 28 days of hospitalisation will be identified and documented by the study nurse in the Case Report Form.

Quality of life, as measured by EuroQol, and quality adjusted life years generated during the 28 days after admission will be assessed in rapid near-patient (Group 1) and molecular diagnostic groups (Group 2) in comparison to traditional laboratory culture (Group 3).

Appropriate use of isolation facilities The time from admission to the Medical Admissions Unit to the time of admission into a single room (isolation cubicle) will be assessed in patients with confirmed influenza and RSV in the rapid near-patient (Group 1) and molecular diagnostic groups (Group 2) in comparison to traditional laboratory culture (Group 3).

The study nurse will document in the CRF where the patient was nursed throughout the first 7 days of admission.

Discharge diagnoses will be obtained from the UHL Leicester hospital activity analysis (i.e. from computerised records).

Financial

Costs of diagnostic tests, estimated by means of an 'ingredients' approach where all items needed to carry out the test are recorded and costed using appropriate local and national data, e.g., items to collect and transport specimens, media and reagents for the test, equipment to process specimens, technical support costs, etc. Costs will be identified for the following technologies:

- (a) Rapid near-patient test for influenza (Quidel).
- (b) Rapid near-patient test for pneumococcus (BinaxNOW).
- (c) Molecular (multiplex PCR) tests for influenza A and B and RSV A and B.
- (d) Culture (blood and sputum) for *S. pneumoniae*.
- (e) Gram staining of sputum samples.
- (f) Cell culture for influenza A and B.
- (g) Cell culture for RSV A and B.
- (h) Other tests that may be applied, e.g. immunofluorescence.

Care costs Cost of inpatient stay will be determined using information on length of stay and hospital costs to determine a 'hotel' cost of routine care. To this will be added the cost of any additional clinical care received such as diagnostic tests, drugs, etc. For patients who are discharged within 28 days of admission, health care resource use in the period after discharge will be recorded using a simple questionnaire administered in a telephone interview. These will be costed using appropriate national data, for example NHS reference costs unit costs compiled by the PSSRU at the University of Kent.

Cost-savings, which accrue from (i) a reduction in the use of resources; and (ii) earlier discharge from the hospital, will be identified by comparison of the costs for participants in Groups 1, and 2, compared with traditional laboratory culture (Group 3).

Economic evaluation of near-patient and rapid molecular diagnostic tests will be assessed by two main outcomes measures –

- (a) cost per case detected.
- (b) cost per QALY.

Laboratory

Diagnostic accuracy, (sensitivity, specificity, positive and negative predictive values) and discrepant analysis of near-patient and molecular diagnostic tests, will be estimated in comparison with traditional and other (e.g., serology) laboratory tests.

Ease of use of rapid near-patient and molecular tests The ease of use of molecular, near patient, and traditional laboratory culture will scored independently by three investigators in terms of whether they can be done:

On site:

- Require special laboratory facilities.
- Require special equipment.
- The number of reagents required.
- The number of steps.
- Ease of disposal/decontamination of used equipment and reagents.
- Technical competency required of the operator.
- Training period required to reliably carry out the test, and any
- Health and safety implications.

Speed of tests will be assessed in terms of the median time from specimen collection to result:

- Appearing in the case notes.
- Appearing on Pathology Department results' database (APEX), and/or
- Being phoned to the ward.
- Being acted upon – in comparison to traditional laboratory culture.

Observational

Admission rates For influenza, RSV, and *S. pneumoniae* in the target population, taking into consideration the total population estimates, stratified by age, and the proportion of all patients by ICD code that were sampled.

Study procedures

Baseline (day 1)

Written informed consent from patient or assent from relative or carer, Inclusion/exclusion criteria,

- Randomisation.
- Basic demography.
- Medical history/regular medication.
- Presenting symptoms and the interval between their onset and admission.
- Clinical findings.
- Quality of Life assessment.
- Investigations ordered by the admitting physicians.
- Specimen collection (blood for antibody tests, sputum, nasopharyngeal specimen, and urine) for trial specific diagnostic tests.
- Rapid near-patient diagnostic testing for influenza & pneumococcus (Group 1) on, or adjacent to, the ward. Results will be delivered to the nursing and/or medical team on the MAU and entered into the case notes. The time when the results were entered into the case notes will be recorded in the patient's CRF together with the results.
- Processing and transport of specimens to the laboratory of diagnostic specimens (Groups 1, 2, 3).
- Antimicrobial and antiviral treatments prescribed/dose/frequency/route.
- Isolation status.
- Information relating to the above activities will be documented in the CRF.

Follow-up (days 2, 3, 4, 5, 6, 7, 8, 9, 10, and 28)

The following will be performed, updated and recorded in the CRF:

- Time when diagnostic tests were made available to the nursing/medical staff.
- Treatment, specifically the relationship between the timing/availability of diagnostic tests and changes in antimicrobial therapy. The nature of treatment given to all patients within 10 days of admission will be documented.
- Isolation, specifically the relationship between the timing/availability of diagnostic tests and changes in isolation status. The isolation status of all patients throughout the first 7 days of admission will be carefully documented.
- Admission to ITU and ventilatory support (within 28 days of hospitalisation).
- Pyrexia – the timepoint when the patient first became afebrile ($< 37.2^{\circ}\text{C}$), and remained so for > 24 hours (during days 1–10).
- Oxygen requirement – the timepoint when supplemental oxygen was no longer required, and was not given for > 24 hours (during days 1–10).
- Diagnostic studies (within 28 days of hospitalisation).
- Duration of hospitalisation.
- Deaths (within 28 days of hospitalisation).
- EuroQol (days 7 and 28).
- Discharge diagnosis.
- Convalescent serum sample (days 10–90).

End points:

Clinical

Impact of test result on prescribing, specifically:

- (a) Time, from admission to MAU, to first administration of 'narrow-spectrum' antibiotics, for patients in Groups 1, 2, and 3, who are prescribed antibiotics.
- (b) Time, from admission to MAU, to first administration of oral antibiotics, for patients in Groups 1, 2, and 3, who are prescribed antibiotics.
- (c) Time (hours) from admission to MAU to prescription of 'no antibiotics' (oral or intravenous) administered to patients in Groups 1, 2, and 3, who have influenza or RSV, and
- (d) Proportion of patients with influenza in Groups 1, 2, and 3 who are prescribed neuraminidase inhibitors.

Clinical outcomes, specifically:

- (a) *Length of hospital stay* until discharge: First, for all patients in Groups 1, 2, and 3. Second, for all patients with (i) influenza; (ii) RSV; and (iii) *S. pneumoniae* infection in Groups 1, 2, and 3.
- (b) *Fever duration* (during the first 10 days of hospitalisation) Time from admission (hours) until the patient first became afebrile (temperature $< 37.2^{\circ}\text{C}$), and remained so for a period of at least 24 hours: First, in all patients in Groups 1, and 2 in comparison to Group 3. Second, in patients with *S. pneumoniae* in Groups 1, and 2, in comparison to Group 3.
- (c) *Supplemental oxygen dependence and CPAP dependence* (during the first 10 days of hospitalisation) Times from admission (hours) until the patient required (i) no supplemental oxygen, and (ii) no CPAP, for a period of at least 24 hours: First, in all patients in Groups 1, and 2 in comparison to Group 3. Second, in patients with *S. pneumoniae* in Groups 1, and 2, in comparison to Group 3.
- (d) *Admissions to Intensive Care* (during the first 10 days of hospitalisation) First, the proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3. Second, to better define the burden of influenza and RSV, the proportion of all patients with (i) influenza, and (ii) RSV who require ITU support.

- (e) *Ventilatory support* (during the first 10 days of hospitalisation): First, the proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3. Second, to better define the burden of influenza and RSV, the proportion of all patients with (i) influenza and (ii) RSV who require ventilatory support.
- (f) *Deaths* (within 28 days of hospitalisation): First, the proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3. Second, to better define the burden of influenza and RSV, the proportion of all patients with (i) influenza, and (ii) RSV, who die.

Quality of life, as measured by EuroQol, and quality adjusted life years generated during the 28 days after admission, will be assessed:

- (a) In all patients in Groups 1, and 2 in comparison to Group 3.
- (b) Second, in patients with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* in Groups 1, and 2, in comparison to Group 3.

Use of isolation facilities:

- (a) The time from admission to the MAU to the time of admission to a single room (isolation cubicle) will be compared for patients with confirmed influenza or RSV in Groups 1, 2, and 3.
- (b) The proportion of patients with influenza or RSV in Groups 1, 2, and 3 who are isolated at any stage during the first 120 hours of the admission.
- (c) The proportion of patients with *S. pneumoniae* infection in Groups 1, 2, and 3 who are inappropriately isolated for > 12 hours.

Financial

Costs of diagnostic tests Costs will be identified for:

- (a) Rapid near-patient test for influenza (Quidel).
- (b) Rapid near-patient test for pneumococcus (BinaxNOW).
- (c) Molecular (multiplex PCR) tests for influenza A and B and RSV A and B.
- (d) Culture (blood and sputum) for *S. pneumoniae*.
- (e) Gram staining of sputum samples.
- (f) Cell culture for influenza A and B.
- (g) Cell culture for RSV A and B.
- (h) Other tests that may be applied, e.g., immunofluorescence.

Care costs of inpatient stay (+95% CI) will be determined for:

- (a) All patients in Groups 1, 2, and 3.
- (b) All patients (in all groups) with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* infection, and,
- (c) Patients with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* infection in Groups 1, 2, and 3.

For patients who are discharged within 28 days of admission, health care resource use in the period after discharge will be recorded using a simple questionnaire administered in a telephone interview or by post.

Cost-savings that accrue from earlier use of narrow-spectrum antibiotics, oral therapy, or avoidance, or discontinuation of antibiotics will be assessed in:

- (a) All patients in Groups 1, 2, and 3.
- (b) Patients with (i) influenza, (ii) RSV, and (iii) *S. pneumoniae* infection in Groups 1, 2, and 3.

Economic evaluation of near-patient and rapid molecular diagnostic tests will be assessed by two main outcomes measures:

- (a) Cost per case detected.
- (b) Cost per QALY.

Laboratory

Diagnostic accuracy:

- (a) Sensitivity.
- (b) Specificity.
- (c) Positive predictive value.
- (d) Negative predictive value.

and discrepant analysis of near-patient and molecular diagnostic tests, will be estimated in comparison with traditional and other (e.g. serology) laboratory tests.

Ease of use of rapid near-patient and molecular tests: molecular, near-patient, and traditional laboratory culture diagnostic tests will be scored independently for ease of use by three investigators.

Speed of tests will be assessed in terms of the median time from specimen collection to result:

- (a) Appearing in the case-notes.
- (b) Appearing on Pathology Department results' database (APEX).
- (c) Being phoned to the ward.
- (d) Being acted upon – in comparison to traditional laboratory culture.

Speed of tests will be determined for –

- (a) All patients in Groups 1, 2, and 3.
- (b) Patients with influenza; RSV, and *S. pneumoniae* infection in Groups 1, 2, and 3.

Observational

Admission rates, for:

- (a) Influenza.
- (b) RSV, and
- (c) *S. pneumoniae*.

Analysis

Sample size

The sample size is based on the admissions during 2002–03 and 2003–04 (September 1 – April 30) for elderly (> 65 years old) patients with acute cardio-pulmonary conditions, excluding angina and myocardial infarction. There were 2762 acute cardio-pulmonary admissions during September 1 – April 30 2002–03, and 2852 during 2003–04, i.e. an average of 11.57 admissions (> 65 years) per day.

The study will run for at 666 days (242 during each of Years 1 and 2, and 183 during Year 3), i.e. the number of eligible patients is estimated at $666 \times 11.57 = 7705.6$. We plan to recruit 5 days per week, which reduces the eligible number of patients to $(5 \div 7) \times 7705.6 = 5504$. We understand that two-thirds are admitted during the period 09:00–21:00h, which reduces the evaluable pool to 3669. We estimate that three-quarters of eligible subjects will participate, i.e. we expect to recruit 2752 elderly (> 65 years old) patients with acute cardio-pulmonary conditions. Of these, 664 are expected to have ICD codes for pneumonia; 556 are expected to have unspecified acute lower respiratory tract infections; 683 are expected to have exacerbations of chronic obstructive pulmonary disease; and 735 are expected to be admitted with heart failure.

We estimated the number of admissions in 'high-risk' 18–64 year-olds by extrapolation using (i) national cardio-pulmonary hospital admission data for patients aged 15–59 years, 60–74 years, and 75 years and older and (ii) the number of cardio-pulmonary admissions aged > 65 years in Leicester.

We assumed that half of the patients admitted with pneumonia, unspecified lower respiratory tract infections, and exacerbations of COPD have underlying high-risk conditions. We expect to recruit 83 18–64-year old patients with pneumonia, 93 with unspecified lower respiratory tract infections, and 181 with COPD. These have not been included in the following estimates:

On the basis of historical data we expect that one-third of elderly patients with pneumonia have pneumococcal disease (i.e. 221) but expect the number identified by the pneumococcal antigen test to be higher. Of the 221, ~73 should be randomly allocated to the rapid near-patient test (BinaxNOW) (Group 1); the remainder will be randomised to the group tested by traditional methods (Groups 2 & 3). However, as identical sample sets will be taken from each individual, diagnostic accuracy will be assessed in a minimum of 221 subjects.

We expect that 10% of the 2752 (elderly) patients will have influenza A or B. Of the 275, one third (~91) will be allocated to Groups 1, 2, and 3. Identical sample sets will be taken from each individual, so the diagnostic accuracy of the tests will be assessed in all 275 subjects.

We expect that 5% of the 2752 (elderly) patients will have RSV A or B. Of the 137, one third (~45) will be allocated to the rapid molecular group (Group 2); the remainder (~90) will be allocated to the groups tested by traditional methods (Group 1 & 3). Identical sample sets will be taken from each individual, so the diagnostic accuracy of the tests will be assessed in all 137 subjects.

While the numbers of patients with influenza and RSV who are allocated to the 'rapid' near-patient or molecular tests are comparatively small, the impact of a 'viral' infection (RSV or influenza) infection on patient isolation, antimicrobial prescribing, and clinical outcomes may be compared using larger combined groups – i.e., rapid influenza & RSV (i.e. Quickview + molecular tests) $n = (91 + 91 + 45) = 227$ traditional influenza & RSV $n = (91 + 45 + 45) = 182$.

Statistical power:

This has been estimated for one laboratory and two clinical end points for the elderly population only.

Diagnostic accuracy

Assuming that the average sensitivity/specificity of the tests is 80%[90%] then allowing for a 20% dropout rate, a sample of 2752 (2000) i.e. only 2 winters) elderly (> 65 years) patients randomised into the trial would enable the sensitivity/specificity to be estimated to within, i.e. 2SE, 7.6% (8.9%) [5.7% (6.7%)] for a disease prevalence of 10%, and 5.4% (6.3%) [4.0% (4.7%)] for a disease prevalence of 5%.

Length of stay

2752 patients would enable a Minimum Clinically Significant Difference (MCSD) [between diagnostic policies] of 1 day in the mean length of stay (assuming SD = 6 days) to be detected at the 5% significance level with over 80% power, assuming a 20% dropout rate and adjusting for the fact that there are 3 groups.

Appropriate isolation levels: 2752 patients would also enable a Minimum Clinically Significant Difference (MCSD) [between diagnostic policies] of an improvement in appropriate use of isolation facilities from 5% to 15% to be detected at the 1% significance level with over 95% power, assuming a 20% dropout rate and adjusting for the fact that there are 3 groups.

Statistical methods:

All analyses for both process and clinical outcomes will be based on Intention to Treat (ITT) analyses.

Impact of test result on prescribing

The time to prescription of 'narrow spectrum', 'oral antibiotics' or 'no antibiotics' between the three groups will be assessed using survival analysis techniques, whilst the use of neuraminidase inhibitors in those with influenza will be assessed using chi-squared tests, together with 95% CIs. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of Cox proportional hazards regression modelling in the case of time to appropriate prescribing and logistic regression techniques in the case of neuraminidase inhibitors.

Length of hospital stay

Length of hospital stay in the three diagnostic groups will initially be compared using non-parametric methods. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of generalised linear models in order to accommodate any skewness in the data.

Mortality rates

Mortality rates between the three diagnostic testing groups will be compared by means of a Log-Rank Test and Kaplan–Meier survival curves. Adjustment for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of Cox proportional hazards regression methods.

Diagnostic accuracy

Sensitivity, specificity, positive and negative predictive values of molecular and near-patient diagnostic tests in comparison to traditional laboratory methods will be calculated together with 95% CIs. Heterogeneity in the sensitivity and specificity with respect to patient demographics and baseline clinical characteristics will be explored as secondary analyses using patient defined sub-groups.

Admission to Intensive Care

The proportions of patients in the three groups who are admitted to intensive care within the first 10 days of admission will be compared using chi-squared tests, together with 95% CIs. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of logistic regression techniques.

Ventilatory support

The proportions of patients in the three groups who receive ventilatory support within the first 10 days of admission will be compared using chi-squared tests, together with 95% CIs. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of logistic regression techniques.

Appropriate use of isolation facilities

In patients with confirmed influenza or RSV the time taken from admission to the MAU to admission to a single room (isolation cubicle) will be compared between the three diagnostic groups by means of a Log-Rank Test and Kaplan–Meier survival curves. Adjustment for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of Cox proportional hazards regression methods.

Quality of life (EQ-5D)

Quality of life in the three diagnostic groups will initially be compared using non-parametric methods. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of generalised linear models in order to accommodate any skewness in the data.

Speed of tests

Time taken to receive test results in the three diagnostic groups will initially be compared using non-parametric methods. Further analyses to allow for potential differences in patient demographics and baseline clinical characteristics between the three diagnostic test groups, and not allowed by stratification, will make use of generalised linear models in order to accommodate any skewness in the data.

Cost data

Cost data will be analysed using parametric and non-parametric statistical methods which explicitly allow for the censoring of (indirect & total) costs at 28 days, i.e. for those patients who are not discharged from hospital within 28 days and thus enable an unbiased assessment of potential cost differences between the three diagnostic groups to be made. Estimation of the cost distribution over longer timescales will make use of extrapolation techniques using time of discharge obtained from hospital information systems.

Trial plan and schedule of assessment

Assessments	Study day		
	Admission (day 1)	Days 2, 3, 4, 7 (± 1), & 10 (± 1)	Day 28 (± 2)
Pre-study assessment by admitting medical team	✓		
Note time of admission (CRF)	✓		
Inclusion/Exclusion criteria check (CRF)	✓		
Written informed Consent (or Assent) (CRF)	✓	✓ (Consent upon recovery)	
Demography/immunisation status check (CRF)	✓		
Medical history/concomitant medications check (CRF)	✓		
Symptom assessment (CRF)	✓		
Clinical findings, including body weight and temperature (CRF). Establish when patient first becomes apyrexial ($\leq 37.2^{\circ}\text{C}$), requires supplemental O_2 , and remains so for > 24 hours (CRF)	✓	✓ (temperature, O_2)	
EuroQol. Quality of Life assessment (CRF)	✓	✓ (day 7)	✓
Diagnostic studies ordered by the admitting medical team (CRF)	✓	✓	
Collection of trial specific diagnostic specimens (CRF):			
Nasopharyngeal (Quidel & virus culture)	✓		
Sputum (Gram stain & culture)	✓		
Urine (BinaxNOW)	✓		
Blood (Blood cultures, serum antibodies)	✓	✓ (antibody, day 10)	
Record time when diagnostic test results were made available to the ward nurses, and/or admitting team (CRF)	✓	✓	
Record antimicrobials & antivirals (identity, route, dose, time of administration) prescribed by admitting medical team (CRF)	✓		
Note the time of any changes in antimicrobials & antivirals (identity, route, dose, time of administration) prescribed by admitting medical team (CRF)		✓	
Bed location, i.e., record bay or a single room (CRF)	✓		
Note time of any subsequent change in isolation status (CRF)		✓	
ITU and ventilatory support: Document whether admitted or required ventilatory support (CRF)	✓	✓	
Date of hospital discharge/Death within 28 days of admission (CRF)		✓	✓
Discharge diagnosis (CRF)		✓	✓
Note: Patients <u>WILL NOT</u> be rerecruited if readmission occurs during the 28-day follow-up.			

Appendix 2 BinaxNOW pneumococcal antigen test



INTENDED USE

The Binax NOW® *Streptococcus pneumoniae* Test is an *in vitro* rapid immunochromatographic (ICT) assay for the detection of *Streptococcus pneumoniae* (*S. pneumoniae*) antigen in the urine of patients with pneumonia and in the cerebrospinal fluid (CSF) of patients with meningitis. It is intended, in conjunction with culture and other methods, to aid in the diagnosis of both pneumococcal pneumonia and pneumococcal meningitis.

SUMMARY AND EXPLANATION OF THE TEST

S. pneumoniae is the leading cause of community-acquired pneumonia and may be the most important agent in community-acquired pneumonia of unknown etiology.^{1,2} Pneumococcal pneumonia has a mortality rate as high as 30%, depending on bacteraemia, age, and underlying diseases.^{1,2} When not properly diagnosed and treated, *S. pneumoniae* infection can lead to bacteraemia, meningitis, pericarditis, empyema, purpura fulminans, endocarditis and/or arthritis.^{4,5}

Pneumococcal meningitis, a condition that frequently leads to permanent brain damage or death, can occur as a complication of other pneumococcal infection or may arise spontaneously without any preceding illness.⁶ It affects persons of all ages, but is most common in children under 5 years, teenagers and young adults, and in the elderly.⁷ Progression from mild illness to coma can occur within hours, making immediate diagnosis and antimicrobial treatment critical. Twenty to thirty percent of all pneumococcal meningitis patients will die, often despite several days of appropriate antibiotic treatment.⁶ Mortality is even higher among very young and very old patients.⁶

The BinaxNOW® *Streptococcus pneumoniae* Test provides a simple, rapid method for the diagnosis of pneumococcal pneumonia using a urine sample that is conveniently collected, stored and transported. It also provides an immediate and highly accurate diagnosis of pneumococcal meningitis when CSF is tested.

PRINCIPLES OF THE PROCEDURE

The BinaxNOW® *Streptococcus pneumoniae* Test is an immunochromatographic membrane assay used to detect pneumococcal soluble antigen in human urine and CSF. Rabbit anti-*S. pneumoniae* antibody, the Sample Line, is adsorbed onto nitrocellulose membrane. Control antibody is adsorbed onto the same membrane as a second stripe. Both rabbit anti-*S. pneumoniae* and anti-species antibodies

are conjugated to visualizing particles that are dried onto an inert fibrous support. The resulting conjugate pad and the striped membrane are combined to construct the test strip. This test strip and a well to hold the swab specimen are mounted on opposite sides of a hinged, book-shaped test device.

To perform the test (U.S. Patent Nos: 6,017,767; 6,548,309; 6,824,997), a swab is dipped into the specimen (either urine or CSF), removed, and then inserted into the test device. Reagent A, a buffer solution, is added from a dropper bottle. The device is then closed, bringing the sample into contact with the test strip. Pneumococcal antigen present in the sample reacts to bind anti-*S. pneumoniae* conjugated antibody. The resulting antigen-conjugate complexes are captured by immobilized anti-*S. pneumoniae* antibody, forming the Sample Line. Immobilized control antibody captures anti-species conjugate, forming the Control Line.

Test results are interpreted by the presence or absence of visually detectable pink-to-purple colored lines. A positive test result, read in 15 minutes depending on the concentration of antigen present in the specimen, will include the detection of both a Sample and a Control Line. A negative test result, read in 15 minutes, will produce only a Control Line, indicating that *S. pneumoniae* antigen was not detected in the sample. Failure of the Control Line to appear, whether the Sample Line is present or not, indicates an invalid assay.

REAGENTS AND MATERIALS

Materials Provided

Refer to illustration on pull-out flap.

1 Test Devices: A membrane coated with rabbit antibody specific for *S. pneumoniae* antigen and with control antibody is combined with rabbit anti-*S. pneumoniae* antigen and anti-species conjugates in a hinged test device.

2 Reagent A: Citrate / Phosphate buffer with sodium lauryl sulfate, Tween® 20, and sodium azide.

3 Sample Swabs: Designed for use in the BinaxNOW® *Streptococcus pneumoniae* Test. **Do not use other swabs.**

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4 Positive Control Swab: Inactivated *S. pneumoniae* antigen dried onto swab.

5 Negative Control Swab: *S. pneumoniae* negative swab.

Materials Not Provided

Clock, timer, or stopwatch; standard urine collection containers, or CSF transport tubes

Accessory Item

BinaxNOW® *Streptococcus pneumoniae* Test Control Swab Pack (catalog number 710-010) containing 5 positive and 5 negative control swabs.

PRECAUTIONS

Control swabs require six (6) drops of Reagent A. Patient specimens require three (3) drops of Reagent A.

1. INVALID RESULTS: Indicated by no Control Line, can occur when an insufficient volume of Reagent A is added to the test device. To ensure delivery of an adequate volume, hold vial vertically, ½ - 1 inch above the swab well, and slowly add free falling drops.

2. For *in vitro* diagnostic use.

3. The test device is sealed in a protective foil pouch. Do not use if pouch is damaged or open. Remove test device from pouch just prior to use. Do not touch the reaction area of the test device.

4. Do not use kit past its expiration date.

5. Do not mix components from different kit lots.

6. Swabs in this kit are approved for use in the BinaxNOW® Test. Do not use other swabs.

7. Solutions used to make the control swabs are inactivated using standard methods. However, patient samples, controls, and test devices should be handled as though they could transmit disease. Observe established precautions against microbial hazards.

8. Clean catch urine is not necessary for the BinaxNOW® Test. Therefore, urine specimens used for this test may not be appropriate for bacteriological culture.

9. Once the Binax swab is dipped into CSF specimen, the sample is no longer sterile and may not be appropriate for culture. If CSF specimen will be cultured, either perform culture first or split CSF sample.

STORAGE AND STABILITY

Store kit at room temperature (59-86°F, 15-30°C). The BinaxNOW® *Streptococcus pneumoniae* test kit and reagents are stable until the expiration dates marked on their outer packaging and containers. Do not use the kit beyond its labeled expiration date.

SPECIMEN COLLECTION

Allow all specimens to equilibrate to room temperature (59-86°F, 15-30°C) before testing in the BinaxNOW® *Streptococcus pneumoniae* Test. Just before testing, mix specimen by swirling gently.

URINE (for diagnosis of pneumonia)

Collect urine specimens in standard containers. Store at room temperature (59-86°F, 15-30°C) if assayed within 24 hours of collection. Alternatively, store urine at 2-8°C, or frozen for up to 14 days, before testing. Boric acid may be used as a preservative.

When necessary, ship urine specimens in leakproof containers at 2-8°C or frozen.

CSF (for diagnosis of meningitis)

Collect CSF according to standard procedures and store at room temperature (59-86°F, 15-30°C) for up to 24 hours before testing. Alternatively, properly collected CSF may be refrigerated (2-8°C) or frozen (-20°C) for up to 1 week before testing.

QUALITY CONTROL

Daily Quality Control:

The BinaxNOW® *Streptococcus pneumoniae* Test contains built-in positive and negative procedural controls. The manufacturer's minimum recommendation for daily quality control is to document these procedural controls for the first sample tested each day.

Positive Procedural Control

The pink-to-purple line at the "Control" position can be considered an internal positive procedural control. If capillary flow has occurred and the

functional integrity of the device was maintained, this line will always appear.

Negative Procedural Control

The clearing of background color in the result window provides a negative background control. The background color in the window should be light pink to white within 15 minutes and should not interfere with the reading of the test result.

External Positive and Negative Controls:

Good laboratory practice recommends the use of positive and negative controls to assure functionality of reagents and proper performance of assay procedure. Positive Control Swabs and Negative Control Swabs that will monitor the entire assay are provided in the test kits and should be tested using the Control Swab procedure. Controls should be tested once with each test kit opened, and as otherwise required by your laboratory's standard Quality Control procedures. Additional controls may be tested according to the requirements of local, state and/or federal regulations or of accrediting organizations.

If expected control results are not obtained, do not report patient results. Review the procedure and repeat control testing or contact Inverness Medical.

CONTROL SWAB PROCEDURE Binax NOW® Swab Controls

NOTE: Use 6 drops of Reagent A for Control Swabs.

1. Remove device from the pouch **just before use**. Lay device flat.
2. There are two holes on the inner right panel of the device. Insert swab into the **BOTTOM** hole. Firmly push upwards so that the swab tip is fully visible in the top hole. **DO NOT REMOVE SWAB**.
3. Hold Reagent A vial vertically, 1/2 to 1 inch above the device. Slowly add **six (6)** free falling drops of Reagent A to the **BOTTOM** hole.
4. Immediately peel off adhesive liner from the right edge of the test device. Close and securely seal the device. Read result in window 15 minutes after closing the device. Results read beyond 15 minutes may be inaccurate. However, the Positive Control Swab sample line may be visible in less than 15 minutes.

TEST PROCEDURE

Urine Samples, CSF Samples and Liquid Controls

Use a **URINE** sample when testing for **PNEUMOCOCCAL PNEUMONIA** and a **CSF** sample when testing for **PNEUMOCOCCAL MENINGITIS**.

NOTE: Use 3 drops of Reagent A when testing liquid samples. Refer to illustration on pull-out flap.

1. Bring patient sample(s) and/or liquid control(s) to room temperature (59-86°F, 15-30°C), then swirl gently to mix. Remove device from its pouch **just before use** and lay flat.
2. Dip a Binax swab into the sample to be tested, completely covering the swab head. If the swab drips, touch swab to side of collection container to remove excess liquid.
3. There are two holes on the inner right panel of the device. Insert swab into the **BOTTOM** hole (swab well). Firmly push upwards so that the swab tip is fully visible in the top hole. **DO NOT REMOVE SWAB**.
4. Hold Reagent A vial vertically, 1/2 to 1 inch above the device. Slowly add **three (3)** free falling drops of Reagent A to the **BOTTOM** hole.
5. Immediately peel off adhesive liner from the right edge of the test device. Close and securely seal the device. Read result in window 15 minutes after closing the device. Results read beyond 15 minutes may be inaccurate. However, some positive patients may produce a visible sample line in less than 15 minutes.

NOTE: For convenience, the swab shaft has been scored and may be snapped off **after** closing the device. Avoid dislodging the swab from the well when doing so.

INTERPRETATION OF RESULTS

A **negative sample** will give a single pink-to-purple colored Control Line in the top half of the window, indicating a presumptive negative result. This Control Line means that the detection part of the test was done correctly, but no *S. pneumoniae* antigen was detected.

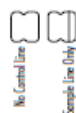


Pink Control Line

A **positive sample** will give two pink-to-purple colored lines. This means that antigen was detected. Specimens with low levels of antigen may give a faint patient line. **Any visible line is positive.**



If no lines are seen, or if just the Sample Line is seen, the assay is **invalid**. Invalid tests should be repeated.



REPORTING OF RESULT

Recommended Report

Result

Positive Urine Positive for pneumococcal pneumonia.

Negative Urine Presumptive negative for pneumococcal pneumonia, suggesting no current or recent pneumococcal infection. Infection due to *S. pneumoniae* cannot be ruled out since the antigen present in the sample may be below the detection limit of the test.

Positive CSF Negative CSF

Positive for pneumococcal meningitis.

Presumptive negative for pneumococcal meningitis. Infection due to *S. pneumoniae* cannot be ruled out since the antigen present in the sample may be below the detection limit of the test.

LIMITATIONS

The BinaxNOW® Streptococcus pneumoniae Test has been validated using urine and CSF samples only. Other samples (e.g. plasma or other body fluids) that may contain *S. pneumoniae* antigen have not been evaluated.

A negative BinaxNOW® Test does not exclude infection with *S. pneumoniae*. Therefore, the results of this test as well as culture results, serology or other antigen detection methods should be used in conjunction with clinical findings to make an accurate diagnosis.

The BinaxNOW® Streptococcus pneumoniae Test has not been evaluated on patients taking antibiotics for greater than 24 hours or on patients who have

recently completed an antibiotic regimen. The effects of over-the-counter drugs have not been determined on persons with pneumococcal meningitis.

Streptococcus pneumoniae vaccine may cause false positive results in urine in the BinaxNOW® Streptococcus pneumoniae Test in the 48 hours following vaccination. The effect of vaccination has not been determined on persons with pneumococcal meningitis. Hence, it is recommended that the BinaxNOW® Streptococcus pneumoniae Test not be administered within 5 days of receiving the *S. pneumoniae* vaccine.

The accuracy of the BinaxNOW® Test in urine has not been proven in young children. Performance on CSF in young children, on the other hand, is established (See Performance Data - CSF).

PERFORMANCE DATA - URINE

ANALYTICAL SENSITIVITY

Serotype Evaluation

Forty-four (44) isolates, representing the 23 *S. pneumoniae* serotypes responsible for at least 90% of serious pneumococcal infection in the United States and worldwide, were grown in culture and found to be positive in the BinaxNOW® Test at concentrations of 10^5 cells/mL.

Limit of Detection

The BinaxNOW® Test limit of detection (LOD), defined as the dilution of positive urine that produces positive BinaxNOW® Test results approximately 95% of the time, was identified by preparing multiple dilutions of a known positive patient urine and running these dilutions in the BinaxNOW® Test.

Five (5) different operators each interpreted 20-40 devices run at each dilution for a total of 100-200 determinations per dilution. The following results identify a 1:250 dilution of this particular patient urine as the BinaxNOW® Test LOD.

Urine Dilution	Positive Results per Devices Run	Overall Detection
1:200	100/100	100%
1:250	95/100	95%
1:300	160/200	80%
1:400	44/100	44%
1:600	8/100	8%

CLINICAL SENSITIVITY AND SPECIFICITY (Retrospective Study)

As part of the retrospective study, urine specimens from 35 blood culture positive pneumococcal pneumonia patients and 338 presumed *S. pneumoniae* negative patients (373 total patients) were collected at 3 different facilities and evaluated in the BinaxNOW® Test. BinaxNOW® Test performance was calculated using standard methods. Sensitivity was 86%, specificity was 94%, and overall accuracy was 93%. Ninety-five percent (95%) confidence intervals are listed below.

BinaxNOW® Result	Blood Culture	
	+	-
+	30	21
-	5	317
Sensitivity	= 86% (71% - 94%)	
Specificity	= 94% (91% - 96%)	
Accuracy	= 93% (90% - 95%)	

CLINICAL SENSITIVITY AND SPECIFICITY (Prospective Study)

In a separate seven-center prospective study, the BinaxNOW® Test was used to evaluate urine specimens collected from 215 hospitalized and outpatients presenting with lower respiratory symptoms or sepsis and from patients otherwise suspected of pneumococcal pneumonia. Patients were considered positive for pneumococcal pneumonia if diagnosed by positive blood culture.

The BinaxNOW® Test performed equivalently on both outpatients and hospitalized patients. Ninety-five percent (95%) confidence intervals are listed below.

Outpatient Performance Blood Culture

BinaxNOW® Result	+		-	
	+	-	+	-
	19	25	2	90
Sensitivity	= 90% (70% - 97%)			
Specificity	= 78% (70% - 85%)			
Accuracy	= 80% (72% - 86%)			

Hospitalized Patient Performance Blood Culture

BinaxNOW® Result	+		-	
	+	-	+	-
	9	20	1	49
Sensitivity	= 90% (60% - 98%)			
Specificity	= 71% (59% - 80%)			
Accuracy	= 73% (62% - 82%)			

CROSS-REACTIVITY

Urine Testing

Two hundred seventy (270) different organisms were isolated from the 338 negative patients tested as part of the above retrospective study. Of the 165 organisms isolated from patients with urinary tract infections, 15 (9%) produced positive results. These were 2/2 *Enterobacter cloacae*, 1/2 *Staphylococcus aureus*, 1/1 *Streptococcus* (non A,B), 1/1 *Streptococcus* (non D), 1/17 *Streptococcus* (Group D), 1/3 *Providencia stuartii*, 5/78 *Escherichia coli* and 3 with no identified pathogen. Of the 59 organisms isolated from patients with pneumonia, 3 (5%) were positive, including 1/3 *Mycobacterium kansasii* and 2/15 *Mycobacterium tuberculosis*. One of the 41 (2%) organisms isolated from bacteremic patients, *Proteus mirabilis*, was positive. There was no cross-reactivity with the 5 enteric isolates. Lastly, 4/100 urine specimens collected from people with no known infection were positive.

Due to the retrospective nature of this study, only a limited number of patients with each infection were available for testing and the complete clinical history of each is not known. Therefore, the presence of *S. pneumoniae* co-infection cannot

be ruled out. When tested in pure culture (data below), these organisms do not cross-react in the BinaxNOW® Test.

Whole Organism Testing

To determine the analytical specificity of the BinaxNOW® Test, a panel of 144 potential cross-reactants was compiled, including organisms associated with pneumonia and those likely to be found in the urogenital tract as normal flora or as a result of urinary tract infection. All were evaluated in the BinaxNOW® Test at concentrations of 10^6 to 10^7 CFU/mL. The BinaxNOW® Test does not cross-react with 143 of the 144 organisms. The single positive organism, *Streptococcus mitis*, is an expected cross-reactant as it shares the antigen against which the BinaxNOW® Test is directed. *Streptococcus mitis* is associated with endocarditis, not pneumonia, and is not likely to appear with any frequency in the population intended to be tested with the BinaxNOW® Test.¹ The following organisms were tested and produced negative results. When more than one strain was tested, the number is listed in parentheses.

<i>Aerobacter</i> sp. (4)	<i>Haemophilus parainfluenzae</i>
<i>Adenovirus</i> ® (283 pooled)	<i>Histoplasma capsulatum</i> ® (2)
<i>Alcaligenes faecalis</i>	<i>Klebsiella oxytoca</i> (2)
<i>Bacillus subtilis</i>	<i>Klebsiella pneumoniae</i> (3)
<i>Blastomyces dermatitidis</i> ®	<i>Lactobacillus</i> sp. (5)
<i>Bordetella pertussis</i>	<i>Legionella pneumophila</i>
<i>Burkholderia caryophylli</i>	<i>Listeria monocytogenes</i>
<i>Candida albicans</i> (3)	<i>Mitococcus luteus</i> (2)
<i>Candida stellatoidea</i>	<i>Moraxella osloensis</i>
<i>Coccidioides immitis</i> ®	<i>Morganella morganii</i>
<i>Corynebacterium</i> sp. (3)	<i>Mycobacterium kansasii</i>
<i>Enterobacter cloacae</i> (4)	<i>Mycobacterium tuberculosis</i>
<i>Enterococcus avium</i> ◆◆	<i>Mycoplasma</i> sp. (3)
<i>Enterococcus durans</i> ◆◆	<i>Neisseria cinerea</i>
<i>Enterococcus faecalis</i> ◆◆ (6)	<i>Neisseria gonorrhoeae</i> (3)
<i>Escherichia coli</i> (8)	<i>Neisseria lactamica</i>
<i>Escherichia coli</i> (2)	<i>Neisseria meningitidis</i>
<i>Flavobacterium</i> sp. (2)	<i>Neisseria polysacchara</i>
<i>Gardnerella vaginalis</i>	<i>Neisseria subflava</i>
<i>Haemophilus influenzae</i> (10)	<i>Neisseria farcinia</i> ®
(types of & nontypeable)	<i>Paracoccidioides brasiliensis</i> ®

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<i>Parainfluenzae</i> ® (2)	<i>Stenotrophomonas maltophilia</i> ◆◆
<i>Proteus mirabilis</i> (2)	<i>Streptococcus anginosus</i> ◆◆
<i>Proteus vulgaris</i> (2)	<i>Streptococcus bovis</i> ◆◆
<i>Providencia stuartii</i>	<i>Streptococcus Group A</i> ◆◆ (2)
<i>Pseudomonas</i> sp. (7)	<i>Streptococcus Group B</i> ◆◆ (8)
<i>Respiratory Syncytial Virus</i> ®	<i>Streptococcus Group C</i> ◆◆
<i>Rhinovirus</i> ®	<i>Streptococcus Group F</i> ◆◆
<i>Serratia</i> sp. (4)	<i>Streptococcus Group G</i> ◆◆
<i>Serratia marcescens</i>	<i>Streptococcus mutans</i> ◆◆
<i>Shigella sonnei</i>	<i>Streptococcus parangauis</i> ◆◆
<i>Staphylococcus aureus</i> (6)	<i>Streptococcus sanguis</i> ◆◆
<i>Staphylococcus</i> sp. (8)	<i>Trichomonas vaginalis</i> (2)

* Pure cultures from CDC believed to be in high concentration.

- ◆ *Streptococcus* Non A, B (Total number of strains is 16)
- ◆ *Streptococcus* Non D (Total number of strains is 17)

INTERFERING SUBSTANCES

Urine specimens with elevated white blood cells (including loaded per low power field), red blood cells* (including loaded per low power field), protein (including 500 mg/dL), glucose (including >2000 mg/dL), and turbidity (including turbid) were evaluated in the BinaxNOW® *Streptococcus pneumoniae* Test and found not to affect test performance.

*Note that one urine with elevated red blood cells produced an invalid result due to extreme coloration of the test membrane which masked line development.

REPRODUCIBILITY STUDY

A blind study of the BinaxNOW® *Streptococcus pneumoniae* Test was conducted at 3 separate point of care settings using a panel of blind coded specimens containing negative, low positive, moderate positive, and high positive samples. Specimens both with and without bovine acid were tested. Participants tested each sample multiple times on 3 different days. Three hundred fifty-seven (357) of the 359 total samples tested (99.4%) produced the expected result.

PERFORMANCE DATA - CSF

ANALYTICAL SENSITIVITY

Limit of Detection

The BinaxNOW® Test limit of detection (LOD) was identified by testing multiple *S. pneumoniae* dilutions in the BinaxNOW® Test.

Ten (10) different operators each interpreted 10 devices run at each dilution for a total of 100 determinations per dilution. The following results identify 5×10^4 cells per milliliter as the BinaxNOW® Test LOD.

Concentration of <i>S. pneumoniae</i>	Positive Results per Devices Run	Overall Detection
7.5×10^4 cells/ml	100/100	100%
5×10^4 cells/ml	100/100	100%
3×10^4 cells/ml	91/100	91%
1.5×10^4 cells/ml	44/100	44%
0 cells/ml	0/100	0%

Serotype Evaluation

The four (4) serotypes (6, 14, 19, 23) most commonly associated with pneumococcal invasive disease were grown in culture, diluted to 5×10^4 cells/ml in CSF and run in the BinaxNOW® Test. Fourteen (14) operators each interpreted 10 devices per serotype for a total of 140 determinations per serotype. All four (4) serotypes were detected 100% of the time at the test LOD (5×10^4 cells/ml).

Clinical Sensitivity and Specificity

In a multi-center (4) prospective study, the BinaxNOW® Test was used to evaluate CSF specimens collected from 590 hospitalized and outpatients presenting with symptoms of meningitis or from patients on whom a lumbar puncture was otherwise indicated. Patients were considered positive for pneumococcal meningitis if diagnosed by positive CSF culture.

BinaxNOW® Test performance was calculated using standard methods. Specificity was 99% (557/560), with a 95% confidence interval of 98% to 100%. Sensitivity was 97% (29/30), with a 95% confidence interval of 84% to 100%. The single culture positive specimen not detected in the BinaxNOW® Test was reported as producing only 2 colonies.

BinaxNOW® Result	CSF		Culture
	+	-	
+	29	1	557
-			
Sensitivity			97% (84% - 100%)
Specificity			99% (98% - 100%)
Accuracy			99% (98% - 100%)

CROSS-REACTIVITY

CSF Testing

Either enterovirus or bacteria was isolated from 61 of the *S. pneumoniae* negative CSF specimens tested as part of the above prospective study. Sixty (60) of these samples tested negative in the BinaxNOW® Test for a specificity of 98%.

The single positive specimen contained *Enterococci*. However, a second clinical CSF containing *Enterococci* tested negative in the BinaxNOW® Test as did the cultured whole organism (see Whole Organism Testing on the next page).

Bacteria/Virus Isolated from CSF	Samples Tested	Specificity
Enterovirus	24	100%
Acinetobacter	3	100%
<i>Cryptococcus neoformans</i>	1	100%
<i>C. diphteriae</i>	1	100%
<i>Enterobacter</i>	2	100%
<i>Enterococci</i>	2	50%
<i>Escherichia coli</i>	2	100%
<i>Haemophilus influenzae</i> type B	1	100%
<i>Klebsiella pneumoniae</i>	2	100%
<i>Morganella morganii</i>	1	100%
<i>Neisseria meningitidis</i>	3	100%
<i>Staphylococcus coagulase negative</i>	9	100%
<i>Staphylococcus coagulase positive</i>	2	100%
<i>Staphylococcus epidermidis</i>	2	100%
<i>Streptococcus Group A</i>	1	100%
<i>Streptococcus Group B</i>	1	100%
<i>Streptococcus viridans</i>	4	100%
Overall Specificity	61	98%

Whole Organism Testing

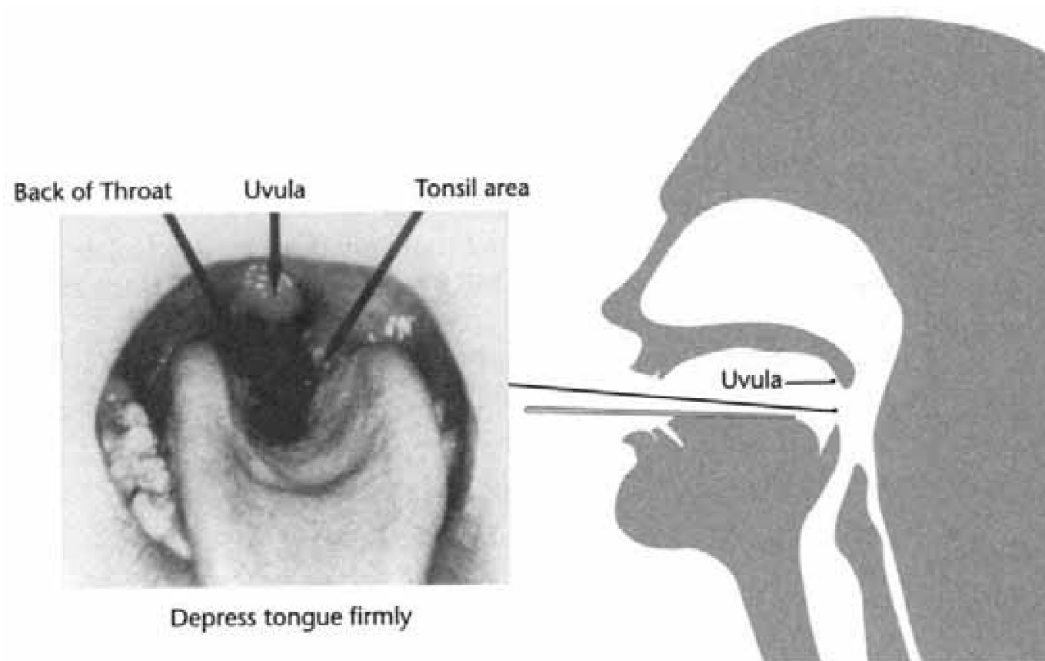
In addition to the bacterial and viral infections encountered as part of the prospective study, Binax compiled a panel of potential cross-reactants, including the most common bacterial and viral agents of meningitis. All bacteria were evaluated in the Binax test at concentrations ranging from 10^7 to 10^8 CFU/mL. Viruses were tested at 10^5 IU/mL or greater. The BinaxNOW® Test demonstrated 100% specificity, producing negative results for all viruses and bacteria tested.

Burkitt's Lymphoma (Epstein Barr)	Haemophilus influenzae, non-typeable (35891)	ORDERING INFORMATION
Coxsackie A7 Virus	Herpes Simplex Virus Type 1	
Coxsackie B3 Virus	Herpes Simplex Virus Type 2	Reorder numbers: 710-012: BinaxNOW® Streptococcus pneumoniae Test (12 test kit) 710-000: BinaxNOW® Streptococcus pneumoniae Test (22 test kit) 710-010: BinaxNOW® Streptococcus pneumoniae Control Swab Pack
Echovirus	Listeria monocytogenes (19115)	
Enterococcus faecium	Listeria monocytogenes (19424)	
Haemophilus influenzae A	Meisseria meningitidis serogroup A	Contact Information: Tel: US: 877-441-7440, OUS: 321-441-7200 Fax: 321-441-7400
Haemophilus influenzae B	Meisseria meningitidis serogroup B	
Haemophilus influenzae C	Meisseria meningitidis serogroup C	
Haemophilus influenzae D	Meisseria meningitidis serogroup D	
Haemophilus influenzae E	Meisseria meningitidis serogroup L	
Haemophilus influenzae F	Streptococcus oralis (35037)	
Haemophilus influenzae, non-typeable (51997)		
INTERFERING SUBSTANCES		
CSF specimens with elevated white blood cells (1 x 10 ⁴ cells/mL), red blood cells (30 cells/ μ L), protein (3 g/dL) and bilirubin (100 μ g/mL) were evaluated in the BinaxNOW® Streptococcus pneumoniae Test and found not to affect test performance.		
REPRODUCIBILITY STUDY		
A blind study of the BinaxNOW® Streptococcus pneumoniae Test was conducted in 3 separate laboratories using a panel of blind coded specimens containing negative, low positive and moderate positive samples. Participants tested each sample multiple times on 3 different days. One hundred percent (100%) of the 270 samples produced the expected result.		

Appendix 3 Collection and transport of nasopharyngeal specimens

The collection of nasopharyngeal specimens for this study followed guidance from the National Influenza Research Laboratory, HPA, Colindale, London, and the manufacturer of the POCT. A good specimen for the detection of influenza or RSV must contain a substantial number of respiratory epithelial cells, which are mainly obtained from the nasal swab. A throat swab alone will contain mainly squamous epithelial cells in which influenza does not replicate. In brief, collection of routine nasopharyngeal swabs was as follows:

- a single swab with cotton wool bud is inserted in one nostril and rubbed against and above the nasal turbinates
- a second swab is used to abrade the tonsils and pharynx
- place both swabs in the *same* bijoux bottle of virus transport medium
- break off the swab sticks (scissors may be used)
- screw lid tightly on to the bottle.



Trial-specific procedures were as follows.

'Near-patient diagnostic group' (QuickVue Influenza A + B test) and Deferred QuickVue test

- The sterile sponge tipped swab provided in the QuickVue Influenza A + B test was inserted into the nostril that presented the most secretions under visual inspection, according to manufacturer's instructions.
- Using gentle rotation, the swab was gently pushed until resistance was met at the level of the turbinates (< 1 inch into the nostril). The swab was rotated a few times against the nasal wall.
- Specimens collected from patients in the 'near-patient diagnostic group' were tested immediately for the presence of Influenza A and B according to the manufacturer's instructions.
- An identical specimen was collected from patients randomised to the molecular diagnostic group and conventional virus culture group. These specimens were collected into virus transport medium and were refrigerated at 4 °C until they were transported at the earliest opportunity by the hospital transport system to the microbiology laboratory. They were processed upon receipt during normal working hours by the QuickVue A + B test.


Deferred QuickVUE influenza A + B test, prompt and deferred molecular testing, and conventional virus culture

- We collected nasal and pharyngeal swabs for molecular and conventional virus culture studies using the *opposite* nostril to that used for the 'near-patient' and 'deferred' QuickVue Influenza A + B tests.
- Using gentle rotation, a dry swab with cotton wool bud was inserted into the nostril and rubbed against and above the nasal turbinates.
- A second swab is used to abrade the tonsils and pharynx.
- The swab tips from both swabs were placed into a single bijoux bottle of virus transport medium, agitated and then cut off, or broken off, into the medium.
- These specimens were refrigerated at 4 °C until they were transported to the Microbiology Laboratory at the earliest opportunity by the hospital transport system.
- Specimens from subjects randomised to the 'prompt' molecular diagnostic group were processed upon receipt during normal working hours. Specimens for 'deferred' molecular diagnostic testing from subjects who were randomised to the 'conventional' diagnostic group were stored at -20 °C
- Specimens from subjects randomised to the 'prompt' and 'conventional' diagnostic groups were processed upon receipt during normal working hours by conventional virus isolation tests.

Appendix 4 Quidel QuickVue Influenza A + B test

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CLIA Complexity: WAIVED

INTENDED USE

The QuickVue Influenza A+B test allows for the rapid, qualitative detection of influenza type A and type B antigens directly from nasal swab, nasopharyngeal swab, nasal aspirate, and nasal wash specimens. The test is intended for use as an aid in the rapid differential diagnosis of acute influenza type A and type B viral infections. The test is not intended to detect influenza C antigens. Negative results should be confirmed by cell culture; they do not preclude influenza virus infection and should not be used as the sole basis for treatment or other management decisions. The test is intended for professional and laboratory use.

SUMMARY AND EXPLANATION

Influenza is a highly contagious, acute, viral infection of the respiratory tract. The causative agents of the disease are immunologically diverse, single-strand RNA viruses known as influenza viruses. There are three types of influenza viruses: A, B, and C. Type A viruses are the most prevalent and are associated with most serious epidemics. Type B viruses produce a disease that is generally milder than that caused by type A. Type C viruses have never been associated with a large epidemic of human disease. Both type A and B viruses can circulate simultaneously, but usually one type is dominant during a given season.¹

Influenza antigens may be detected in clinical specimens by immunoassay. The QuickVue Influenza A+B test is a lateral-flow immunoassay using highly sensitive monoclonal antibodies that are specific for influenza antigens. The test is specific to influenza types A and B antigens with no known cross-reactivity to normal flora or other known respiratory pathogens.

QuickVue Influenza A+B Test
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PRINCIPLE OF THE TEST

The QuickVue Influenza A+B test involves the extraction of influenza A and B viral antigens. The patient specimen is placed in the Extraction Reagent Tube, during which time the virus particles in the specimen are disrupted, exposing internal viral nucleoproteins. After extraction, the Test Strip is placed in the Extraction Reagent Tube where nucleoproteins in the specimen will react with the reagents in the Test Strip.

If the extracted specimen contains influenza A or B antigens, a pink-to-red Test Line along with a blue procedural Control Line will appear on the Test Strip indicating a positive result. The Test Line for influenza A or B will develop at separate specified locations on the same Test Strip. If influenza A or B antigens are not present, or are present at very low levels, only the blue procedural Control Line will appear.

REAGENTS AND MATERIALS SUPPLIED**25-Test Kit: Catalog Number 20183****■ Shelf box containing:**

- ▶ Individually Packaged Test Strips (25): Mouse monoclonal anti-influenza A and anti-influenza B antibodies
- ▶ Extraction Reagent Solution (25): Vials with 340 µL of salt solution
- ▶ Extraction Tubes (25): Lyophilized buffer with detergents and reducing agents
- ▶ Disposable Droppers (25)
- ▶ Sterile Nasal Swabs (25)
- ▶ Positive Influenza Type A Control Swab (1): Swab is coated with non-infectious recombinant influenza A antigen
- ▶ Positive Influenza Type B Control Swab (1): Swab is coated with non-infectious recombinant influenza B antigen
- ▶ Negative Control Swab (1): Swab is coated with formalin-inactivated, non-infectious Streptococcus C antigen
- ▶ Package Insert (1)
- ▶ Procedure Card (1)

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MATERIALS NOT SUPPLIED

- Specimen containers
- Timer or watch

WARNINGS AND PRECAUTIONS

- For *In vitro* diagnostic use.
- Do not use the kit contents beyond the expiration date printed on the outside of the box.
- Use appropriate precautions in the collection, handling, storage, and disposal of patient samples and used kit contents.²
- Use of Nitrile or Latex gloves is recommended when handling patient samples.²
- Dispose of containers and used contents in accordance with Federal, State and Local requirements.
- The Test Strip must remain sealed in the protective foil pouch until use.
- The Extraction Reagent Solution contains a salt solution. If the solution contacts the skin or eye, flush with copious amounts of water.
- To obtain accurate results, you must follow the Package Insert.
- Inadequate or inappropriate specimen collection, storage, and transport may yield false negative test results.
- Seek specific training or guidance if you are not experienced with specimen collection and handling procedures.^{3,4}
- Use the Transport Media recommended in the Package Insert.
- If infection with a novel influenza A virus is suspected based on current clinical and epidemiological screening criteria recommended by public health authorities, specimens should be collected with appropriate infection control precautions for novel virulent influenza viruses and sent to state or local health departments for testing. Viral culture should not be attempted in these cases unless a BSL 3+ facility is available to receive and culture specimens.
- Although this test has been shown to detect cultured avian influenza viruses, including avian influenza A subtype H5N1 virus, the performance characteristics of this test with specimens from humans infected with H5N1 or other avian influenza viruses are unknown.

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KIT STORAGE AND STABILITY

Store the kit at room temperature, 59–86°F (15–30°C), out of direct sunlight. Kit contents are stable until the expiration date printed on the outer box. Do not freeze.

SPECIMEN COLLECTION AND HANDLING

Proper specimen collection, storage, and transport are critical to the performance of this Test.^{3,4}

SPECIMEN COLLECTION***Nasal Swab Sample:***

For optimal test performance with a nasal swab specimen, use the swabs supplied in the kit.

It is important to obtain as much secretion as possible. Therefore, to collect a nasal swab sample, insert the sterile swab into the nostril that presents the most secretion under visual inspection. Using gentle rotation, push the swab until resistance is met at the level of the turbinates (less than one inch into the nostril). Rotate the swab a few times against the nasal wall.

Nasopharyngeal Swab Sample:

It is important to obtain as much secretion as possible. Therefore, to collect a nasopharyngeal swab sample, carefully insert the sterile swab into the nostril that presents the most secretions under visual inspection. Keep the swab near the septum floor of the nose while gently pushing the swab into the posterior nasopharynx. Rotate the swab several times.

Nasal Wash or Aspirate Sample:

Follow your Institution's Protocol for obtaining wash specimens. **Use the minimal amount of saline that your procedure allows**, as excess volume will dilute the amount of antigen in the specimen. The following are examples of procedures used by clinicians:

For Older Children and Adults:

With the patient's head hyper-extended, instill sterile, normal saline (not supplied in the kit) into one nostril with a syringe. To collect the wash, place a clean, dry specimen container directly under the nose with slight pressure on the upper lip. Tilt the head forward and allow the fluid to run out of the nostril into the specimen container. Repeat for the other nostril and collect the fluid into the same specimen container.

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For Younger Children:

The child should sit in the parent's lap facing forward, with the child's head against the parent's chest. Fill the syringe or aspiration bulb with the minimal volume of saline required per the subject's size and age. Instill the saline into one nostril while the head is tilted back. Aspirate the wash specimen back into the syringe or bulb. The aspirated wash sample will likely be at least 1 cc in volume.

Alternatively, following instillation of the saline, tilt the child's head forward and let the saline drain out into a clean collection cup.

SPECIMEN TRANSPORT AND STORAGE

Specimens should be tested as soon as possible after collection. However, if transport of swab samples is required, minimal dilution of the sample is recommended, as this may result in decreased test sensitivity. One (1) milliliter or less is suggested for optimal rapid test performance. The following transport media are compatible with the QuickVue Influenza A+B test:

Transport Media	Recommended Storage Condition		
	2–25°C for 8 hours	2–25°C for 24 hours	2–8°C for 48 hours
BD Universal Viral Transport Media	Yes	Yes	Yes
Bartels Flextrans Media	Yes	No	No
Copan Universal Transport Media	Yes	Yes	Yes
Hank's Balanced Salt Solution	Yes	No	No
M5 Media	Yes	No	No
Saline	Yes	No	No
Storage of sample in a clean, dry, closed container	Yes	No	No

The M4, M4-RT, Liquid Amies-D, Amies Clear, Modified Stuart's and Remel M6 transport media are not compatible with this device.

Nasal wash/aspirate specimens may also be stored frozen (–70°C or colder) for up to one month.

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QUALITY CONTROL

Built-In Control Features

The QuickVue Influenza A+B test contains built-in procedural control features. The manufacturer's recommendation for daily control is to document these built-in procedural controls for the first sample tested each day.

The two-color result format provides a simple interpretation for positive and negative results. The appearance of a blue procedural Control Line provides several forms of positive control by demonstrating sufficient flow has occurred and the functional integrity of the Test Strip was maintained. **If the blue procedural Control Line does not develop at 10 minutes, the test result is considered invalid.**

A built-in negative control is provided by the clearing of red background color, verifying that the test has been performed correctly. Within 10 minutes, the result area should be white to light pink and allow the clear interpretation of the test result. **If background color appears and interferes with interpretation of the test result, the result is considered invalid.** Should this occur, review the procedure and repeat the test with a new Test Strip.

External Quality Control

External controls may also be used to demonstrate that the reagents and assay procedure perform properly.

Quidel recommends that positive and negative controls be run once for each untrained operator, once for each new shipment of kits — provided that each different lot received in the shipment is tested — and as deemed additionally necessary by your internal quality control procedures, and in accordance with local, state, and federal regulations or accreditation requirements.

If the controls do not perform as expected, repeat the test or contact Quidel Technical Support before testing patient specimens.

External Positive and Negative Control Swabs are supplied in the kit and should be tested using the Nasal Swab Test Procedure provided in this Package Insert or in the Procedure Card.

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TEST PROCEDURE

All clinical specimens must be at room temperature before beginning the assay.

Expiration date: Check expiration on each individual test package or outer box before using. Do not use any test past the expiration date on the label.

Nasal/Nasopharyngeal Swab Procedure

1. Dispense all of the Extraction Reagent Solution from the Reagent Tube. Gently swirl the Extraction Tube to dissolve its contents.



2. Place the patient swab with sample into the Extraction Tube. Roll the swab at least three (3) times while pressing the head against the bottom and side of the Extraction Tube.



Leave the swab in the Extraction Tube for one (1) minute.



3. Roll the swab head against the inside of the Extraction Tube as you remove it. Dispose of the used swab in accordance with your biohazard waste disposal protocol.



4. Place the Test Strip into the Extraction Tube with the arrows on the Test Strip pointing down. Do not handle or move the Test Strip until the test is complete and ready for reading.



5. Read result at ten (10) minutes. Some positive results may appear sooner. Do not read result after ten (10) minutes.

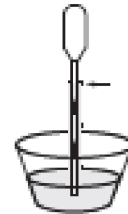


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Nasal Wash/Nasal Aspirate Procedure

1. Fill the dropper to the top/uppermost notch with nasal wash or nasal aspirate sample.



2. Add entire contents of the dropper to the Extraction Tube. Swirl the Extraction Tube gently to dissolve its contents.



3. Place the Test Strip into the Extraction Tube with the arrows on the Test Strip pointing down. Do not handle or move the Test Strip until the test is complete and ready for reading.



4. Read result at ten (10) minutes. Some positive results may appear sooner. Do not read result after ten (10) minutes.



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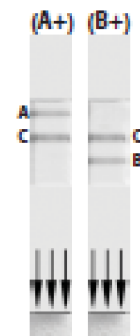
Not to be used for performing assay. Refer to most current package Insert accompanying your test kit.

INTERPRETATION OF RESULTS**Positive Result*:**

At ten minutes, the appearance of **ANY** shade of a pink-to-red Test Line, either above or below the blue Control Line, **AND** the appearance of a blue procedural Control Line Indicates a positive result for the presence of Influenza A and/or B viral antigen.

Hold the test strip with the **arrows pointed down**.

- If the red line is **above** the Control Line, the test results are positive for type A. See Image to the Immediate right (A+).
- If the red line is **below** the Control Line, the test results are positive for type B. See Image to the far right (B+).



**A positive result does not rule out co-infections with other pathogens or identify any specific Influenza A virus subtype.*

Negative Result:**

At ten minutes, the appearance of **ONLY** the blue procedural Control Line Indicates Influenza A and B viral antigen were not detected. A negative result should be reported as a presumptive negative for the presence of Influenza antigen.



***A negative result does not exclude Influenza viral infection. Negative results should be confirmed by cell culture.*

Invalid Result:

If at ten minutes, the blue procedural Control Line does not appear, even if any shade of a pink-to-red Test Line appears, the result is considered invalid. If at ten minutes, the background color does not clear and it interferes with the reading of the test, the result is considered invalid. If the test is invalid, a new test should be performed with a new patient sample and a new Test Strip.



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LIMITATIONS

- The contents of this kit are to be used for the qualitative detection of Influenza A and B antigen from nasal swab, nasopharyngeal swab, nasal wash and nasal aspirate specimens.
- A negative test result may occur if the level of antigen in a sample is below the detection limit of the test.
- Failure to follow the Test Procedure and Interpretations of Test Results may adversely affect test performance and/or invalidate the Test Result.
- Test Results must be evaluated in conjunction with other clinical data available to the physician.
- Negative test results do not rule out possible other non-Influenza viral infections.
- Positive test results do not rule out co-infections with other pathogens.
- Positive test results do not identify specific Influenza A virus subtypes.
- Children tend to shed virus more abundantly and for longer periods of time than adults. Therefore, testing specimens from adults will often yield lower sensitivity than testing specimens from children.
- Positive and negative predictive values are highly dependent on prevalence. False negative test results are more likely during peak activity when prevalence of disease is high. False positive test results are more likely during periods of low Influenza activity when prevalence is moderate to low.
- Individuals who received nasally administered Influenza A vaccine may have positive test results for up to three days after vaccination.
- Monoclonal antibodies may fail to detect, or detect with less sensitivity, Influenza A viruses that have undergone minor amino acid changes in the target epitope region.
- If differentiation of specific Influenza A subtypes and strains is needed, additional testing, in consultation with the state or local public health department, is required.

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EXPECTED VALUES

Seasonal outbreaks of influenza occur worldwide in both the northern and southern hemispheres causing widespread illness each winter. The average attack rate of influenza is 26–33 cases per 100 people per year. The risk of hospitalization is roughly 1/300 of those infected among the very young and elderly. Approximately 36,000 deaths in the U.S. are attributed to influenza or its complications each year. Ninety percent (90%) of deaths occur in those 65 years of age and older. During each of three major epidemics occurring in 1957 and 1968, more than 40,000 people died of influenza in the U.S. alone. In the 1918 pandemic, an estimated 50 million deaths resulted worldwide. In the multi-center clinical study conducted by Quidel during an influenza season in North America, an illness prevalence of 24% for type A and 15% for type B influenza was observed.

PERFORMANCE CHARACTERISTICS**QuickVue Influenza A+B Test Performance vs. Cell Culture*****Background on the 2005 Clinical Studies in Australia***

The performance characteristics for Influenza A were established when Influenza A/H3 and A/H1 were the predominant Influenza A viruses in circulation in Australia. When other Influenza A virus subtypes are emerging as human pathogens, the performance characteristics described below could vary. During this particular Influenza season in this region of Australia, 82% of the type A Influenza viruses isolated from culture were H3N2 and 18% were H1N1.

In the 2005 clinical study, the performance of the QuickVue Influenza A+B test was compared to cell culture methods and confirmed with DFA in a multi-center field clinical study during the Influenza season in Australia. This study was conducted at eight General Practice physician offices located across the Sydney metropolitan area in New South Wales, Australia. In this multi-center, point-of-care (POC) field trial, two (2) nasal or two (2) nasopharyngeal swab specimens were collected from each of a total of 238 patients. All clinical samples were collected from symptomatic patients. Seven percent (7%) of the population tested were <5 years of age, 24% 5 – <18 years of age, 68% ≥18 years of age, and 56% were male.

On-site testing of one nasal swab or nasopharyngeal swab specimen in the QuickVue Influenza A+B test was performed by physician office personnel within one hour of collection. This swab was incubated for one minute with the Extraction Reagent Solution before addition of the dipstick. The other swab was placed in viral transport media and stored at 2–8°C for up to 18 hours prior to culture. Madin-Darby Canine Kidney (MDCK) cells were inoculated with a portion of the nasal swab or nasopharyngeal swab specimen and incubated at 36°C for 48–96 hours. The inoculated cells were recovered from tissue culture and tested for Influenza A or B by direct fluorescent antibody (DFA) staining.

QuickVue Influenza A+B Test

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Background on the 1998/1999 Clinical Studies in the United States

The performance characteristics for Influenza A were established when influenza A/H3 and A/H1 were the predominant Influenza A viruses in circulation. When other Influenza A virus subtypes are emerging as human pathogens, the performance characteristics described below could vary. During this particular influenza season, 99% of the type A influenza viruses isolated from culture were H3N2 and 1% was H1N1.

In the winter of 1998/1999, the performance of the QuickVue Influenza A+B test was compared to cell culture methods in a multi-center field clinical study. This study was conducted in pediatric, adult and geriatric patient populations in six geographically distinct regions in the United States. In this multi-center, point-of-care (POC) field trial, a combination of nasal swabs and nasal wash/aspirate specimens were collected from a total of two hundred seventy-five (275) patients.

On-site testing of the nasal swab and nasal wash or nasal aspirate specimens in the QuickVue Influenza A+B test was performed by physician office personnel within one hour of specimen collection. The patient's nasal swab was swirled three times in the Extraction Reagent Solution and removed before addition of the dipstick. Viral transport medium was added to all nasal specimens intended for culture transport. Swab specimens in viral transport media and nasal wash/aspirate specimens were stored at 2–8°C for up to 24 hours prior to culture. Rhesus Monkey Kidney (RMK) cells or Madin-Darby Canine Kidney (MDCK) cells were inoculated with a portion of the nasal swab specimen and nasal wash/aspirate and tested for the appearance of cytopathic effect (CPE). Infected cells were recovered from tissue culture and confirmed for Influenza A or B by direct fluorescent antibody (DFA) staining. A total of 363 specimens were tested from 275 patients (270 nasal swabs and 93 nasal wash/aspirate specimens).

Results with Nasal Swab Specimens (2005 Clinical Study)**Results for All Age Groups:**

Nasal swab specimens from one hundred twenty-two patients were tested in QuickVue Influenza A+B and in cell culture. The QuickVue Influenza A+B test correctly identified 94% (16/17) culture-positive Influenza A specimens, 70% (14/20) culture-positive Influenza B specimens, 90% (95/105) culture-negative for Influenza A, and 97% (99/102) culture-negative for Influenza B, with an overall accuracy of 91% (111/122) and 93% (113/122) for Influenza A and B specimens, respectively. These results with nasal swabs are shown in Table 1.

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Table 1
QuickVue Influenza A+B Nasal Swab Results versus Culture (All Age Groups)

TYPE A				TYPE B			
Culture				Culture			
		+	-			+	-
QV Pos	16	10*		QV Pos	14	3**	
QV Neg	1	95		QV Neg	6	99	
Sens = 16/17 = 94% (95% C.I. 71–100%)				Sens = 14/20 = 70% (95% C.I. 48–86%)			
Spec = 95/105 = 90% (95% C.I. 83–95%)				Spec = 99/102 = 97% (95% C.I. 91–99%)			
Accur = 111/122 = 91% (95% C.I. 84–95%)				Accur = 113/122 = 93% (95% C.I. 86–96%)			
PPV = 16/26 = 62%				PPV = 14/17 = 82%			
NPV = 95/96 = 99%				NPV = 99/105 = 94%			

* Of the 10 discrepant results, 7 were subsequently found to be positive by the QuickVue test and by an investigational RT-PCR.

** Of the 3 discrepant results, 2 were subsequently found to be positive by the QuickVue test and by an investigational RT-PCR.

Results Stratified by Age Group:

The results obtained with nasal swab specimens from each age group are shown in Table 2.

Table 2
QuickVue Influenza A+B Nasal Swab Results versus Culture (by Age Group)

	<5 years of age N=14			5 – <18 years of age N=28			≥18 years of age N=80		
	Sens	Spec	Accur	Sens	Spec	Accur	Sens	Spec	Accur
Type A	100% (5/5)	89% (8/9)	93% (13/14)	100% (3/3)	100% (25/25)	100% (28/28)	89% (8/9)	87% (62/71)	88% (70/80)
Type B	100% (1/1)	100% (13/13)	100% (14/14)	70% (7/10)	89% (16/18)	82% (23/28)	67% (6/9)	99% (70/71)	95% (76/80)

Results with Nasal Swab Specimens (1998/1999 Clinical Study)

Compared to culture and confirmed for influenza A or B by DFA, the QuickVue Influenza A+B test correctly identified 72% (46/64) type A positive specimens, 73% (29/40) type B positive specimens, and 96% (159/166) negative specimens. These results with nasal swabs are shown in Table 3.

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Table 3
QuickVue Influenza A+B Nasal Swab Results versus Culture (All Age Groups)

TYPE A				TYPE B			
		Culture				Culture	
		+	-			+	-
QVPos	46	7		QVPos	29	7	
QVNeg	18		159	QVNeg	11		159
Sens = 46/64 = 72% (95% C.I. 60–81%)				Sens = 29/40 = 73% (95% C.I. 57–84%)			
Spec = 159/166 = 96% (95% C.I. 91–98%)				Spec = 159/166 = 96% (95% C.I. 91–98%)			
Accur = 205/230 = 89% (95% C.I. 84–93%)				Accur = 188/206 = 91% (95% C.I. 87–94%)			
PPV = 46/53 = 87%				PPV = 29/36 = 81%			
NPV = 159/177 = 90%				NPV = 159/170 = 94%			

Results with Nasopharyngeal Swab Specimens (2005 Clinical Study)

Results for All Age Groups:

Nasopharyngeal swab specimens from one hundred sixteen patients were tested in QuickVue Influenza A+B and in cell culture. The QuickVue Influenza A+B test correctly identified 83% (20/24) culture-positive Influenza A specimens, 62% (8/13) culture-positive Influenza B specimens, and 89% (82/92) culture-negative for Influenza A, and 98% (101/103) culture-negative for Influenza B, with an overall accuracy of 88% (102/116) and 94% (109/116) for Influenza A and B specimens, respectively. These results with nasopharyngeal swabs are shown in Table 4.

Table 4
QuickVue Influenza A+B Nasopharyngeal Swab Results versus Culture (All Age Groups)

TYPE A				TYPE B			
		Culture				Culture	
		+	-			+	-
QVPos	20	10*		QVPos	8	2**	
QVNeg	4		82	QVNeg	5		101
Sens = 20/24 = 83% (95% C.I. 64–94%)				Sens = 8/13 = 62% (95% C.I. 35–82%)			
Spec = 82/92 = 89% (95% C.I. 81–94%)				Spec = 101/103 = 98% (95% C.I. 93–100%)			
Accur = 102/116 = 88% (95% C.I. 81–93%)				Accur = 109/116 = 94% (95% C.I. 88–97%)			
PPV = 20/30 = 67%				PPV = 8/10 = 80%			
NPV = 82/86 = 95%				NPV = 101/106 = 95%			

* Of the 10 discrepant results, 4 were subsequently found to be positive by the QuickVue test and by an investigational RT-PCR.

** Of the 2 discrepant results, 1 was subsequently found to be positive by the QuickVue test and by an investigational RT-PCR.

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Results Stratified by Age Group:

The results obtained with nasopharyngeal swab specimens for each age group are shown in Table 5.

Table 5
QuickVue Influenza A+B Nasopharyngeal Swab Results versus Culture
(by Age Groups)

	<5 years of age N=3			5 – <18 years of age N=30			≥18 years of age N=83		
	Sens	Spec	Accur	Sens	Spec	Accur	Sens	Spec	Accur
Type A	100% (1/1)	100% (2/2)	100% (3/3)	82% (9/11)	84% (16/19)	83% (25/30)	83% (10/12)	90% (64/71)	89% (74/83)
Type B	NA (0/0)	67% (2/3)	67% (2/3)	67% (2/3)	96% (26/27)	93% (28/30)	60% (6/10)	100% (73/73)	95% (79/83)

Results with Frozen Nasal Washes (2005 Study)

Results for All Age Groups:

The performance of the QuickVue Influenza A+B test was further evaluated in the year 2005 in a retrospective study with 149 frozen, clinical, nasal wash specimens. All clinical samples were collected from symptomatic patients visiting a physician's office in the Northeastern region of the United States. Fifty-eight percent (58%) of the population tested were <5 years of age, 38% 5 – <18 years of age, 4% ≥18 years of age, and 46% were male.

Nasal Wash specimens from one hundred forty-nine patients were tested in QuickVue Influenza A+B and in cell culture. The QuickVue Influenza A+B test correctly identified 86% (56/65) culture-positive influenza A specimens and 95% (80/84) culture-negative specimens as shown in Table 6. No influenza B samples were evaluated in this study.

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Table 6
QuickVue Influenza A+B Frozen Nasal Wash Results versus Culture (All Age Groups)

TYPE A		
	Culture	
	+	-
QV Pos	56	4*
QV Neg	9**	80

Sens = $56/65 = 86\%$
 (95% C.I. 76–93%)
Spec = $80/84 = 95\%$
 (95% C.I. 88–99%)
Accur = $136/149 = 91\%$
 (95% C.I. 86–95%)
PPV = $56/60 = 93\%$
NPV = $80/89 = 90\%$

* Of the 4 discrepant results, 1 was subsequently found to be positive by the QuickVue test and by an investigational RT-PCR. There was too little volume in 1 sample to be analyzed by RT-PCR.

** Of the 9 discrepant results, 2 of 5 samples were subsequently found to be negative by the QuickVue test and by an investigational RT-PCR. There was too little volume in 4 samples to be analyzed by RT-PCR.

Results Stratified by Age Group:

The results obtained with frozen nasal wash specimens for each age group are shown in Table 7.

Table 7
QuickVue Influenza A+B Frozen Nasal Wash Results versus Culture (by Age Groups)

	<5 years of age N=87			5 – <18 years of age N=56			≥18 years of age N=6		
	Sens	Spec	Accur	Sens	Spec	Accur	Sens	Spec	Accur
Type A	90% (35/39)	96% (46/48)	93% (81/87)	87% (20/23)	94% (31/33)	91% (51/56)	33% (1/3)	100% (3/3)	67% (4/6)

Results with Fresh Nasal Wash/Aspirate Specimens (1998/1999 Clinical Study)

Compared to culture and confirmed for Influenza A or B by DFA, the QuickVue Influenza A+B test correctly identified 77% (10/13) type A positive specimens, 82% (9/11) type B positive specimens, and 99% (68/69) negative specimens. These samples were tested within one hour of collection and had not been frozen. These results with nasal wash/aspirate specimens are shown in Table 8.

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Table 8
QuickVue Influenza A+B Fresh Nasal Wash/Aspirate Results versus Culture
(All Age Groups)

TYPE A				TYPE B			
Culture			Sens = 10/13 = 77% (95% C.I. 49–93%)	Culture			Sens = 9/11 = 82% (95% C.I. 51–96%)
	+	–			+	–	
QVPos	10	1	Spec = 68/69 = 99% (95% C.I. 91–100%)	QVPos	9	1	Spec = 68/69 = 99% (95% C.I. 91–100%)
QVNeg	3	68		QVNeg	2	68	
Accur = 78/82 = 95% (95% C.I. 88–98%)				Accur = 77/80 = 96% (95% C.I. 89–99%)			
PPV = 10/11 = 91%				PPV = 9/10 = 90%			
NPV = 68/71 = 96%				NPV = 68/70 = 97%			

ANALYTICAL SPECIFICITY AND CROSS-REACTIVITY

The QuickVue Influenza A+B test was evaluated with a total of 62 bacterial and viral isolates. Bacterial Isolates were evaluated at a concentration between 10^7 and 10^8 org/mL. Viral Isolates were evaluated at a concentration of at least 10^4 – 10^6 TCID₅₀/mL. Adenovirus 18 and Parainfluenza virus 3 were tested at 10^5 TCID₅₀/mL. None of the organisms or viruses listed below in Table 9 gave a positive result in the QuickVue Influenza A+B test.

Table 9
Analytical Specificity and Cross-Reactivity

Bacterial Panel:

Acinetobacter calcoaceticus
Bacteroides fragilis
Bordetella pertussis
Branhamella catarrhalis
Candida albicans
Corynebacterium diphtheriae
Enterococcus faecalis
Escherichia coli
Gardnerella vaginalis
Haemophilus influenzae
Klebsiella pneumoniae
Lactobacillus casei
Lactobacillus plantarum
Legionella pneumophila

Mycoplasma pneumoniae
Neisseria gonorrhoeae
Neisseria meningitidis
Neisseria sicca
Neisseria subflava
Proteus vulgaris
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus mutans
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus sanguis

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Bacterial Panel:

Listeria monocytogenes
Mycobacterium avium
Mycobacterium Intracellulare
Mycobacterium tuberculosis
Mycoplasma orale

Streptococcus sp. Gp. B
Streptococcus sp. Gp. C
Streptococcus sp. Gp. F
Streptococcus sp. Gp. G

Viral Panel:

Adenovirus 5 (Ad. 75)
 Adenovirus 7 (Gomen)
 Adenovirus 10 (J.J.)
 Adenovirus 18 (D.C.)
 Coronavirus OC43
 Coxsackievirus A9 (Bozek)
 Coxsackievirus B5 (Faulkner)
 Cytomegalovirus (Towne)
 Echovirus 2 (Cornelis)
 Echovirus 3 (Morrisey)
 Echovirus 6 (D'Amori)
 Herpes simplex virus 1
 Herpes simplex virus 2

Human Rhinovirus 2 (HGP)
 Human Rhinovirus 14 (1059)
 Human Rhinovirus 16 (11757)
 Measles (Edmonston)
 Mumps (Enders)
 Parainfluenza virus 1 (Sendai)
 Parainfluenza virus 2 (CA/Greer)
 Parainfluenza virus 3 (C243)
 Respiratory Syncytial virus (A-2)
 Respiratory Syncytial virus
 (Subgroup A, Long chain)
 Rubella (RA 27/3)
 Varicella-Zoster (Ellen)

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ANALYTICAL SENSITIVITY

Analytical sensitivity was demonstrated using a total of forty-seven (47) strains of human influenza viruses: thirty-four (34) Influenza A and thirteen (13) Influenza B (Table 10).

Table 10
Analytical Sensitivity with Human Isolates of Influenza A and B

Viral Strain	Viral Type	Sub-Type	Minimum Detectable Level	Viral Strain	Viral Type	Sub-Type	Minimum Detectable Level
			TCID ₅₀ /mL				pfu/mL**
New Caledonia/20/99	A	H1N1	1.63×10^2	Shandong	A	H3N2	8.40×10^2
California/04/09*	A	H1N1	4.4×10^2	Maryland/91	A	H1N1	1.00×10^4
			pfu/mL**	Japan/305/57	A	H2N2	1.30×10^4
Hong Kong	A	H3N2	6.60×10^{-1}	Johannesburg/94	A	H3N2	1.44×10^4
Beijing/32/92	A	H3N2	3.30×10^4	Brazil	A	H1N1	1.70×10^4
Shanghai/11	A	H3N2	6.70×10^4	Sydney	A	H3N2	2.00×10^4
Shanghai/16	A	H3N2	1.00×10^4	Bangkok	A	H3N2	3.30×10^4
Victoria	A	H3N2	3.30×10^4	Wuhan	A	H3N2	3.30×10^4
Singapore/1/57	A	H2N2	6.70×10^4	Beijing/353/89	A	H3N2	3.30×10^4
Port Chalmers	A	H3N2	1.24×10^2	Singapore/86	A	H1N1	6.60×10^5
USSR	A	H1N1	2.00×10^4	Texas/91	A	H1N1	1.60×10^7
Puerto Rico/8/34	A	H1N1	2.60×10^4	Victoria	B		1.40×10^4
New Jersey	A	H1N1	2.70×10^4	Taiwan	B		1.10×10^4
Taiwan	A	H1N1	3.30×10^4	Panama	B		1.00×10^4
Tokyo/3/67	A	H2N2	3.40×10^4	Ann Arbor	B		3.30×10^4
Bayern	A	H1N1	6.60×10^4	Singapore	B		3.30×10^4
Sichuan	A	H3N2	6.60×10^4	Lee	B		6.60×10^4
Beijing/352/89	A	H3N2	7.70×10^2	Hong Kong	B		7.00×10^4
NWS/33	A	H1N1	1.00×10^3	Beijing/184/93	B		1.66×10^2
Fort Warren/1/50	A	H1N1	1.70×10^2	California	B		3.30×10^3
Mississippi	A	H3N2	1.70×10^4	Maryland	B		6.60×10^2
Texas/77	A	H1N1	3.30×10^4	Yamagata/16/88	B		6.70×10^4
Fort Monmouth/1/47	A	H1N1	6.70×10^4	Harbin	B		1.40×10^4
Alchi	A	H3N2	3.20×10^4	Stockholm	B		3.30×10^4

TCID₅₀/mL = 50% tissue culture infectious dose; pfu/mL = plaque-forming unit per milliliter

* Although this test has been shown to detect the 2009 H1N1 virus cultured from a positive human respiratory specimen, the performance characteristics of this device with clinical specimens that are positive for the 2009 H1N1 influenza virus have not been established. The QuickVue Influenza A+B test can distinguish between influenza A and B viruses, but it cannot differentiate influenza subtypes.

** These viral strains were obtained from American Type Culture Collection (ATCC) with titer information, and the titers were not verified by Quidel. The performance characteristics for influenza A virus subtypes emerging as human pathogens have not been established.

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Analytical sensitivity was further evaluated using a total of twenty-four (24) Influenza A viruses isolated from birds and mammals. The QuickVue Influenza A+B test detected all of the strains examined (Table 11).

Table 11
Analytical Sensitivity with Bird and Mammal Isolates of Influenza A

Viral Strain*	Viral Type	Viral Subtype
Duck/Tottori/723/80	A	H1N1
Duck/Alberta	A	H1N1
Duck/Hokkaido/17/01	A	H2N2
Duck/Mongolia/4/03	A	H3N8
Duck/Ukraine/1/63	A	H3N8
Equine/Miami/1/63	A	H3N8
Duck/Czech/56	A	H4N6
Hong Kong/483/97	A	H5N1
Hong Kong/156/97	A	H5N1
Chicken/Yamaguchi/7/04	A	H5N1
A/Chicken/Vietnam/33/04	A	H5N1
A/Vietnam/3028/04	A	H5N1
A/Thailand/MK2/04	A	H5N1
Duck/Pennsylvania/10128/84	A	H5N2
Turkey/Massachusetts/3740/65	A	H6N2
Seal/Massachusetts/1/80	A	H7N7
Turkey/Ontario/67	A	H8N4
Turkey/Wisconsin/66	A	H9N2
Chicken/Germany/N/49	A	H10N7
Duck/England/56	A	H11N6
Duck/Alberta/60/76	A	H12N5
Gull/Maryland/704/77	A	H13N6
Mallard/Astrakhan/263/82	A	H14N5
Duck/Australia/341/83	A	H15N8

* Performance characteristics for detecting influenza A virus from human specimens when these or other influenza A virus subtypes are emerging as human pathogens have not been established.

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INTERFERING SUBSTANCES

Whole blood, and several over-the-counter (OTC) products and common chemicals were evaluated and did not interfere with the QuickVue Influenza A+B test at the levels tested: whole blood (2%); three OTC mouthwashes (25%); three OTC throat drops (25%); three OTC nasal sprays (10%); 4-Acetamidophenol (10 mg/mL); Acetylsalicylic Acid (20 mg/mL); Chlorpheniramine (5 mg/mL); Dextromethorphan (10 mg/mL); Diphenhydramine (5 mg/mL); Ephedrine (20 mg/mL); Gualacol glyceryl ether (20 mg/mL); Oxymetazoline (10 mg/mL); Phenylephrine (100 mg/mL); and Phenylpropanolamine (20 mg/mL).

PRECISION STUDIES

The total, within-run, and between-run performance of the QuickVue Influenza A+B test was evaluated for precision. A panel consisting of two different levels of influenza A antigen (Johanneburg/82/96; weak positive and strong positive) and two different levels of influenza B antigen (Harbin/7/94; weak positive and strong positive) were repeated five times with a single lot of QuickVue Influenza A+B test on three different days. One hundred percent (100%) accuracy was obtained for all specimens tested.

PHYSICIAN OFFICE LABORATORY (POL) STUDIES

An evaluation of the QuickVue Influenza A+B test was conducted at three Physicians' Offices using a panel of 180 coded specimens. Testing was performed by physician office personnel with diverse educational backgrounds and work experiences at three different locations. The proficiency panel contained negative, low positive and moderate positive specimens. Each specimen level was tested at each site in replicates of at least six over a period of three days.

The results obtained at each site agreed >99% with the expected results. No significant differences were observed within run (six replicates), between runs (three different days) or between sites (three POL sites).

ASSISTANCE

If you have any questions regarding the use of this product, please call Quidel's Technical Support Number (800) 874-1517 (toll-free in the U.S.A.) or (858) 552-1100, Monday through Friday, between 7:00 a.m. and 5:00 p.m., Pacific Time, U.S.A. If outside the United States contact your local distributor or technicalsupport@quidel.com.

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4. The Clinical Virology Laboratory, Department of Laboratory Medicine at Yale: <http://info.med.yale.edu/labmed/virology/booklet.html>.

REF 20183 – QuickVue Influenza A+B 25 Test Kit

IVD



EC REP

MDSS GmbH
Schiffgraben 41
30175 Hannover,
Germany



QuickVue Influenza A+B Test

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Appendix 5 Case report form, clinical study

CASE REPORT FORM

Full title of study: Randomised controlled trial to evaluate 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 adults

REC reference number: 05/Q2502/76
HTA Project number: 03/39/18

Group ☐

1. Subject number:

2. Surname:

3. First & middle names:

4. Address:

5. Postcode:

6. Home telephone:

7. Mobile:

8. Hospital Number:

9. Date and time of admission: - - :
 (To Admissions' Unit) dd mm yy hrs (24) min

10. Sex (M or F):

11. Date of birth: - -
 dd mm yy

12. Age (years):

13. General Practitioner:

14. Address:

15. Postal code:

16. GP Telephone:

ELIGIBILITY: The following Inclusion (Page 1) and Exclusion (Page 2) criteria must be satisfied to qualify for enrolment.

INCLUSION CRITERIA:

If any of the following answers are NO , the subject <u>must not be entered</u> .		Enter Yes=1, or 2=No, in the box
1. Age ≥ 18 years		1=Yes <input type="checkbox"/> 2=No
2. Able and willing to give INFORMED CONSENT , OR a relative or carer is able and willing to give INFORMED ASSENT ,		1=Yes <input type="checkbox"/> 2=No
3. Have an acute exacerbation of chronic cardio-pulmonary illness of ≤ 168 hours (7 days) duration, or an acute cardio-pulmonary illness or influenza-like illness of ≤ 7 days duration, including:		1=Yes <input type="checkbox"/> 2=No
<ul style="list-style-type: none"> • Pneumonia* • Influenza/influenza-like illness* • Exacerbation of chronic obstructive pulmonary Disease* (COPD) • Bronchitis* • Asthma* • Congestive heart failure* • Cardiac arrhythmia* 		
4. Can be recruited to the study within a 16-hour period of initial assessment by an on-call doctor on the Medical Admissions Unit, or another ward accepting acute medical admissions,		1=Yes <input type="checkbox"/> 2=No
5. Able and willing to adhere to the procedures stated in the protocol, (Patients who are able to provide Informed Consent)		1=Yes <input type="checkbox"/> 2=No
6. Have access to a telephone.		1=Yes <input type="checkbox"/> 2=No

*NOTE: these are provisional or suspected clinical diagnoses that have been made either by the referring general medical practitioner or by the admitting medical team in the differential diagnosis. **In general**, it is expected that participants will have at least one respiratory symptom and one systemic symptom, OR ≥ 2 respiratory symptoms from at least two of the following bullet points, including:

Respiratory symptoms:

- Sore throat and/or hoarseness
- Nasal symptoms (stiffness, and/or runny nose, and/or thick nasal discharge, or sneezing)
- Cough (new or increased)
- Sputum (new or increased)
- Wheezing (new or increased)
- Difficulty breathing/shortness of breath (new or increased)
- Chest pain with breathing

Systemic symptoms:

- Feverishness/sweating
- Chills, shivers, or rigors
- Tiredness or fatigue
- Decrease or loss of appetite
- Headache
- Muscle or body aches
- Generally feel unwell

Record the patient's symptoms on Page 4, after checking the Inclusion and Exclusion Eligibility criteria on Pages 1 and 2.

ELIGIBILITY: The following Exclusion criteria must be satisfied to qualify for enrolment**EXCLUSION CRITERIA:**

If any of the following answers are YES , the subject <u>must not be entered</u> .		Enter Yes=1, or 2=No, in the box
1. Inclusion criteria not met,	1=Yes <input type="checkbox"/> 2=No	
2. Were previously recruited to this study within 28 days of this current admission,	1=Yes <input type="checkbox"/> 2=No	
3. Has an admission diagnosis of Angina OR Myocardial infarction,	1=Yes <input type="checkbox"/> 2=No	
4. Could not be recruited to the study within a 16-hour period of initial assessment by a doctor on the Medical Admissions Unit, or another ward accepting acute medical admissions,	1=Yes <input type="checkbox"/> 2=No	
5. Enrolment in a study of antimicrobial therapy of the illness for which the patient has been admitted.	1=Yes <input type="checkbox"/> 2=No	

INCLUSION AND EXCLUSION CRITERIA MET?

Did the subject meet all study entry criteria specified in the protocol?

1=Yes ☐ 2=No

If No, explain:

CONSENT/ ASSENT?If both of the following answers are **NO**, the subject **must not be entered**.

Has the Consent Form been signed by the Patient?

1=Yes ☐ 2=No

Has Assent been provided by a Relative or Carer?

1=Yes ☐ 2=NoSurname of person giving **Assent**: First & middle names: Address of Assent giver: Postal code: Telephone: **Date and time of admission to the study (i.e., when consent/assent obtained)**Date . . Time .

CLINICAL FEATURES (SYMPTOMS) OF THIS ILLNESS:

Respiratory symptoms:

	Enter Yes=1, or 2=No, in the box	Duration (hrs) (No new symptom should exceed 168h)
1. Sore throat and/or Hoarseness	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
2. Nasal symptoms (stuffiness, and/or runny nose, and/or thick nasal discharge, or sneezing)	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
3. New cough?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
3a. Is cough productive ?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
3b. If Chronic cough, is sputum darker, and/or volume & thickness increased?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
3c. If the cough is productive, is the sputum purulent ?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
3d. Is the sputum frothy ?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
3e. Has the patient coughed up blood , or ' rusty ' sputum?	1=Yes <input type="text"/> 2=No <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> hrs
4. Has the patient wheezed ?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
5. Has the patient found it difficult to breathe?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
6. Has the patient been breathless ?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
7. Breathless on lying down? (Orthopnoea , or PND)	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
8. Has the patient had pleuritic chest pain?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs

Systemic symptoms:

	Enter Yes=1, or 2=No, in the box	Duration (hrs) (No new symptom should exceed 168h)
1. Feverishness/sweats	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
2. Chills, shivers, or rigors?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
3. Tiredness, fatigue?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
4. Decreased appetite?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
5. Headache?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
6. Muscle or body aches?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs
7. Generally unwell?	1=Yes <input type="text"/> 2=No <input type="text"/>	If Yes <input type="text"/> <input type="text"/> <input type="text"/> hrs

EXAMINATION FINDINGS ON ADMISSION:

1. Admission temperature °C	<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> °C
2. Admission systolic blood pressure (mm Hg)	<input type="text"/> <input type="text"/> <input type="text"/> (Pneumonia graded severe if <90mm Hg)
3. Admission diastolic blood pressure (mm Hg)	<input type="text"/> <input type="text"/> <input type="text"/> (Pneumonia graded severe if ≤ 60mm Hg)
4. Admission pulse/min	<input type="text"/> <input type="text"/> <input type="text"/>
5. Admission respiratory rate/min	<input type="text"/> <input type="text"/> <input type="text"/> (Pneumonia graded severe if ≥ 30/min)
6. Admission oxygen saturation (%)	<input type="text"/> <input type="text"/> <input type="text"/> . <input type="text"/> <input type="text"/> (Pneumonia graded severe if <92%)
Enter Yes=1, 2=No, 3=Not documented, in the box	
7. Normal sinus rhythm?	1=Yes <input type="text"/> 2=No <input type="text"/>
8. Evidence of right ventricular failure? (Elevated JVP, or enlarged tender liver, or pitting ankle/sacral pad oedema)	1=Yes <input type="text"/> 2=No <input type="text"/>
9. Inspiratory crackles on auscultation of the lungs?	1=Yes <input type="text"/> 2=No <input type="text"/>
10. Bronchial breathing?	1=Yes <input type="text"/> 2=No <input type="text"/>
11. Dullness to percussion?	1=Yes <input type="text"/> 2=No <input type="text"/>

PROVISIONAL DIAGNOSIS ON ADMISSION:

(Tick ✓one box only)

1. ☐ Pneumonia
2. ☐ Influenza/influenza-like illness
3. ☐ Exacerbation of COPD
4. ☐ Exacerbation of asthma
5. ☐ Acute bronchitis
6. ☐ Congestive heart failure
7. ☐ Arrhythmia
8. ☐ Other

If 'Other', specify: _____

ADMISSION ISOLATION STATUS

1. What is the location of the patient's bed currently? (Enter 1, 2 or 3 as appropriate)

 1=Isolation cubicle, 2=Side-room, 3=Bay

QUALITY OF LIFE ASSESSMENT

1. Who completed the Quality of Life Assessment? (Enter 1, 2 or 3 as appropriate)

☐ 1=The patient; 2= Study nurse + patient; 3= Proxy

2. If Proxy, please record name, address, and telephone number if different to person providing ASSENT:

Surname of **PROXY**:

First & middle names:

Address of **PROXY**:

Postal code:

Telephone:

BASELINE EUROQOL 5D

Enter the relevant number in ONE box in each group below:

1. Mobility

(a) I have no problems in walking about ☐ 1 (b) I have some problems in walking about ☐ 2 (c) I am confined to bed ☐ 3

2. Self-care

(a) I have no problems with self-care ☐ 1 (b) I have some problems with washing or dressing myself ☐ 2 (c) I am unable to wash or dress myself ☐ 3

3. Usual activities

(a) I have no problems with performing my usual activities ☐ 1 (b) I have some problems with performing my usual activities ☐ 2 (c) I am unable to perform my usual activities ☐ 3

4. Pain/Discomfort

(a) I have no pain or discomfort ☐ 1 (b) I have moderate pain or discomfort ☐ 2 (c) I have extreme pain or discomfort ☐ 3

5. Anxiety/Depression

(a) I am not anxious or depressed ☐ 1 (b) I am moderately anxious or depressed ☐ 2 (c) I am extremely anxious or depressed ☐ 3

PATIENT'S PERCEIVED BASELINE EUROQOL 5-D HEALTH STATUS SCORE

- The patient's health state score today, on a scale of 0 – 100, with 0 = Worst imaginable health state & 100 = Best imaginable health state

Complete this page if the patient is randomised to Group 1
(Complete Page 8 if the patient is randomised to Group 2 or 3)

GROUP 1:

A. Blood

1. Blood culture (10mls), Time collected .
(Send to Microbiology Dept) (24hr clock)

2. Blood for antibody studies (10mls) Time collected .
(Send to Microbiology Dept) (24hr clock)

B. Nasopharyngeal specimens

Quidel test

3. One nostril only (Tick ✓)

☐

Left

☐

Right

(Collect from nostril producing most mucus)

4. Time specimen collected

 .

5. Quidel result (Tick ✓)

☐

Positive

☐

Negative

6. Time Quidel result made available to nursing/medical team

 . hrs

(24hr clock)

7. Who (name, Dr/nurse) was informed of the test result?

8. Adhesive label in notes (Tick ✓)

☐

Yes

☐

No

PCR test

9. Nasal swabs from both nostrils, Time collected .

10. Throat swab, Time collected .

(Collect Nose and throat swabs into Virus Transport Medium & send to Microbiology Dept)

(24hr clock)

C. Sputum

11. Sputum sample for Gram stain and culture, Time collected .
(Send to Microbiology Dept) (24hr clock)

D. Urine

BinaxNOW pneumococcal antigen test

12. Time urine specimen collected

 .

13. BinaxNOW result (Tick ✓)

☐

Positive

☐

Negative

14. Time BinaxNOW result made available to nursing/medical team

 . hrs

(24hr clock)

15. Who (name, Dr/nurse) was informed of the test result?

16. Adhesive label in notes (Tick ✓)

☐

Yes

☐

No

GROUPS 2 AND 3:

A. Blood

1. Blood culture (10mls), Time collected .
(Send to Microbiology Dept) (24hr clock)

2. Blood for antibody studies (10mls) Time collected .
(Send to Microbiology Dept) (24hr clock)

B. Nasopharyngeal specimens**Quidel test**

3. One nostril only (Tick ✓)

☐

Left

☐

Right

(Collect from nostril producing most mucus)

4. Time specimen collected . (24hr clock)

PCR test

5. Nasal swabs from both nostrils, Time collected .

6. Throat swab, Time collected .
(Collect Nose and throat swabs into Virus Transport Medium & send to Microbiology Dept) (24hr clock)

C. Sputum

7. Sputum sample for Gram stain and culture, Time collected .
(Send to Microbiology Dept) (24hr clock)

D. Urine (10mls)

8. Time urine specimen collected . (24hr clock)

DEMOGRAPHICS:**Ethnicity:** (Tick ✓ one box only)

1. ☐ White:
2. ☐ Mixed:
3. ☐ Indian:
4. ☐ Pakistani/Bangladeshi:
5. ☐ Afro-Caribbean:
6. ☐ Black African:
7. ☐ Chinese:
8. ☐ Hispanic:
9. ☐ Other:

If 'Other', specify: _____

Measurements of height and weight:

Weight (kgs): <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="margin: 0 5px;">.</div> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> </div> <div style="display: flex; justify-content: space-between; padding: 0 5px;"> 10. </div>	Height (m): <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="margin: 0 5px;">.</div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> </div> <div style="display: flex; justify-content: space-between; padding: 0 5px;"> 11. </div>	Body mass index = (Weight (kg)/height ² (m)) <div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="margin: 0 5px;">.</div> <div style="border: 1px solid black; width: 20px; height: 20px;"></div> </div> <div style="display: flex; justify-content: space-between; padding: 0 5px;"> 12. </div>
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Accommodation:

Enter Yes=1, or 2=No, in the box	
13. Does the patient live in a household? e.g., a flat or house	1=Yes <input style="width: 30px;" type="text"/> 2=No
14. Does the patient live in sheltered accommodation? i.e., <u>warden controlled</u>	1=Yes <input style="width: 30px;" type="text"/> 2=No
15. Does he/she live in a <u>Residential Home</u> ?	1=Yes <input style="width: 30px;" type="text"/> 2=No
16. Does he/she live in a <u>Nursing Home</u> ?	1=Yes <input style="width: 30px;" type="text"/> 2=No
17. How many <i>other</i> <u>adults</u> live in the household/residential facility?	<div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> Number
18. How many <u>children</u> live in the household/residential facility?	<div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> Number
19. Estimated number of contacts with children each week?	<div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> Number
20. Estimated number of visits each week to a Day-care Centre?	<div style="display: flex; align-items: center;"> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> <div style="border: 1px solid black; width: 20px; height: 20px; margin-right: 5px;"></div> </div> Number

Social:

	Enter Yes=1, or 2=No, in the box
21. Is the patient a current smoker?	1=Yes <input type="text"/> 2=No
22. If YES, how many cigarettes does he/she smoke each day?	<input type="text"/> <input type="text"/> Number
23. If the patient is not a current smoker, has he/she ever smoked?	1=Yes <input type="text"/> 2=No
24. If a previous smoker, how many years ago did they stop smoking?	<input type="text"/> <input type="text"/> Number
25. How many units of alcohol does he/she drink each week?	<input type="text"/> <input type="text"/> Number

Hospital admissions:

26. Total number of hospital admissions (All causes) during previous winter? (Oct-Mar inclusive)	<input type="text"/> <input type="text"/> Number
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Influenza and pneumococcal vaccination:

	Enter Yes=1, or 2=No, in the box
27. Has the participant been vaccinated against flu in <u>this</u> winter?	1=Yes <input type="text"/> 2=No
28. <input type="checkbox"/> Last winter? 29. <input type="checkbox"/> Winter before? 30. <input type="checkbox"/> Ever?	
Tick ✓ as appropriate	
31. Has he/she had pneumococcal vaccine <u>this</u> year?	1=Yes <input type="text"/> 2=No
32. <input type="checkbox"/> Last year? 33. <input type="checkbox"/> Year before? 34. <input type="checkbox"/> Ever?	
Tick ✓ as appropriate	

Past medical history:

	Significant abnormality, past or current medical condition (including surgery)	Diagnosis Date (mm-yyyy) (enter date or ✓ box)
1.		<div> <div> <div></div> <div></div> </div> <div>-</div> <div> <div></div> <div></div> <div></div> <div></div> </div> </div> <div> <input type="checkbox"/> Unknown </div>
2.		<div> <div> <div></div> <div></div> </div> <div>-</div> <div> <div></div> <div></div> <div></div> <div></div> </div> </div> <div> <input type="checkbox"/> Unknown </div>
3.		<div> <div> <div></div> <div></div> </div> <div>-</div> <div> <div></div> <div></div> <div></div> <div></div> </div> </div> <div> <input type="checkbox"/> Unknown </div>
4.		<div> <div> <div></div> <div></div> </div> <div>-</div> <div> <div></div> <div></div> <div></div> <div></div> </div> </div> <div> <input type="checkbox"/> Unknown </div>
5.		<div> <div> <div></div> <div></div> </div> <div>-</div> <div> <div></div> <div></div> <div></div> <div></div> </div> </div> <div> <input type="checkbox"/> Unknown </div>
6.		<div> <div> <div></div> <div></div> </div> <div>-</div> <div> <div></div> <div></div> <div></div> <div></div> </div> </div> <div> <input type="checkbox"/> Unknown </div>
7.		<div> <div> <div></div> <div></div> </div> <div>-</div> <div> <div></div> <div></div> <div></div> <div></div> </div> </div> <div> <input type="checkbox"/> Unknown </div>
8.		<div> <div> <div></div> <div></div> </div> <div>-</div> <div> <div></div> <div></div> <div></div> <div></div> </div> </div> <div> <input type="checkbox"/> Unknown </div>
9.		<div> <div> <div></div> <div></div> </div> <div>-</div> <div> <div></div> <div></div> <div></div> <div></div> </div> </div> <div> <input type="checkbox"/> Unknown </div>
10.		<div> <div> <div></div> <div></div> </div> <div>-</div> <div> <div></div> <div></div> <div></div> <div></div> </div> </div> <div> <input type="checkbox"/> Unknown </div>

Regular medication prescribed by GP (NOT for this acute medical problem):

	Name of medication	Dose (mg)	Frequency/24h	Indication: BNF chapter
1.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
2.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
3.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
4.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
5.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
6.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
7.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
8.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
9.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
10.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
11.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
12.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>

Note: BNF chapter Drugs and preparations for the:

1: Gastrointestinal system
 2: Cardiovascular system
 3: Respiratory system
 4: Central Nervous system
 5: Infections
 6: Endocrine system
 7: Obstetrics, Gynaecology, and Urinary Tract disorders

BNF chapter Drugs and preparations for the:

8: Malignant disease and Immunosuppression
 9: Nutrition and Blood
 10: Musculoskeletal and Joint disease
 11: Eye
 12: Ear, Nose, and Oropharynx
 13: Skin

Antibiotic(s) prescribed by GP for this acute medical problem?

Enter Yes=1, or 2=No, in the box		
1. Did the GP give the patient an antibiotic before admission?	1=Yes	<input type="text"/> 2=No
2. If YES, name, dose & frequency/24h:		
Name 1:	Dose (mg) <input type="text"/>	Frequency (Number) <input type="text"/>
Name 2:	Dose (mg) <input type="text"/>	Frequency (Number) <input type="text"/>

CONSENT: This page must be completed IF:

1. Assent was provided by a relative or carer, AND
2. The patient is no longer so breathless or confused that he/she is unable to assimilate information regarding the study to judge whether to participate.

CONSENT

		Enter Yes=1, or 2=No, in the box
Has the Consent Form been signed by the Patient?		1=Yes <input type="checkbox"/> 2=No
Date and time when Informed Consent was provided:		
Date	dd	mm
	<input type="text"/>	<input type="text"/>
	<input type="text"/>	<input type="text"/>
Time	<input type="text"/>	<input type="text"/>
	<input type="text"/>	<input type="text"/>

[illegible]

1.	Quidel	(+) ve <input type="checkbox"/> 1 (-) ve <input type="checkbox"/> 2 Indeterminate <input type="checkbox"/> 3	Date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> d d m m y y Time <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> •	Telephone <input type="checkbox"/> 1 Verbally <input type="checkbox"/> 2 Adhesive label <input type="checkbox"/> 3	Intranet <input type="checkbox"/> 4 'Other' <input type="checkbox"/> 5 Specify, if 'Other': <input type="text"/>
Recorders signature/date:					

2.	BinaxNOW	(+) ve <input type="checkbox"/> 1 (-) ve <input type="checkbox"/> 2 Indeterminate <input type="checkbox"/> 3	Date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> d m y Time <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> h m s	Telephone <input type="checkbox"/> 1 Verbally <input type="checkbox"/> 2 Adhesive label <input type="checkbox"/> 3	Intranet <input type="checkbox"/> 4 'Other' <input type="checkbox"/> 5 Specify, if 'Other': <input type="text"/>
Recorders signature/date:					

		Observation	
3.	Sputum Gram & ZN stain	(+) ve <input type="checkbox"/> 1 (-) ve <input type="checkbox"/> 2 Indeterminate <input type="checkbox"/> 3	Date <input type="text"/> ^d <input type="text"/> <input type="text"/> ^m <input type="text"/> <input type="text"/> ^y <input type="text"/> <input type="text"/> Time <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
		Telephone <input type="checkbox"/> 1 Verbally <input type="checkbox"/> 2 Adhesive label <input type="checkbox"/> 3 Intranet <input type="checkbox"/> 4	Filed after death/discharge <input type="checkbox"/> 5 'Other' <input type="checkbox"/> 6 Specify, if 'Other': <input type="text"/>
Recorders signature/date:			

Test		Result		Date/time when result made known to the nursing/medical team		How was medical/nursing team informed of result?		Observation	
4.	Sputum culture (bacteriology)	(+) ve <input type="checkbox"/> 1 (-) ve <input type="checkbox"/> 2 Indeterminate <input type="checkbox"/> 3	Date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Time <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Telephone <input type="checkbox"/> 1 Verbally <input type="checkbox"/> 2 Adhesive label <input type="checkbox"/> 3 Intranet <input type="checkbox"/> 4	Filed after death/discharge <input type="checkbox"/> 5 'Other' <input type="checkbox"/> 6 Specify, if 'Other': _____	1= <i>S. pneumoniae</i> 2= <i>H. influenzae</i> 3= <i>M. catarrhalis</i> 4= <i>S. aureus</i> 5= <i>Pseudomonas</i> spp. 6= <i>Klebsiella</i> 7= <i>M. tuberculosis</i> 8= Other Insert code No. <input type="checkbox"/> 1-8 Specify if 'Other' _____			
Recorders signature/date:									
5.	Blood culture	(+) ve <input type="checkbox"/> 1 (-) ve <input type="checkbox"/> 2 Indeterminate <input type="checkbox"/> 3	Date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Time <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Telephone <input type="checkbox"/> 1 Verbally <input type="checkbox"/> 2 Adhesive label <input type="checkbox"/> 3 Intranet <input type="checkbox"/> 4	Filed after death/discharge <input type="checkbox"/> 5 'Other' <input type="checkbox"/> 6 Specify, if 'Other': _____	1= <i>S. pneumoniae</i> 2= <i>H. influenzae</i> 3= <i>M. catarrhalis</i> 4= <i>S. aureus</i> 5= <i>Pseudomonas</i> spp. 6= <i>Klebsiella</i> 7= <i>M. tuberculosis</i> 8= Other Insert code No. <input type="checkbox"/> 1-8 Specify if 'Other' _____			
Recorders signature/date:									
6.	Rapid molecular test	(+) ve <input type="checkbox"/> 1 (-) ve <input type="checkbox"/> 2 Indeterminate <input type="checkbox"/> 3	Date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Time <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Telephone <input type="checkbox"/> 1 Verbally <input type="checkbox"/> 2 Adhesive label <input type="checkbox"/> 3 Intranet <input type="checkbox"/> 4	Filed after death/discharge <input type="checkbox"/> 5 'Other' <input type="checkbox"/> 6 Specify, if 'Other': _____	1= Influenza A 2= Influenza B 3= RSV A 4= RSV B Insert code No. <input type="checkbox"/> 1-4			
Recorders signature/date:									

**How was medical/nursing team
informed of result?**

**Date/time when result made known
to the nursing/medical team**

Result

Test

Observation

7.	Viral culture	(+) ve <input type="checkbox"/> 1 (-) ve <input type="checkbox"/> 2 Indeterminate <input type="checkbox"/> 3	Date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Time <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Telephone <input type="checkbox"/> 1 Verbally <input type="checkbox"/> 2 Adhesive label <input type="checkbox"/> 3 Intranet <input type="checkbox"/> 4	Filed after <input type="checkbox"/> 5 death/discharge 'Other' <input type="checkbox"/> 6 Specify, if 'Other': _____	1= Influenza 2= RSV 3= Other Insert code No. <input type="checkbox"/> 1-3 Specify if 'Other'
Recorders signature/date:						

8.	Serology	(+) ve <input type="checkbox"/> 1 (-) ve <input type="checkbox"/> 2 Indeterminate <input type="checkbox"/> 3	Date <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> Time <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Telephone <input type="checkbox"/> 1 Verbally <input type="checkbox"/> 2 Adhesive label <input type="checkbox"/> 3 Intranet <input type="checkbox"/> 4	Filed after <input type="checkbox"/> 5 death/discharge 'Other' <input type="checkbox"/> 6 Specify, if 'Other': _____	1= Influenza 2= RSV 3= C. pneumoniae. 4= C. psittaci. 5= M. pneumoniae. 6= Coxiella burnetii 7= Other 8= Dual Insert code No. <input type="checkbox"/> 1-8 Specify if 'Other'
Give Code No. for dual infections, i.e., 12 for 'flu + RSV', 24 for RSV+ C. psittaci, etc.						
Recorders signature/date:						

ADMISSION INVESTIGATIONS (within 12h of admission to Admissions Unit) ordered by admitting medical team:

	Enter Yes=1, or 2=No, in the box	List any other tests ordered within 12h of <i>admission</i>
1. Full blood count	1=Yes <input type="checkbox"/> 2=No	18. _____
2. Biochemistry (E & U, LFTs)	1=Yes <input type="checkbox"/> 2=No	19. _____
3. Blood sugar	1=Yes <input type="checkbox"/> 2=No	20. _____
4. Cardiac enzymes	1=Yes <input type="checkbox"/> 2=No	21. _____
5. Troponin	1=Yes <input type="checkbox"/> 2=No	22. _____
6. d-dimers	1=Yes <input type="checkbox"/> 2=No	23. _____
7. Oxygen saturation	1=Yes <input type="checkbox"/> 2=No	24. _____
8. Blood gases	1=Yes <input type="checkbox"/> 2=No	25. _____
9. Blood culture	1=Yes <input type="checkbox"/> 2=No	26. _____
10. Antibody studies	1=Yes <input type="checkbox"/> 2=No	27. _____
11. Sputum culture	1=Yes <input type="checkbox"/> 2=No	28. _____
12. Urine culture	1=Yes <input type="checkbox"/> 2=No	29. _____
13. Throat swab (Bacteriology)	1=Yes <input type="checkbox"/> 2=No	30. _____
14. Throat swab (Virology)	1=Yes <input type="checkbox"/> 2=No	
15. ECG	1=Yes <input type="checkbox"/> 2=No	
16. Ward urinalysis	1=Yes <input type="checkbox"/> 2=No	
17. Chest X-ray	1=Yes <input type="checkbox"/> 2=No	

Continue on the next page if more than six different drugs are given up to midnight on the day of admission.

	Name of DRUG	Dose	Route Oral=1 IV=2 IM=3	Frequency /24h (n)	Date (dd-mm-yy) and time (24h clock) of first dose	Date/time of last dose
1.	<div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div><div></div></div>	Dose (mg) <div><div></div><div></div><div></div><div></div></div>	<div><div></div></div>	n= <div><div></div><div></div></div>	Date <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> y y Time <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> . Date <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> d d Time <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> . Date <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> m m Time <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> . Date <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> y y	Date <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> y y Time <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> . Date <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> d d Time <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> . Date <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> m m Time <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> . Date <div><div></div><div></div><div></div><div></div></div> <div><div></div><div></div><div></div><div></div></div> y y
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	Name of DRUG	Dose	Route Oral=1 IV=2 IM=3	Frequency /24h (n)	Date (dd-mm-yy) and time (24h clock) of first dose	Date/time of last dose
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NIHR Journals Library www.journalslibrary.nihr.ac.uk

SPECTRUM, of antibiotic combination on DAY 2 (Including antibiotics that were prescribed previously and are still being given) if more than one antibiotic is given:

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

SPECTRUM, of antibiotic combination on DAY 4 (Including antibiotics that were prescribed previously and are still being given) if more than one antibiotic is given:

[illegible]

SPECTRUM, of antibiotic combination on DAY 5 (Including antibiotics that were prescribed previously and are still being given) if more than one antibiotic is given:

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

SPECTRUM, of antibiotic combination on DAY 6 (Including antibiotics that were prescribed previously and are still being given) if more than one antibiotic is given:

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

SPECTRUM, of antibiotic combination on DAYS 8, 9, & 10 (Including antibiotics that were prescribed previously and are still being given) if more than one antibiotic is given:

ISOLATION STATUS

Enter details of the patient's isolation status at MID-DAY on each of the following days. (Day 2 begins at midnight following the admission of the patient, i.e., Day 2 is the first full 24 hour period in the hospital.

DAY 2

A What is the location of the patient's bed currently?

☐ Enter code 1-5.

1= Isolation cubicle;

2= Side-room;

3=Bay area of ward

4= ITU bed, open area of ITU

5= Side-room, ITU

B If in a cubicle, or side-room, please enter the *given* reason:

☐ Enter code 1-8.

1= No other bed available

2= Impending death/privacy

3= Suspected respiratory virus infection

4= Known respiratory virus

5= MRSA

6= C. difficile

7= Diarrhoea

8= Other

If 'Other', Please provide brief details:

C If in a cubicle, or side-room, please enter details of when the patient was admitted there:

Date . .

Time .

Recorder's signature/date:

DAY 3

A What is the location of the patient's bed currently?

☐ Enter code 1-5.

1= Isolation cubicle;

2= Side-room;

3=Bay area of ward

4= ITU bed, open area of ITU

5= Side-room, ITU

B If in a cubicle, or side-room, please enter the *given* reason:

☐ Enter code 1-8.

1= No other bed available

2= Impending death/privacy

3= Suspected respiratory virus infection

4= Known respiratory virus

5= MRSA

6= C. difficile

7= Diarrhoea

8= Other

If 'Other', Please provide brief details:

C If in a cubicle, or side-room, please enter details of when the patient was admitted there:

Date . .

Time .

Recorder's signature/date:

ISOLATION STATUS

DAY 4

A What is the location of the patient's bed currently?

☐ Enter code 1-5.

1= Isolation cubicle;

2= Side-room;

3=Bay area of ward

4= ITU bed, open area of ITU

5= Side-room, ITU

B If in a cubicle, or side-room, please enter the *given* reason:

☐ Enter code 1-8.

1= No other bed available

2= Impending death/privacy

3= Suspected respiratory virus infection

4= Known respiratory virus

5= MRSA

6= C. difficile

7= Diarrhoea

8= Other

If 'Other', Please provide brief details:

C If in a cubicle, or side-room, please enter details of when the patient was admitted there:

Date . .

Time .

Recorder's signature/date:

DAY 5

A What is the location of the patient's bed currently?

☐ Enter code 1-5.

1= Isolation cubicle;

2= Side-room;

3=Bay area of ward

4= ITU bed, open area of ITU

5= Side-room, ITU

B If in a cubicle, or side-room, please enter the *given* reason:

☐ Enter code 1-8.

1= No other bed available

2= Impending death/privacy

3= Suspected respiratory virus infection

4= Known respiratory virus

5= MRSA

6= C. difficile

7= Diarrhoea

8= Other

If 'Other', Please provide brief details:

C If in a cubicle, or side-room, please enter details of when the patient was admitted there:

Date . .

Time .

Recorder's signature/date:

ISOLATION STATUS

DAY 7

A What is the location of the patient's bed currently?

☐ Enter code 1-5.

1= Isolation cubicle;

2= Side-room;

3= Bay area of ward

4= ITU bed, open area of ITU

5= Side-room, ITU

B If in a cubicle, or side-room, please enter the *given* reason:

☐ Enter code 1-8.

1= No other bed available

2= Impending death/privacy

3= Suspected respiratory virus infection

4= Known respiratory virus

5= MRSA

6= C. difficile

7= Diarrhoea

8= Other

If 'Other', Please provide brief details:

C If in a cubicle, or side-room, please enter details of when the patient was admitted there:

Date . .

Time .

Recorder's signature/date:

SUMMARY ISOLATION STATUS

1. Was the patient admitted to a single room at any stage during the first seven days of admission for the presenting illness? ☐ Yes=1, No=2

2. If YES, Enter the dates and times when the patient was first isolated, and when taken out of isolation:

Time when first isolated

Date . . Time .

Time when removed from isolation

Date . . Time .

3. Period of isolation (hours)

4. Was the patient **re-admitted** to a single room at any stage during the First seven days of admission for the presenting illness? ☐ Yes=1, No=2

5. If YES, Enter the dates and times when the patient was re-isolated, and when taken out of isolation:

Time when first isolated

Date . . Time .

Time when removed from isolation

Date . . Time .

Recorder's signature/date:

SEVERITY INDICES

RESPIRATORY RATE, OXYGENATION AND REQUIREMENT FOR SUPPLEMENTAL OXYGEN

- It is expected that patients who are entered into the study will have their respiratory rate measured at least 6-hourly for at least 24 hours after admission, and at least every 8 hours thereafter, until shown to be satisfactory or improving (by the admitting medical team).
- It is expected that patients who are entered into the study will have their oxygen saturation measured at least 6-hourly for at least 24 hours after admission, and at least every 8 hours thereafter, until shown to be satisfactory, or improving.
- The need for arterial blood gas levels will be assessed by the admitting medical team

1. When breathing air, did the patient have one or more of the following: ☐ Yes=1, No=2
(a) Respiratory rate of ≥ 30 breaths/min; (b) $\text{SaO}_2 < 92\%$; (c) $\text{PaO}_2 < 8$ kPa, either on admission, or within 5 days of admission?
2. If YES, Did the patient require an inspired oxygen concentration of over 60% to maintain adequate oxygenation? ☐ Yes=1, No=2
3. If YES, Enter the date and time when supplemental oxygen was first given and discontinued for a period of ≥ 24 hours:
 Date and time when supplemental oxygen **first prescribed**
 Date . . Time .
 Date and time when supplemental oxygen **discontinued**
 Date . . Time .
4. Period (hours) of oxygen therapy
5. Time (hours) between admission and discontinuation of supplemental oxygen
6. Was the patient given CPAP? ☐ Yes=1, No=2
7. If YES, Enter the date and time when CPAP was first given and discontinued:
 Date and time when CPAP was **first used**
 Date . . Time .
 Date and time when CPAP was **discontinued**
 Date . . Time .
8. Period (hours) of CPAP therapy
9. Time (hours) between admission and discontinuation of CPAP

Recorder's signature/date:

SEVERITY INDICES

BLOOD PRESSURE

- The research nurse should ensure that patients who are entered into the study have their pulse and blood pressure measured at least three times daily.
- A low systolic (<90 mm Hg) or diastolic (≤ 60 mmHg) blood pressure are recognised poor prognostic factors in the presence of septic shock: they may be of relevance in this study. Please examine the patient's records to identify whether he/she had a low systolic or diastolic blood pressure during the first 5 days of admission, and when the blood pressure first exceeded these levels and remained normal for a period of at least 24 hours.

1. During the first 5 days of admission, did the patient develop a low systolic or diastolic blood pressure? ☐ Yes=1, No=2

2. If YES, Enter the date and time when low systolic or diastolic blood pressure was first noted and confirmed on retesting:

Date and time when low systolic and/or diastolic pressure **first noted**

Date . . Time .

d d m m y y

3. If YES, Enter the date and time when low systolic or diastolic blood pressure returned to normal and remained so for a period of at least 24 hours:

Date and time when systolic and/or diastolic pressure **returned to 'normal'**

Date . . Time .

d d m m y y

4. Period (hours) of low BP

Recorder's signature/date:

DAY 7 QUALITY OF LIFE ASSESSMENT

1. Who completed the Quality of Life Assessment? (Enter 1, 2 or 3 as appropriate)

☐ 1=The patient; 2= Study nurse + patient; 3= Proxy

2. If Proxy, please record name, address, and telephone number if different to person providing ASSENT:

Surname of **PROXY**:

First & middle names:

Address of **PROXY**:

Postal code:

Telephone:

DAY 7 EUROQOL 5D

*Enter the relevant number in **ONE** box in each group below:*

1. Mobility

(a) I have no problems in walking about ☐ 1 (b) I have some problems in walking about ☐ 2 (c) I am confined to bed ☐ 3

2. Self-care

(a) I have no problems with self-care ☐ 1 (b) I have some problems with washing or dressing myself ☐ 2 (c) I am unable to wash or dress myself ☐ 3

3. Usual activities

(a) I have no problems with performing my usual activities ☐ 1 (b) I have some problems with performing my usual activities ☐ 2 (c) I am unable to perform my usual activities ☐ 3

4. Pain/Discomfort

(a) I have no pain or discomfort ☐ 1 (b) I have moderate pain or discomfort ☐ 2 (c) I have extreme pain or discomfort ☐ 3

5. Anxiety/Depression

(a) I am not anxious or depressed ☐ 1 (b) I am moderately anxious or depressed ☐ 2 (c) I am extremely anxious or depressed ☐ 3

DAY 7 PATIENT'S PERCEIVED BASELINE EUROQOL 5-D HEALTH STATUS SCORE

• The patient's health state score today, on a scale of 0 – 100, with 0 = Worst imaginable health state & 100 = Best imaginable health state

Score =

FEVER DURATION

- The research nurse should ensure that patients who are entered into the study have their temperature measured at least three times daily using a tympanic thermometer.
- Patients with a fever may have a normal temperature for part of the day. Please examine the patient's temperature chart and record when the patient **FIRST** became apyrexial (temperature $\leq 37.2^{\circ}\text{C}$) **AND REMAINED SO** for a period of at least 24 hours.
- Note: If the patient did not have a raised temperature on admission, and remained afebrile during the first 48 hours of admission, please enter the Date and Time of admission to the Admissions' Unit.

1. Was the patient pyrexial ($\geq 37.3^{\circ}\text{C}$) on admission, or during the first 48hrs of admission? ☐ Yes=1, No=2
2. If YES, Did the patient become apyrexial, within 10 days of admission, or before death or discharge home, or elsewhere, if they occurred within 10 days of admission? ☐ Yes=1, No=2
3. If YES, Enter the date and time when the patient first became apyrexial, following the instructions above:

Date . . Time .

d d m m y y

Recorder's signature/date:

DAY 10 CONVALESCENT BLOOD SAMPLE:

Enter details of when the 10ml convalescent blood sample was collected:

Date:
 d d m m y y

Time (24hr clock): .

(Send to Microbiology Dept)

ADMISSIONS TO INTENSIVE CARE AND MECHANICAL VENTILATION

1. Was the patient admitted to ITU during the first 28 days of admission? ☐ Yes=1, No=2
2. If YES, Enter the date and time when the patient was first admitted and eventually left intensive care:
 Date and time of admission to ITU:
 Date . . Time: .
d d m m y y
 Date and time of discharge from ITU:
 Date . . Time: .
d d m m y y
3. Interval (hours) between admission to the hospital and the ITU
4. Was the patient ventilated? ☐ Yes=1, No=2
5. If YES, Enter the dates and times when the patient was first ventilated and eventually taken off the ventilation:
6. Date and time ventilated
 Date . . Time .
d d m m y y
 Date and time taken off ventilator
 Date . . Time .
d d m m y y
6. Period (hours) Ventilated
7. Was the patient admitted to ITU during the first 10 days of admission? ☐ Yes=1, No=2

Recorder's signature/date:

DEATHS AND PERIOD OF HOSPITALISATION

1. Did the patient die within 28 days of this admission? ☐ Yes=1, No=2
2. If YES, Enter the date and time when the patient died:
 Date and time of death
 Date . . Time .
d d m m y y
3. Interval (hours) between admission and death
4. Was the patient discharged within 28 days of admission ☐ Yes=1, No=2
5. If YES, Enter the date and time when the patient was discharged:
 Date and time of discharge
 Date . . Time .
d d m m y y
6. Period (hours) between admission and discharge

Recorder's signature/date:

INVESTIGATIONS ORDERED BY ADMITTING MEDICAL TEAM DURING THE ADMISSION:

Enter the number of tests done:

1.	Full blood counts	<input type="text"/> <input type="text"/>	Number
2.	Biochemistry (E & U, LFTs, renal)	<input type="text"/> <input type="text"/>	Number
3.	Blood sugar	<input type="text"/> <input type="text"/>	Number
4.	Cardiac enzymes	<input type="text"/> <input type="text"/>	Number
5.	Tropinin	<input type="text"/>	Number
6.	d-dimers	<input type="text"/>	Number
7.	Blood gases	<input type="text"/> <input type="text"/>	Number
8.	Blood cultures	<input type="text"/>	Number
9.	Antibody studies (number of different antigens)	<input type="text"/> <input type="text"/>	Number
10.	Sputum culture	<input type="text"/>	Number
11.	Urine culture	<input type="text"/>	Number
12.	Throat swab (Bacteriology)	<input type="text"/>	Number
14.	Throat swab (Virology)	<input type="text"/>	Number
15.	ECG	<input type="text"/>	Number
16.	Ward urinalysis	<input type="text"/>	Number
17.	Chest X-rays	<input type="text"/>	Number
18.	Other X-ray investigations	<input type="text"/> <input type="text"/>	Number
19.	CT/MRI scans	<input type="text"/>	Number
20.	Other 1	<input type="text"/>	Number
21.	Other 2	<input type="text"/>	Number
22.	Other 3	<input type="text"/>	Number

SUMMARY INFORMATION ON USE OF ANTIBIOTICS GIVEN DURING THE HOSPITAL ADMISSION

1. Were antibiotics administered during this admission? (If NO, proceed to 8 below)	<div> <div> <div>1=Yes</div> <div>2=No</div> </div> <div> <input type="checkbox"/> </div> </div> Enter 1 or 2		
2. If YES, by reference to preceding Tables, please enter the dates and times when BROAD SPECTRUM antibiotics were first, and last administered.	<div> <div> <div>First administered</div> <div> <div>Date</div> <div> <div> <div></div> <div></div> </div> <div> <div>d</div> <div></div> </div> <div> <div>m</div> <div></div> </div> <div> <div>y</div> <div></div> </div> </div> <div> <div>Time</div> <div> <div> <div></div> <div></div> </div> <div> <div>.</div> <div></div> </div> </div> </div> </div> <div> <div>Last administered</div> <div> <div>Date</div> <div> <div> <div></div> <div></div> </div> <div> <div>d</div> <div></div> </div> <div> <div>m</div> <div></div> </div> <div> <div>y</div> <div></div> </div> </div> <div> <div>Time</div> <div> <div> <div></div> <div></div> </div> <div> <div>.</div> <div></div> </div> </div> </div> </div> </div> </div></div>		<div> <div>Duration of broad spectrum antibiotics (to nearest whole hour) (Enter 0, if only narrow spectrum antibiotics were used)</div> <div> <div>hours</div> <div> <div></div> <div></div> </div> </div> </div>
3. If YES, by reference to preceding Tables, please enter the dates and times when INTRAVENOUS ANTIBIOTICS were first and last administered.	<div> <div> <div>First administered</div> <div> <div>Date</div> <div> <div> <div></div> <div></div> </div> <div> <div>d</div> <div></div> </div> <div> <div>m</div> <div></div> </div> <div> <div>y</div> <div></div> </div> </div> <div> <div>Time</div> <div> <div> <div></div> <div></div> </div> <div> <div>.</div> <div></div> </div> </div> </div> </div> <div> <div>Last administered</div> <div> <div>Date</div> <div> <div> <div></div> <div></div> </div> <div> <div>d</div> <div></div> </div> <div> <div>m</div> <div></div> </div> <div> <div>y</div> <div></div> </div> </div> <div> <div>Time</div> <div> <div> <div></div> <div></div> </div> <div> <div>.</div> <div></div> </div> </div> </div> </div> </div> </div></div>		<div> <div>Duration of intravenous antibiotics (to nearest whole hour)</div> <div> <div>hours</div> <div> <div></div> <div></div> </div> </div> </div>
4. If YES, by reference to preceding Tables, enter date and time when ANY ANTIBIOTICS were first and last administered.	<div> <div> <div>First administered</div> <div> <div>Date</div> <div> <div> <div></div> <div></div> </div> <div> <div>d</div> <div></div> </div> <div> <div>m</div> <div></div> </div> <div> <div>y</div> <div></div> </div> </div> <div> <div>Time</div> <div> <div> <div></div> <div></div> </div> <div> <div>.</div> <div></div> </div> </div> </div> </div> <div> <div>Last administered</div> <div> <div>Date</div> <div> <div> <div></div> <div></div> </div> <div> <div>d</div> <div></div> </div> <div> <div>m</div> <div></div> </div> <div> <div>y</div> <div></div> </div> </div> <div> <div>Time</div> <div> <div> <div></div> <div></div> </div> <div> <div>.</div> <div></div> </div> </div> </div> </div> </div> </div></div>		<div> <div>Duration of antibiotics (to nearest whole hour)</div> <div> <div>hours</div> <div> <div></div> <div></div> </div> </div> </div>
5. Was an antiviral (NEURAMINIDASE INHIBITOR) administered during this admission? (If NO, proceed to)	<div> <div> <div>1=Yes</div> <div>2=No</div> </div> <div> <input type="checkbox"/> </div> </div> Enter 1 or 2		

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	Name of DRUG	Dose	Route Oral=1 IV=2 IM=3	Frequency /24h (n)	Date (dd-mm-yy) and time (24h clock) of first dose	Date/time of last dose
1.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>
2.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>
3.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>
4.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>
5.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>
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71.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> <div></div>

	Name of DRUG	Dose	Route Oral=1 IV=2 IM=3	Frequency /24h (n)	Date (dd-mm-yy) and time (24h clock) of first dose	Date/time of last dose
8.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .
9.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .
10.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .
11.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .
12.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .
13.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .
14.	<div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> </div>	Dose (mg) <div> <div></div> <div></div> <div></div> <div></div> </div>	<div> <div></div> </div>	n= <div> <div></div> </div>	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .	Date <div> <div></div> <div></div> <div></div> <div></div> </div> Time <div> <div></div> <div></div> <div></div> <div></div> </div> .

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[illegible]

DISCHARGE MEDICATION

	Name of DRUG	Dose	Frequency /24h (n)	No. of days
1.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
2.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
3.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
4.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
5.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
6.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
7.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
8.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
9.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
10.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
11.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
12.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
13.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
14.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>
15.	<input type="text"/>	Dose (mg) <input type="text"/>	Number <input type="text"/>	Number <input type="text"/>

Recorder's signature:

1

SUMMARY OF INTRAVENOUS FLUIDS, BLOOD, AND BLOOD PRODUCTS GIVEN DURING THE ADMISSION:

	Product	Number given
1.	IV solutions (Saline, dextrose saline) (500ml)	<input type="text"/> <input type="text"/>
2.	Other IV solutions (smaller volumes for drug delivery)	<input type="text"/> <input type="text"/>
3.	Blood (Units)	<input type="text"/> <input type="text"/>
4.	Platelets (Units)	<input type="text"/> <input type="text"/>
5.	FFP	<input type="text"/> <input type="text"/>

Recorder's signature:

DAY 28 QUALITY OF LIFE ASSESSMENT

1. Who completed the Quality of Life Assessment? (Enter 1, 2 or 3 as appropriate)

☐ 1=The patient; 2= Study nurse + patient; 3= Proxy

2. If Proxy, please record name, address, and telephone number if different to person providing ASSENT:

Surname of **PROXY**:

First & middle names:

Address of **PROXY**:

Postal code:

Telephone:

DAY 28 EUROQOL 5D

Enter the relevant number in ONE box in each group below:

1. Mobility

(a) I have no problems in walking about ☐ 1 (b) I have some problems in walking about ☐ 2 (c) I am confined to bed ☐ 3

2. Self-care

(a) I have no problems with self-care ☐ 1 (b) I have some problems with washing or dressing myself ☐ 2 (c) I am unable to wash or dress myself ☐ 3

3. Usual activities

(a) I have no problems with performing my usual activities ☐ 1 (b) I have some problems with performing my usual activities ☐ 2 (c) I am unable to perform my usual activities ☐ 3

4. Pain/Discomfort

(a) I have no pain or discomfort ☐ 1 (b) I have moderate pain or discomfort ☐ 2 (c) I have extreme pain or discomfort ☐ 3

5. Anxiety/Depression

(a) I am not anxious or depressed ☐ 1 (b) I am moderately anxious or depressed ☐ 2 (c) I am extremely anxious or depressed ☐ 3

DAY 28 PATIENT'S PERCEIVED BASELINE EUROQOL 5-D HEALTH STATUS SCORE

• The patient's health state score today, on a scale of 0 – 100, with 0 = Worst imaginable health state & 100 = Best imaginable health state

Score =

POST-DISCHARGE GP CONSULTATIONS FOR THIS ILLNESS:

		Enter Yes=1, or 2=No, in the box	
1.	Has the patient seen his/her GP after discharge as a result of admission illness?	1=Yes <input type="checkbox"/>	2=No <input type="checkbox"/>
2.	If YES, how many times at the surgery (in hours)?	<input type="text"/> <input type="text"/>	Number
3.	If YES, how many times at the patient's home?	<input type="text"/> <input type="text"/>	Number
4.	If YES, how many times at an Out-of-Hours Centre?	<input type="text"/> <input type="text"/>	Number

DRUGS PRESCRIBED BY GP POST-DISCHARGE SPECIFICALLY FOR THIS ILLNESS

	Name of DRUG	Dose	Frequency /24h (n)	No. of days
1.	<input type="text"/>	Dose (mg) <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Number <input type="text"/>	Number <input type="text"/> <input type="text"/>
2.	<input type="text"/>	Dose (mg) <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Number <input type="text"/>	Number <input type="text"/> <input type="text"/>
3.	<input type="text"/>	Dose (mg) <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Number <input type="text"/>	Number <input type="text"/> <input type="text"/>
4.	<input type="text"/>	Dose (mg) <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Number <input type="text"/>	Number <input type="text"/> <input type="text"/>
5.	<input type="text"/>	Dose (mg) <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Number <input type="text"/>	Number <input type="text"/> <input type="text"/>

Appendix 6 Publications that were screened for the meta-analysis

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Agoritsas, 2006 ⁹¹	USA	2 weeks to 18 years	None	Seasonal	PCR and culture (R-mix)	QuickVue Influenza A + B	NPS: 85 (50/59)	NPS: 98 (62/63)	NPS: 98 (50/51)	NPS: 87 (62/71)
							NPW: 69 (41/59)	NPW: 98 (62/63)	NPW: 98 (41/42)	NPW: 78 (62/80)
							NS: 78 (46/59)	NS: 97 (61/63)	NS: 96 (46/48)	NS: 82 (61/74)
Andresen, 2010 ¹⁶⁸	Australia	0–18 years	None	Pandemic	PCR	QuickVue Influenza A + B	NPA: 84 (122/145)	NPA: 98	–	–
							Swabs: 66 (47/71)	Swabs: 100	–	–
Balish, 2009 ²⁴¹	USA	Included, age not specified	Included, age not specified	Pandemic	PCR	Directigen EZ Flu A + B	49 (21/43)	–	–	–
		Included, age not specified	Included, age not specified	H1N1	PCR	Directigen EZ Flu A + B	75 (3/4)	–	–	–
		Included, age not specified	Included, age not specified	H3N2	PCR	Directigen EZ Flu A + B	83 (10/12)	–	–	–
		Included, age not specified	Included, age not specified	Pandemic	PCR	NOW Flu A + B	40 (18/45)	–	–	–

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Bellei, 2003 ¹⁸⁹	Brazil	Included, age not specified	Included, age not specified	H1N1	PCR	NOW Flu A + B	60 (3/5)	–	–	–
		Included, age not specified	Included, age not specified	H3N2	PCR	NOW Flu A + B	80 (12/15)	–	–	–
		Included, age not specified	Included, age not specified	Pandemic	PCR	QuickVue Influenza A + B	69 (31/45)	–	–	–
		Included, age not specified	Included, age not specified	H1N1	PCR	QuickVue Influenza A + B	80 (4/5)	–	–	–
		Included, age not specified	Included, age not specified	H3N2	PCR	QuickVue Influenza A + B	80 (12/15)	–	–	–
		None	18–56 years	Seasonal	Culture on MDCK cells	QuickVue Influenza A + B	74 (29/39)	83 (48/58)	–	–
Bellman-Weiler, 2011 ²⁴²	Austria	None	Included, age not specified	Pandemic	PCR	Directigen EZ Flu A + B	32 (8/25)	93 (66/71)	62 (8/13)	79.5 (66/83)
		None	Included, age not specified	Pandemic	PCR	NOW Flu A + B	28 (8/29)	99 (77/78)	89 (8/9)	79 (77/98)
		Included, age not specified	Included, age not specified	Seasonal	PCR	NOW Flu A + B	75.3 (64/85)	98 (458/469)	–	–
Biggs, 2010 ²⁴³	USA	Included, age not specified	Included, age not specified	Seasonal	PCR	NOW Flu A + B	75.3 (64/85)	98 (458/469)	–	–

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Blyth, 2009 ²⁴⁴	Australia	Included, age not specified	Included, age not specified	Pandemic	PCR	QuickVue Influenza A + B	25 (5/20)			
Booth, 2006 ¹⁹⁰	Australia	1–16 years	Included, age not specified	Seasonal, influenza A	Culture on MDCK cells and IFA	ImmunoCard Stat! Flu A&B	80 (28/35)	98 (185/189)	87.5 (28/32)	96 (185/192)
		1–16 years	Included, age not specified	Seasonal, influenza B	Culture on MDCK cells and IFA	ImmunoCard Stat! Flu A&B	47 (7/15)	100 (209/209)	100 (7/7)	96 (209/217)
		1–16 years	Included, age not specified	Seasonal, influenza A	Culture on MDCK cells and IFA	NOW Flu A + B	80 (28/35)	99 (188/189)	97 (28/29)	96 (188/195)
		1–16 years	Included, age not specified	Seasonal, influenza B	Culture on MDCK cells and IFA	NOW Flu A + B	47 (7/15)	100 (208/209)	88 (7/8)	96 (208/216)
Cazacu, 2004 ²⁰⁰	USA	From ≥ 3 days	To 55.8 years	Seasonal	Culture on RMK cells	Directigen Flu A + B	44 (96/219)	100 (3863/3873)	90.5 (96/106)	97 (3863/3986)
Cazacu, 2004 ²⁰¹		Included, age not specified	Included, age not specified	Seasonal	Culture on RMK cells	XPECT Flu A + B	94 (118/125)	100 (275/275)	100 (118/118)	97.5 (275/282)
Chan, 2002 ¹⁴⁷	USA	From < 2 years	To > 55 years	Seasonal, influenza A	Culture on MDCK cells	Directigen EZ Flu A + B	100 (22/22)	99 (225/228)	88 (22/25)	100 (225/225)
		From < 2 years	To > 55 years	Seasonal, influenza B	Culture on MDCK cells	Directigen EZ Flu A + B	88 (28/32)	97 (211/218)	80 (28/35)	98 (211/215)
Chen, 2010 ¹⁹¹	China	Included, age not specified	Included, age not specified	Influenza A	Culture on MDCK cells	Flu A Dot	88.5 (69/78)	99 (146/147)	99 (69/70)	94 (146/155)
Cheng, 2010 ¹⁴⁸	China	From 5 months	To 77 years	Pandemic	PCR and culture on MDCK cells	Fujirebio Espline Influenza A&B-N	62 (37/60)			

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV %	NPV %
Cheng, 2011 ²⁴⁵		From 6 months	To 86 years	Seasonal and pandemic	PCR	Directigen Flu A	72 (169/235)	100 (571/572)	99 (169/170)	90 (571/637)
		From 6 months	To 86 years	Seasonal and pandemic	PCR	Flu A Dot	91 (214/235)	100 (570/572)	99 (214/216)	96 (570/591)
		From 5 months	To 78 years	Pandemic	PCR	NOW Flu A + B	64.5 (91/141) ≥ 21 years: 47	95 (107/113)	94 (91/97)	68 (107/157)
Choi, 2010 ¹⁷²	Korea	From 5 months	To 78 years	Pandemic	PCR		Illness onset: 56.3			
		From 5 months	To 78 years	Pandemic	PCR	SD Bioline Influenza A/B/A(H1N1) Pandemic rapid test	69.5 (98/141) ≥ 21 years: 57.9	100 (113/113)	100 (98/98)	72 (113/156)
		From 2 weeks	To 83 years	Pandemic	PCR	SD Bioline Influenza A/B/A(H1N1) Pandemic rapid test	Illness onset: 31.3			
Choi, 2010 ¹⁷⁰		From 2 weeks	To 83 years	Pandemic	PCR		77 (241/313)	100 (445/446)		
Chomel, 1992 ¹⁸¹	France	Included, age not specified	Included, age not specified	Seasonal, influenza A	ELISA	Directigen Flu A	87.9 (87/99)	97 (59/61)	83 (59/71)	97 (87/89)
		Included, age not specified	Included, age not specified	Seasonal, influenza A	Culture on LLCMK2 cells	Directigen Flu A	84 (21/25)			
		From 2 months	To 76 years	Seasonal	Culture on RMK cells	BioStar OIA Flu A/B	80.1 (121/151)	73 (185/253)		
Covalciuc, 1999 ¹⁹³	USA	From 2 months	To 76 years	Seasonal	PCR	Clearview Exact Influenza A & B	19 (55/297)	100	100	75
de la Tabla, 2010 ²⁴⁶	Spain	From 3 months	To 97 years	Pandemic	PCR					

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
D'Heilly, 2008 ⁶⁹	USA	None	18–91 years	Seasonal	Culture	FLU OIA A/B	65 (49/75)	97	89	89
Diederin, 2010 ¹⁹⁵	Netherlands	From birth	To 81 years	Pandemic	PCR	NOW Flu A + B	47 (18/38)	95 (92/97)	78 (18/23)	82 (92/112)
Drexler, 2009 ¹⁶⁹	Germany	Included, age not specified	Included, age not specified	Pandemic	PCR	NOW Flu A + B	11.1 (16/144)			
Faix, 2009 ²⁴⁷	USA	Included, age not specified	Included, age not specified	Pandemic	PCR	QuickVue Influenza A + B	51 (20/39)	99		
		Included, age not specified	Included, age not specified	Influenza A (H1N1)	PCR	QuickVue Influenza A + B	63 (12/19)	99		
		Included, age not specified	Included, age not specified	Influenza A (H1N1)	PCR	QuickVue Influenza A + B	31 (6/19)	99		
Fernandez, 2010 ²⁴⁸	USA	From < 2 years	To > 65 years	Seasonal and Pandemic	R-mix culture and DFA	QuickVue Influenza A + B	77 (113/147)	85	74	87
Fuenzalida, 2010 ²⁴⁹	Spain	From 4 days	To 87 years	Pandemic	PCR	NOW Flu A + B	60.3 (137/227)	94	88	75
Ghebremedhin, 2009 ²⁵⁰	Germany	7 weeks to 6.5 years	None	Influenza A	PCR	Actim Influenza A&B	69.2 (9/13)	100 (460/460)	100 (9/9)	99 (460/464)
		7 weeks to 6.5 years	None	Influenza B	PCR	Actim Influenza A&B	60 (6/10)	100 (463/463)	100 (6/6)	98 (463/467)
		7 weeks to 6.5 years	None	Influenza A	PCR	NOW Flu A + B	57 (4/7)	100		
		7 weeks to 6.5 years	None	Influenza A	PCR	NOW Flu A + B	43 (3/7)	100		

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV %	NPV %
Gimeno, 2010 ²⁵¹	Spain	From < 1 year	To 87 years	Pandemic	PCR	SD Bioline Influenza A/B/A(H1N1) Pandemic rapid test	26.9 (24/49) NPS: 35 <i>Oropharyngeal swabs: 13</i>			
Gordon, 2009 ²⁵²	Nicaragua	2–12 years	None	Seasonal	PCR	QuickVue Influenza A + B	68.5 (246/359)	98		
		2–12 years	None	Influenza A	PCR	QuickVue Influenza A + B	65.2 (146/224)			
		2–12 years	None	Influenza B	PCR	QuickVue Influenza A + B	74.1 (100/135)			
Gordon, 2010 ²⁵³		2–14 years	None	Pandemic	PCR	QuickVue Influenza A + B	64.1 (59/92)	98		
Hamilton, 2002 ¹⁹²	USA	12 days to 19 years	None	Seasonal	Culture on RMK cells	Directigen Flu A + B	75 (49/65)	93 (218/235)	74 (49/66)	93 (218/234)
		12 days to 19 years	None	Seasonal	Culture on RMK cells	Zstat Flu-II	88 (57/65)	92 (216/235)	75 (57/76)	96 (216/224)
Hara, 2008 ¹⁸⁷	Japan	4 months to 19 years	None	Seasonal, influenza A	Culture on MDCK cells	Directigen EZ Flu A + B	100 (53/53)	99 (438/441)	100 (53/53)	100 (441/441)
		4 months to 19 years	None	Seasonal, influenza B	Culture on MDCK cells	Directigen EZ Flu A + B	76 (206/270)	99 (221/224)	99 (206/209)	78 (221/285)

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Hawkes, 2010 ¹⁸⁴	Canada	4 months to 19 years	None	Seasonal, influenza A	Culture on MDCK cells	Fujirebio Espline Influenza A&B-N	100 (53/53)	100 (441/441)	100 (53/53)	100 (441/441)
		4 months to 19 years	None	Seasonal, influenza B	Culture on MDCK cells	Fujirebio Espline Influenza A&B-N	86 (232/270)	100 (224/224)	100 (232/232)	85 (224/262)
		4 months to 19 years	None	Seasonal, influenza A	Culture on MDCK cells	NOW Flu A + B	100 (53/53)	98 (430/441)	100 (531/531)	100 (441/441)
		4 months to 19 years	None	Seasonal, influenza B	Culture on MDCK cells	NOW Flu A + B	78 (211/270)	99 (221/224)	99 (211/214)	79 (221/280)
		1 month to 17 years	None	Pandemic	PCR	NOW Flu A + B	62 (66/107)	99 (70/71)	99 (66/67)	63 (70/111)
		1 month to 17 years	None	Influenza A	DFA	NOW Flu A + B	69 (72/104)	99 (567/575)	90 (72/80)	95 (567/599)
		1 month to 17 years	None	Influenza A	Culture and DFA	NOW Flu A + B	68 (75/111)	99 (590/596)	93 (75/81)	94 (590/626)
		1 month to 17 years	None	Influenza B	DFA	NOW Flu A + B	72 (51/71)	100 (605/608)	93 (75/81)	97 (605/625)
Heinonen, 2011 ⁸⁶	Finland	1 month to 17 years	None	Influenza B	Culture and DFA	NOW Flu A + B	68 (52/77)	100 (628/630)	96 (52/54)	96 (628/653)
		1–3 years	None	Influenza A	PCR, culture on MDCK and TR-FIA	Actim Influenza A&B	90 (28/31)	99 (127/128)	97 (28/29)	98 (127/130)
		1–3 years	None	Influenza B	PCR, culture on MDCK and TR-FIA	Actim Influenza A&B	25 (2/8)	100 (150/150)	100 (2/2)	96 (150/156)
Herrmann, 2011 ²⁵⁴	Sweden	From 2 months	To 83 years	Seasonal	PCR	BioStar OIAFlu A/B	56.5 (52/92)	89.1		

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Hurt, 2007 ⁸⁸	Australia	From 4 days	To 64 years	Influenza A	RETICIF	Directigen EZ Flu A + B	69 (34/49)	100 (128/128)	100 (34/34)	90 (128/143)
		From 4 days	To 64 years	Influenza B	RETICIF	Directigen EZ Flu A + B	30 (3/10)	100 (167/167)	100 (3/3)	96 (167/174)
		From 4 days	To 64 years	Influenza A	RETICIF	Denka Seiken Quick Ex-Flu	71 (35/49)	100 (128/128)	100 (35/35)	90 (128/142)
		From 4 days	To 64 years	Influenza B	RETICIF	Denka Seiken Quick Ex-Flu	30 (3/10)	100 (167/167)	100 (3/3)	96 (167/174)
		From 4 days	To 64 years	Influenza A	RETICIF	Fujirebio Espline Influenza A&B-N	67 (33/49)	100 (128/128)	100 (5/5)	89 (128/144)
		From 4 days	To 64 years	Influenza B	RETICIF	Fujirebio Espline Influenza A&B-N	30 (3/10)	100 (167/167)	100 (3/3)	96 (167/174)
		From 4 days	To 64 years	Influenza A	RETICIF	NOW Flu A + B	73 (36/49)	99 (127/128)	97 (36/37)	91 (127/140)
		From 4 days	To 64 years	Influenza B	RETICIF	NOW Flu A + B	30 (3/10)	100 (167/167)	100 (3/3)	96 (167/174)
		From 4 days	To 64 years	Influenza A	RETICIF	QuickVue Influenza A + B	67 (33/49)	100 (12/128)	100 (33/33)	89 (128/144)
		From 4 days	To 64 years	Influenza B	RETICIF	QuickVue Influenza A + B	30 (3/10)	100 (167/167)	100 (3/3)	96 (167/174)
		From 4 days	To 64 years	Influenza B	RETICIF	Rockeby Influenza A Antigen Test	10 (5/49)	100 (128/128)	100 (5/5)	74 (128/172)

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Kim, 2010 ²⁰²	Korea	From 2 months	To 78 years	Pandemic	PCR	SD Bioline Influenza A/B/A(H1N1) Pandemic rapid test	70 (182/260)	98 (677/688)	94 (182/193)	90 (677/755)
Kok, 2010 ²⁵⁵	Australia	Included, age not specified	Included, age not specified	Pandemic	PCR	QuickVue Influenza A + B	53.4 (93/174)	100	100	76
						QuickVue Influenza A + B	77.2 (68/88)	100	100	92
						QuickVue Influenza A + B	74.2 (72/97)	100	100	90
						NOW Flu A + B	53 (70/132)	98	97	63
Landry, 2008 ²⁵⁶	USA	From 4 months	to 93 years	Seasonal	PCR	NanoSign Influenza A/B Ag	79.4 (158/199)	97 (801/824)	87 (158/181)	95 (801/842)
Lee, 2010 ²⁵⁷	Korea	Yang, 2011	Taiwan	Pandemic	PCR	SD Bioline Influenza A/B/A(H1N1) Pandemic rapid test	39.3 (22/56)	100	100	59.5
Leveque, 2011 ²⁵⁸	France	Included, age not specified	Included, age not specified	Pandemic	PCR	QuickVue Influenza A + B	66 (266/404)	84 (250/299)	84 (266/315)	64 (250/388)
Louie, 2010 ²⁵⁹	USA	From < 1 year	To 80 years	Pandemic	PCR	QuickVue Influenza A + B	15 (2/13)	99 (1464/1479)	12 (2/17)	99 (1464/1475)
Lucas, 2011 ¹⁹⁸	USA	From < 5 years	To > 60 years	Influenza A	PCR	QuickVue Influenza A + B	31 (4/13)	99 (610/615)	44 (4/9)	98 (610/619)

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV %	NPV %
Mehlmann, 2007 ¹⁴⁹	USA	From < 5 years	To > 60 years	Pandemic	PCR	QuickVue Influenza A + B	20 (6/30)	99 (1464/1479)	29 (6/21)	98 (1076/1096)
		From 3 months	To 86 years	Seasonal	Culture (Rmix)	QuickVue Influenza A + B	93 (53/57)	100 (49/49)	100 (53/53)	92 (49/53)
		From 3 months	To 86 years	Seasonal	PCR	QuickVue Influenza A + B	87 (53/61)	97	98	92
Nilsson, 2008 ⁸³	Sweden	None	19–86 years	Seasonal	PCR	NOW Flu A + B	52 (63/120)	100		73
Nougairède, 2010 ¹⁸³	France	Included, age not specified	Included, age not specified	Pandemic	PCR	Directigen EZ Flu A + B	57.7 (64/111)	100 (1910/1910)	100 (64/64)	97.5 (1910/1957)
Poehling, 2002 ¹⁵⁰	USA	3 months to 18 years	None	Seasonal	PCR and culture on RMK cells	QuickVue Influenza A + B	73.7 (14/19)	98	74	98
Poehling, 2006 ²⁶⁰		0–59 months	None	Seasonal	PCR and culture on RMK cells	QuickVue Influenza A + B	82 (42/51)	99	98	94
Pongthanapichit, 2011 ²⁶¹	Thailand	6 months to 15 years	None	Pandemic and seasonal	PCR	Osom Influenza A&B	69.5 (114/164)	100 (46/46)	100 (114/114)	48 (46/96)
		6 months to 15 years	None	Pandemic and seasonal	PCR	QuickVue Influenza A + B	58.5 (96/164)	100 (46/46)	100 (96/96)	40 (46/114)
		6 months to 15 years	None	Pandemic and seasonal	PCR	SD Bioline Influenza A/B/A(H1N1) Pandemic rapid test	45.1 (74/164)	100 (46/46)	100 (74/74)	34 (46/136)

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Pregliasco, 2004 ²⁶²	Italy	0–14 years	None	Seasonal	Culture on MDCK cells	QuickVue Influenza A + B	54.5 (6/11)	98.5 (323/328)	54.5 (6/11)	98.5 (323/328)
		0–14 years	None	Seasonal	PCR	QuickVue Influenza A + B	58.3 (7/12)	98.8 (323/327)	63.6 (7/11)	98.5 (323/328)
Quach, 2002 ¹⁹⁹	Canada	Included, age not specified	None	Seasonal	Culture on RMK and MDCK cells	QuickVue Influenza A + B	79.2 (42/53)	82.6 (204/247)	49.4 (42/85)	94.9 (204/215)
Rahman, 2007 ¹⁹⁶	USA	From 6 months	To ≥ 65 years	Seasonal	Culture on RMK cells	Directigen EZ Flu A + B	42 (18/43)	96 (72/75)	86 (18/21)	74 (72/97)
Rahman, 2008 ¹⁵¹	USA	From 6 months	To ≥ 65 years	Seasonal	PCR and culture on RMK cells	NOW Flu A + B	61 (11/18)	100 (55/55)	100 (11/11)	89 (55/62)
Rashid, 2007 ¹⁸²	UK and Saudi Arabia	From 1 year	To 85 years	Seasonal	PCR	QuickVue Influenza A + B	22 (13/58)	99 (492/497)	72 (13/18)	92 (492/537)
Rodriguez, 2002 ¹⁸⁵	USA	From < 3 years	To > 21 years	Seasonal	Culture and DFA	BioStar OIA Flu A/B	93 (54/58)	82 (47/57)	84 (54/64)	92 (47/51)
		From < 3 years	To > 21 years	Seasonal	Culture and DFA	Directigen EZ Flu A + B	95 (55/58)	84 (49/58)	86 (55/64)	94 (49/52)
		From < 3 years	To > 21 years	Seasonal	Culture and DFA	QuickVue Influenza A + B	95 (54/57)	76 (42/55)	81 (54/67)	93 (42/45)
		From < 3 years	To > 21 years	Seasonal	Culture and DFA	Zstat Flu AB	72 (41/57)	83 (48/58)	80 (41/51)	75 (48/64)
Rouleau, 2009 ²⁶³	Canada	From < 1 year	To 82 years	Seasonal	PCR	QuickVue Influenza A + B	19.5 (52/267)	99.1 (219/221)	96 (52/54)	51 (219/434)

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Ruest, 2003 ¹⁵²	Canada	From 1 day	To 98 years	Seasonal	Culture on MDCK cells	Directigen Flu A + B	86 (57/66)	94 (115/122)	89 (57/64)	92 (115/124)
		From 1 day	To 98 years	Seasonal	PCR	Directigen Flu A + B	80 (63/79)	98 (121/123)	97 (63/65)	88 (121/137)
		From 1 day	To 98 years	Seasonal	Culture on MDCK cells	QuickVue Influenza A + B	91 (64/70)	86 (105/122)	79 (64/81)	95 (105/111)
		From 1 day	To 98 years	Seasonal	PCR	QuickVue Influenza A + B	85 (72/84)	92 (127/138)	87 (72/83)	90 (114/127)
Sabetta, 2009 ¹⁸⁶	USA	Included, age not specified	Included, age not specified	Pandemic	PCR	XPECT Flu A + B	47 (23/49)	86 (12/14)	92 (23/25)	32 (12/38)
		≤ 17 years	None	Influenza A	PCR	QuickVue Influenza A + B	Swabs: Foam 81 (30/37) Flocked 59 (22/37)	Swabs: Foam 98 (62/63) Flocked 98 (62/63)	Swabs: Foam 97 (30/31) Flocked 96 (22/23)	Swabs: Foam 90 (81/90) Flocked 81 (62/77)
Scansen, 2010 ⁹⁰	USA	≤ 17 years	None	Influenza B	PCR	QuickVue Influenza A + B	Swabs: Foam 53 (10/19) Flocked 42 (8/19)	Swabs: Foam 100 (81/81) Flocked 100 (81/81)	Swabs: Foam 100 (10/10) Flocked 100 (8/8)	Swabs: Foam 90 (81/90) Flocked 88 (81/92)
		≤ 17 years	None	Influenza A	Culture: R-Mix and DFA	QuickVue Influenza A + B	Swabs: Foam 85 (29/34) Flocked 65 (22/34)	Swabs: Foam 97 (64/66) Flocked 97 (64/66)	Swabs: Foam 94 (29/31) Flocked 92 (22/24)	Swabs: Foam 93 (64/69) Flocked 84 (64/76)

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Simmerman, 2007 ¹⁵³	Thailand	≤17 years	None	Influenza B	Culture: R-Mix and DFA	QuickVue Influenza A + B	Swabs:	Swabs:	Swabs:	Swabs:
							<i>Foam 60</i> (9/15)	<i>Foam 99</i> (84/85)	<i>Foam 90</i> (9/10)	<i>Foam 93</i> (84/90)
							<i>Flocked 53</i> (8/15)	<i>Flocked 100</i> (85/85)	<i>Flocked 100</i> (8/8)	<i>Flocked 92</i> (85/92)
Stripeli, 2010 ⁸⁴	Thailand	From 1 month	To 86 years	Seasonal	Culture on MDCK cells	QuickVue Influenza A + B	77 (158/205)	96	82	95
Stripeli, 2010 ⁸⁴	Greece	6 months to 14 years	None	Seasonal	PCR	QuickVue Influenza A + B	67.5 (27/40)	96 (169/176)	79 (27/34)	93 (169/182)
Suntarattiwong, 2010 ²⁶⁴	Thailand	6 months to 2 years	None	Pandemic	PCR	QuickVue Influenza A + B	76.7 (23/30)			
Shoji, 2009 ¹⁸⁸	Japan	From 1 year	To 88 years	Influenza A	Culture	QuickVue Influenza A + B	62.7 (89/142)	99.2 (235/237)	97.8 (89/91)	81.6 (235/288)
							69.2 (27/39)			
							87.8 (72/82)	90.1 (322/357)	67.3 (72/107)	97 (322/332)
Shoji, 2009 ¹⁸⁸	Japan	From 1 year	To 88 years	Influenza B	Culture	QuickVue Influenza A + B	80.4 (176/219)	95 (209/220)	94.1 (176/187)	83 (209/252)

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV %	NPV %
Tsao, 2011 ²⁶⁵	Taiwan	Included, age not specified	Included, age not specified	Pandemic	PCR	Formosa One Sure Flu A/B Rapid Test	53.2 (33/62)			
		Included, age not specified	Included, age not specified	Pandemic	PCR	QuickVue Influenza A + B	45.2 (28/62)	100		
Vasoo, 2009 ⁸⁵	USA	From 7 months	To 58 years	Pandemic	PCR	Directigen EZ Flu A + B	46.7 (28/60)	100	100	89.6
		From 7 months	To 58 years	Pandemic	PCR	NOW Flu A + B	38.3 (23/60)	100	100	88.2
		From 7 months	To 58 years	Pandemic	PCR	QuickVue Influenza A + B	53.3 (32/60)	100	100	90.8
Velasco, 2010 ²⁶⁶	Philippines	From 6 months	To 73 years	Pandemic	PCR	QuickVue Influenza A + B	63 (142/226)	96 (110/114)	97 (142/146)	57 (110/194)
Waner, 1991 ¹⁹⁴	USA	From < 2 months	None	Seasonal	Culture on RMK cells	Directigen Flu A	100 (23/23)	91.6 (153/167)	62 (23/37)	100 (153/153)
		From < 2 months	None	Seasonal	IFA	Directigen Flu A	100 (24/24)	95 (152/160)	75 (24/32)	100 (152/152)
Watanabe, 2009 ²⁶⁷	Japan	1–13 years	None	Seasonal	Culture on MDCK cells	Capilia FluA, B	76.9 (444/577)			
Watcharaanan, 2010 ²⁶⁸	Thailand	From 3 months	To 73 years	Pandemic	PCR	QuickVue Influenza A + B	75 (9/12)	80 (41/51)	47 (9/19)	93 (41/44)
		From 3 months	To 73 years	Seasonal	PCR	QuickVue Influenza A + B	50 (7/14)	80 (41/51)	41 (7/17)	85 (41/48)

Author	Location	Children	Adults	Influenza	Gold standard	POCT	Sensitivity (%)	Specificity (%)	PPV%	NPV%
Weitzel, 2007 ²⁶⁹	Germany	From 4 years	To 80 years	Seasonal	PCR and culture on MDCK cells	ImmunoCard Stat! Flu A&B	67 (18/27)	99 (175/176)	95 (18/19)	95 (175/184)
Yang, 2011 ²⁷⁰	Taiwan	From < 1 year	To > 60 years	Pandemic	PCR	Fujirebio Espline Influenza A&B-N	54.6 (425/778)			
		From < 1 year	To > 60 years	Influenza A H3N2	PCR	Fujirebio Espline Influenza A&B-N	72.3 (164/227)			
Yoo, 2007 ¹⁹⁷	Korea	3 months to 15 years	18.5–81.9 years	Seasonal	Culture (R-mix)	QuickVue Influenza A + B	46.7 (35/75)	94.5 (208/220)	74.5 (35/47)	83.9 (208/248)
		3 months to 15 years	18.5–81.9 years	Influenza A	Culture (R-mix)	SD Bioline Influenza A/B/A(H1N1) Pandemic rapid test	61.9 (26/42)	96.8 (245/253)	76.5 (26/34)	93.9 (245/261)
		3 months to 15 years	18.5–81.9 years	Influenza B	Culture (R-mix)	SD Bioline Influenza A/B/A(H1N1) Pandemic rapid test	54.5 (18/33)	100 (262/262)	100 (18/18)	94.6 (262/277)

DFA, direct fluorescent antibody; IFA, immunofluorescence assay; MDCK, Madin–Darby Canine Kidney; NPS, nasopharyngeal swab; NPW, nasopharyngeal wash; NS, nose swab; RETCIF, rapid enhanced tissue culture immunofluorescence; RMK, Rhesus monkey kidney; TR-FIA, time-resolved fluorimmunoassay.

Appendix 7 Ease-of-use scores

TABLE 38 Component EoU scores for the QuickVUE Influenza A&B POCT for the diagnosis of influenza

Categories	Criteria for categorisation	EoU score		
Test site	Is a POCT	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Requires purpose-built accommodation, ventilation systems and dedicated space			
Equipment	No specialised equipment required and is readily transferred between hospital facilities	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised equipment is essential and non-portable			
Materials and reagents	Are stable, pre-packaged and/or pre-measured, and require no special handling steps or storage	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	May be labile, requiring special storage or require special handling steps; their preparation requires manual steps, e.g. volumetric measurement			
Operational steps	Either automatically executed or easily controlled	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Require close monitoring and control, and may require special preparation, precise temperature control or timing, accurate pipetting or extensive calculations			
Training, experience and knowledge	Require minimal scientific and technical knowledge and experience; and knowledge to perform test can be obtained through on-job instruction (commensurate with AFC Band 4, or less)	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised scientific and technical knowledge essential and substantial experience required (commensurate with AFC Band 7, or higher)			
Calibration and quality control	Calibration is either automatic or not required; quality control materials are included, or readily available, and are stable	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Calibration and quality control materials, if available, may be labile or unavailable; or technical expertise is required for calibration			
Interpretation and judgement	Minimal interpretation and judgement are required, and problems require limited interpretation, judgement and decision-making	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Extensive interpretation and judgement are required; resolution of problems requires extensive interpretation, judgement and decision-making			

continued

TABLE 38 Component EoU scores for the QuickVUE Influenza A&B POCT for the diagnosis of influenza (continued)

Categories	Criteria for categorisation	EoU score		
Test system troubleshooting and equipment maintenance	Test system troubleshooting is automatic or self-correcting or clearly described or requires minimal judgement	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Test system troubleshooting is not automatic or self-correcting and requires decision-making to resolve most problems; or equipment maintenance requires special knowledge, skills and abilities			
Time to reporting of results	Results are reported within 4 hours of collection of almost all specimens	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Median time to reporting of results exceeds the median duration of hospitalisations/time to death			
Health and safety	The test is completed using low levels of personal protection, i.e. gloves	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	One or more operational steps requires bio-safety level Category 3, or higher			
Storage and disposal of waste test materials and reagents	Waste materials and reagents are stored and disposed using medium duty 'Clinical waste' plastic bags and 'Sharps' containers, or a sluice	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Waste materials or reagents include hazardous materials that require special attention			
Total EoU score		11		

TABLE 39 Component EoU scores for the BinaxNOW *S. pneumoniae* test POCT

Categories	Criteria for categorisation	EoU score		
Test site	Is a POCT	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Requires purpose-built accommodation, ventilation systems and dedicated space			
Equipment	No specialised equipment required and is readily transferred between hospital facilities	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised equipment is essential and non-portable			
Materials and reagents	Are stable, pre-packaged and/or pre-measured, and require no special handling steps or storage	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	May be labile, requiring special storage or require special handling steps; their preparation requires manual steps, e.g. volumetric measurement			
Operational steps	Either automatically executed or easily controlled	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Require close monitoring and control, and may require special preparation, precise temperature control or timing, accurate pipetting or extensive calculations			
Training, experience and knowledge	Require minimal scientific and technical knowledge and experience; and knowledge to perform test can be obtained through on-job instruction (commensurate with AFC Band 4, or less)	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised scientific and technical knowledge essential and substantial experience required (commensurate with AFC Band 7, or higher)			
Calibration and quality control	Calibration is either automatic or not required; quality control materials are included, or readily available, and are stable	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Calibration and quality control materials, if available, may be labile or unavailable; or technical expertise is required for calibration			
Interpretation and judgement	Minimal interpretation and judgement are required, and problems require limited interpretation, judgement and decision-making	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Extensive interpretation and judgement are required; resolution of problems requires extensive interpretation, judgement and decision-making			
Test system troubleshooting and equipment maintenance	Test system troubleshooting is automatic or self-correcting or clearly described or requires minimal judgement	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Test system troubleshooting is not automatic or self-correcting and requires decision-making to resolve most problems; or equipment maintenance requires special knowledge, skills and abilities			

continued

TABLE 39 Component EoU scores for the BinaxNOW *S. pneumoniae* test POCT (continued)

Categories	Criteria for categorisation	EoU score		
Time to reporting of results	Results are reported within 4 hours of collection of almost all specimens	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Median time to reporting of results exceeds the median duration of hospitalisations/time to death			
Health and safety	The test is completed using low levels of personal protection, i.e. gloves	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	One or more operational steps requires bio-safety level Category 3, or higher			
Storage and disposal of waste test materials and reagents	Waste materials and reagents are stored and disposed using medium duty 'Clinical waste' plastic bags and 'Sharps' containers, or a sluice	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Waste materials or reagents include hazardous materials that require special attention			
	Total EoU score	11		

TABLE 40 Component EoU scores for semi-nested multiplex PCR for influenza A subtypes H1 and H3, influenza B, and RSV A and B

Categories	Criteria for categorisation	EoU score		
Test site	Is a POCT			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Requires purpose-built accommodation, ventilation systems and dedicated space			
Equipment	No specialised equipment required and is readily transferred between hospital facilities			
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised equipment is essential and non-portable			3
Materials and reagents	Are stable, pre-packaged and/or pre-measured, and require no special handling steps or storage			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	May be labile, requiring special storage or require special handling steps; their preparation requires manual steps, e.g. volumetric measurement			
Operational steps	Either automatically executed or easily controlled			
	Intermediate between descriptions listed for scores of 1 and 3			
	Require close monitoring and control, and may require special preparation, precise temperature control or timing, accurate pipetting or extensive calculations			3
Training, experience and knowledge	Require minimal scientific and technical knowledge and experience; and knowledge to perform test can be obtained through on-job instruction (commensurate with AFC Band 4, or less)			
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised scientific and technical knowledge essential and substantial experience required (commensurate with AFC Band 7, or higher)			3
Calibration and quality control	Calibration is either automatic or not required; quality control materials are included, or readily available, and are stable			
	Intermediate between descriptions listed for scores of 1 and 3			
	Calibration and quality control materials, if available, may be labile or unavailable; or technical expertise is required for calibration			3
Interpretation and judgement	Minimal interpretation and judgement are required, and problems require limited interpretation, judgement and decision-making			
	Intermediate between descriptions listed for scores of 1 and 3			
	Extensive interpretation and judgement are required; resolution of problems requires extensive interpretation, judgement and decision-making			3

continued

TABLE 40 Component EoU scores for semi-nested multiplex PCR for influenza A subtypes H1 and H3, influenza B, and RSV A and B (*continued*)

Categories	Criteria for categorisation	EoU score		
Test system troubleshooting and equipment maintenance	Test system troubleshooting is automatic or self-correcting or clearly described or requires minimal judgement			
	Intermediate between descriptions listed for scores of 1 and 3			
	Test system troubleshooting is not automatic or self-correcting and requires decision-making to resolve most problems; or equipment maintenance requires special knowledge, skills, and abilities			3
Time to reporting of results	Results are reported within 4 hours of collection of almost all specimens			
	Intermediate between descriptions listed for scores of 1 and 3	2		
	Median time to reporting of results exceeds the median duration of hospitalisations/time to death			
Health and safety	The test is completed using low levels of personal protection, i.e. gloves			
	Intermediate between descriptions listed for scores of 1 and 3			
	One or more operational steps requires bio-safety level Category 3, or higher			3
Storage and disposal of waste test materials and reagents	Waste materials and reagents are stored and disposed using medium duty 'Clinical waste' plastic bags and 'Sharps' containers, or a sluice			
	Intermediate between descriptions listed for scores of 1 and 3			
	Waste materials or reagents include hazardous materials that require special attention			3
Total EoU score		30		

TABLE 41 Component EoU scores for one-step, real-time RT-PCR tests for influenza A subtypes H1 and H3, influenza B, and RSV A and B

Categories	Criteria for categorisation	EoU score		
Test site	Is a POCT			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Requires purpose-built accommodation, ventilation systems and dedicated space			
Equipment	No specialised equipment required and is readily transferred between hospital facilities			
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised equipment is essential and non-portable			3
Materials and reagents	Are stable, pre-packaged and/or pre-measured, and require no special handling steps or storage	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	May be labile requiring special storage or require special handling steps; their preparation requires manual steps, e.g. volumetric measurement			
Operational steps	Either automatically executed or easily controlled			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Require close monitoring and control, and may require special preparation, precise temperature control or timing, accurate pipetting or extensive calculations			
Training, experience and knowledge	Require minimal scientific and technical knowledge and experience; and knowledge to perform test can be obtained through on-job instruction (commensurate with AFC Band 4, or less)			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Specialised scientific and technical knowledge essential and substantial experience required (commensurate with AFC Band 7, or higher)			
Calibration and quality control	Calibration is either automatic or not required; quality control materials are included, or readily available, and are stable			
	Intermediate between descriptions listed for scores of 1 and 3			
	Calibration and quality control materials, if available, may be labile or unavailable; or technical expertise is required for calibration			3
Interpretation and judgement	Minimal interpretation and judgement are required, and problems require limited interpretation, judgement and decision-making			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Extensive interpretation and judgement are required; resolution of problems requires extensive interpretation, judgement and decision-making			

continued

TABLE 41 Component EoU scores for one-step, real-time RT-PCR tests for influenza A subtypes H1 and H3, influenza B, and RSV A and B (*continued*)

Categories	Criteria for categorisation	EoU score		
Test system troubleshooting and equipment maintenance	Test system troubleshooting is automatic or self-correcting or clearly described or requires minimal judgement			
	Intermediate between descriptions listed for scores of 1 and 3	2		
	Test system troubleshooting is not automatic or self-correcting and requires decision-making to resolve most problems; or equipment maintenance requires special knowledge, skills and abilities			
Time to reporting of results	Results are reported within 4 hours of collection of almost all specimens			
	Intermediate between descriptions listed for scores of 1 and 3	2		
	Median time to reporting of results exceeds the median duration of hospitalisations/time to death			
Health and safety	The test is completed using low levels of personal protection, i.e. gloves			
	Intermediate between descriptions listed for scores of 1 and 3			
	One or more operational steps requires bio-safety level Category 3, or higher		3	
Storage and disposal of waste test materials and reagents	Waste materials and reagents are stored and disposed using medium duty 'Clinical waste' plastic bags and 'Sharps' containers, or a sluice			
	Intermediate between descriptions listed for scores of 1 and 3			
	Waste materials or reagents include hazardous materials that require special attention		3	
Total EoU score		25		

TABLE 42 Component EoU scores for two-step, real-time, RT-PCR tests for influenza A subtypes H1 and H3, influenza B, and RSV A and B

Categories	Criteria for categorisation	EoU score		
Test site	Is a POCT			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Requires purpose-built accommodation, ventilation systems and dedicated space			
Equipment	No specialised equipment required and is readily transferred between hospital facilities			
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised equipment is essential and non-portable			3
Materials and reagents	Are stable, pre-packaged and/or pre-measured, and require no special handling steps or storage	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	May be labile requiring special storage or require special handling steps; their preparation requires manual steps, e.g. volumetric measurement			
Operational steps	Either automatically executed or easily controlled			
	Intermediate between descriptions listed for scores of 1 and 3			
	Require close monitoring and control, and may require special preparation, precise temperature control or timing, accurate pipetting or extensive calculations			3
Training, experience and knowledge	Require minimal scientific and technical knowledge and experience; and knowledge to perform test can be obtained through on-job instruction (commensurate with AFC Band 4, or less)			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Specialised scientific and technical knowledge essential and substantial experience required (commensurate with AFC Band 7, or higher)			
Calibration and quality control	Calibration is either automatic or not required; quality control materials are included, or readily available, and are stable			
	Intermediate between descriptions listed for scores of 1 and 3			
	Calibration and quality control materials, if available, may be labile or unavailable; or technical expertise is required for calibration			3
Interpretation and judgement	Minimal interpretation and judgement are required, and problems require limited interpretation, judgement and decision-making			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Extensive interpretation and judgement are required; resolution of problems requires extensive interpretation, judgement and decision-making			

continued

TABLE 42 Component EoU scores for two-step, real-time, RT-PCR tests for influenza A subtypes H1 and H3, influenza B, and RSV A and B (*continued*)

Categories	Criteria for categorisation	EoU score		
Test system troubleshooting and equipment maintenance	Test system troubleshooting is automatic or self-correcting or clearly described or requires minimal judgement			
	Intermediate between descriptions listed for scores of 1 and 3	2		
	Test system troubleshooting is not automatic or self-correcting and requires decision-making to resolve most problems; or equipment maintenance requires special knowledge, skills and abilities			
Time to reporting of results	Results are reported within 4 hours of collection of almost all specimens			
	Intermediate between descriptions listed for scores of 1 and 3	2		
	Median time to reporting of results exceeds the median duration of hospitalisations/time to death			
Health and safety	The test is completed using low levels of personal protection, i.e. gloves			
	Intermediate between descriptions listed for scores of 1 and 3			
	One or more operational steps requires bio-safety level Category 3, or higher			3
Storage and disposal of waste test materials and reagents	Waste materials and reagents are stored and disposed using medium duty 'Clinical waste' plastic bags and 'Sharps' containers, or a sluice			
	Intermediate between descriptions listed for scores of 1 and 3			
	Waste materials or reagents include hazardous materials that require special attention			3
Total EoU score		26		

TABLE 43 Component EoU scores for virus culture for the diagnosis of influenza A and B, and RSV

Categories	Criteria for categorisation	EoU score		
Test site	Is a POCT			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Requires purpose-built accommodation, ventilation systems and dedicated space			
Equipment	No specialised equipment required and is readily transferred between hospital facilities			
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised equipment is essential and non-portable			3
Materials and reagents	Are stable, pre-packaged and/or pre-measured, and require no special handling steps or storage			
	Intermediate between descriptions listed for scores of 1 and 3			
	May be labile requiring special storage or require special handling steps; their preparation requires manual steps, e.g. volumetric measurement			3
Operational steps	Either automatically executed or easily controlled			
	Intermediate between descriptions listed for scores of 1 and 3			
	Require close monitoring and control, and may require special preparation, precise temperature control or timing, accurate pipetting or extensive calculations			3
Training, experience and knowledge	Require minimal scientific and technical knowledge and experience; and knowledge to perform test can be obtained through on-job instruction (commensurate with AFC Band 4, or less)			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Specialised scientific and technical knowledge essential and substantial experience required (commensurate with AFC Band 7, or higher)			
Calibration and quality control	Calibration is either automatic or not required; quality control materials are included, or readily available, and are stable	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Calibration and quality control materials, if available, may be labile or unavailable; or technical expertise is required for calibration			
Interpretation and judgement	Minimal interpretation and judgement are required, and problems require limited interpretation, judgement and decision-making			
	Intermediate between descriptions listed for scores of 1 and 3			
	Extensive interpretation and judgement are required; resolution of problems requires extensive interpretation, judgement and decision-making			3

continued

TABLE 43 Component EoU scores for virus culture for the diagnosis of influenza A and B, and RSV (*continued*)

Categories	Criteria for categorisation	EoU score		
Test system troubleshooting and equipment maintenance	Test system troubleshooting is automatic or self-correcting or clearly described or requires minimal judgement			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Test system troubleshooting is not automatic or self-correcting and requires decision-making to resolve most problems; or equipment maintenance requires special knowledge, skills and abilities			
Time to reporting of results	Results are reported within 4 hours of collection of almost all specimens			
	Intermediate between descriptions listed for scores of 1 and 3			
	Median time to reporting of results exceeds the median duration of hospitalisations/time to death			3
Health and safety	The test is completed using low levels of personal protection, i.e. gloves			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	One or more operational steps requires bio-safety level Category 3, or higher			
Storage and disposal of waste test materials and reagents	Waste materials and reagents are stored and disposed using medium duty 'Clinical waste' plastic bags and 'Sharps' containers, or a sluice			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Waste materials or reagents include hazardous materials that require special attention			
Total EoU score		26		

TABLE 44 Component EoU scores for the BacT/ALERT 3D blood culture system

Categories	Criteria for categorisation	EoU score		
Test site	Is a POCT			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Requires purpose-built accommodation, ventilation systems and dedicated space			
Equipment	No specialised equipment required and is readily transferred between hospital facilities			
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised equipment is essential and non-portable			3
Materials and reagents	Are stable, pre-packaged and/or pre-measured, and require no special handling steps or storage	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	May be labile requiring special storage or require special handling steps; their preparation requires manual steps, e.g. volumetric measurement			
Operational steps	Either automatically executed or easily controlled	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Require close monitoring and control, and may require special preparation, precise temperature control or timing, accurate pipetting or extensive calculations			
Training, experience and knowledge	Require minimal scientific and technical knowledge and experience; and knowledge to perform test can be obtained through on-job instruction (commensurate with AFC Band 4, or less)			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Specialised scientific and technical knowledge essential and substantial experience required (commensurate with AFC Band 7, or higher)			
Calibration and quality control	Calibration is either automatic or not required; quality control materials are included, or readily available, and are stable			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Calibration and quality control materials, if available, may be labile or unavailable; or technical expertise is required for calibration			
Interpretation and judgement	Minimal interpretation and judgement are required, and problems require limited interpretation, judgement and decision-making			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Extensive interpretation and judgement are required; resolution of problems requires extensive interpretation, judgement and decision-making			

continued

TABLE 44 Component EoU scores for the BacT/ALERT 3D blood culture system (*continued*)

Categories	Criteria for categorisation	EoU score		
Test system troubleshooting and equipment maintenance	Test system troubleshooting is automatic or self-correcting or clearly described or requires minimal judgement	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Test system troubleshooting is not automatic or self-correcting and requires decision-making to resolve most problems; or equipment maintenance requires special knowledge, skills and abilities			
Time to reporting of results	Results are reported within 4 hours of collection of almost all specimens			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Median time to reporting of results exceeds the median duration of hospitalisations/time to death			
Health and safety	The test is completed using low levels of personal protection, i.e. gloves			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	One or more operational steps requires bio-safety level Category 3, or higher			
Storage and disposal of waste test materials and reagents	Waste materials and reagents are stored and disposed using medium duty 'Clinical waste' plastic bags and 'Sharps' containers, or a sluice			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Waste materials or reagents include hazardous materials that require special attention			
Total EoU score		20		

TABLE 45 Component EoU scores for sputum culture

Categories	Criteria for categorisation	EoU score		
Test site	Is a POCT			
	Intermediate between descriptions listed for scores of 1 and 3			
	Requires purpose-built accommodation, ventilation systems and dedicated space			3
Equipment	No specialised equipment required and is readily transferred between hospital facilities			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Specialised equipment is essential and non-portable			
Materials and reagents	Are stable, pre-packaged and/or pre-measured, and require no special handling steps or storage			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	May be labile requiring special storage or require special handling steps; their preparation requires manual steps, e.g. volumetric measurement			
Operational steps	Either automatically executed or easily controlled	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Require close monitoring and control, and may require special preparation, precise temperature control or timing, accurate pipetting or extensive calculations			
Training, experience and knowledge	Require minimal scientific and technical knowledge and experience; and knowledge to perform test can be obtained through on-job instruction (commensurate with AFC Band 4, or less)			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Specialised scientific and technical knowledge essential and substantial experience required (commensurate with AFC Band 7, or higher)			
Calibration and quality control	Calibration is either automatic or not required; quality control materials are included, or readily available, and are stable	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Calibration and quality control materials, if available, may be labile or unavailable; or technical expertise is required for calibration			
Interpretation and judgement	Minimal interpretation and judgement are required, and problems require limited interpretation, judgement and decision-making			
	Intermediate between descriptions listed for scores of 1 and 3			
	Extensive interpretation and judgement are required; resolution of problems requires extensive interpretation, judgement and decision-making			3

continued

TABLE 45 Component EoU scores for sputum culture (*continued*)

Categories	Criteria for categorisation	EoU score		
Test system troubleshooting and equipment maintenance	Test system troubleshooting is automatic or self-correcting or clearly described or requires minimal judgement			
	Intermediate between descriptions listed for scores of 1 and 3			
	Test system troubleshooting is not automatic or self-correcting and requires decision-making to resolve most problems; or equipment maintenance requires special knowledge, skills and abilities			3
Time to reporting of results	Results are reported within 4 hours of collection of almost all specimens			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Median time to reporting of results exceeds the median duration of hospitalisations/time to death			
Health and safety	The test is completed using low levels of personal protection, i.e. gloves			
	Intermediate between descriptions listed for scores of 1 and 3			
	One or more operational steps requires bio-safety level Category 3, or higher			3
Storage and disposal of waste test materials and reagents	Waste materials and reagents are stored and disposed using medium duty 'Clinical waste' plastic bags and 'Sharps' containers, or a sluice			
	Intermediate between descriptions listed for scores of 1 and 3			
	Waste materials or reagents include hazardous materials that require special attention			3
Total EoU score		25		

TABLE 46 Component EoU scores for sputum Gram stain and microscopy

Categories	Criteria for categorisation	EoU score		
Test site	Is a POCT			
	Intermediate between descriptions listed for scores of 1 and 3			
	Requires purpose-built accommodation, ventilation systems and dedicated space			3
Equipment	No specialised equipment required and is readily transferred between hospital facilities			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Specialised equipment is essential and non-portable			
Materials and reagents	Are stable, pre-packaged and/or pre-measured, and require no special handling steps or storage			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	May be labile requiring special storage or require special handling steps; their preparation requires manual steps, e.g. volumetric measurement			
Operational steps	Either automatically executed or easily controlled			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Require close monitoring and control, and may require special preparation, precise temperature control or timing, accurate pipetting or extensive calculations			
Training, experience and knowledge	Require minimal scientific and technical knowledge and experience; and knowledge to perform test can be obtained through on-job instruction (commensurate with AFC Band 4, or less)			
	Intermediate between descriptions listed for scores of 1 and 3			
	Specialised scientific and technical knowledge essential and substantial experience required (commensurate with AFC Band 7, or higher)			3
Calibration and quality control	Calibration is either automatic or not required; quality control materials are included, or readily available, and are stable	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Calibration and quality control materials, if available, may be labile or unavailable; or technical expertise is required for calibration			
Interpretation and judgement	Minimal interpretation and judgement are required, and problems require limited interpretation, judgement and decision-making			
	Intermediate between descriptions listed for scores of 1 and 3		2	
	Extensive interpretation and judgement are required; resolution of problems requires extensive interpretation, judgement and decision-making			

continued

TABLE 46 Component EoU scores for sputum Gram stain and microscopy (*continued*)

Categories	Criteria for categorisation	EoU score		
Test system troubleshooting and equipment maintenance	Test system troubleshooting is automatic or self-correcting or clearly described or requires minimal judgement			
	Intermediate between descriptions listed for scores of 1 and 3	2		
	Test system troubleshooting is not automatic or self-correcting and requires decision-making to resolve most problems; or equipment maintenance requires special knowledge, skills and abilities			
Time to reporting of results	Results are reported within 4 hours of collection of almost all specimens			
	Intermediate between descriptions listed for scores of 1 and 3	2		
	Median time to reporting of results exceeds the median duration of hospitalisations/time to death			
Health and safety	The test is completed using low levels of personal protection, i.e. gloves			
	Intermediate between descriptions listed for scores of 1 and 3			
	One or more operational steps requires bio-safety level Category 3, or higher		3	
Storage and disposal of waste test materials and reagents	Waste materials and reagents are stored and disposed using medium duty 'Clinical waste' plastic bags and 'Sharps' containers, or a sluice	1		
	Intermediate between descriptions listed for scores of 1 and 3			
	Waste materials or reagents include hazardous materials that require special attention			
Total EoU score		23		

Appendix 8 Sample of WinBUGS code used

A. WinBUGS code (model A)

3 WS: Cost-effectiveness analysis

*****1 = costs, 2 = QALYs*****

*****group: 1 = POCT, 2 = PCR, 3 = culture*****

Model

```
model {
  for(j in 1:N) {

    y[j, 1:2] ~ dmnorm(mu[group[j],], tau[group[j],,])

  }

  # Prior distributions

  for (i in 1:3) {

    mu[i,1] ~ dnorm(0.0,1.0E-8)

    mu[i,2] ~ dnorm(0.0,100)

    tau[i,1:2,1:2] ~ dwish(A[,], f)

  }
}
```

Data – original scale

list(N = 1252)

group[]	y[,1]	y[,2]
1	1042.02	NA
1	8763.113	0.0037973
2	959.1775	0.0068849
2	529.565	NA
3	NA	NA

1	1240.867	0.0042
3	1011.275	0.0025507
2	NA	0.0084479
.		
.		
.		
.		
.		
2	NA	0.0084671
1	NA	0.0006808
3	NA	0.016474

END

Specifying prior distributions for Wishart distribution

list(f = 2)

Covariance matrix prior estimate

A[,1]	A[,2]
-------	-------

10000	0
-------	---

0	0.01
---	------

END

B. Markov chain Monte Carlo sensitivity analyses

Table 47 displays the results of various sensitivity analyses exploring the impact of length of 'burn-in' and sample, different initial/starting values, and changing the prior distributions used in terms of their impact on the posterior mean costs and QALYs for the three patient groups.

TABLE 47 Markov chain Monte Carlo sensitivity analyses

Parameter	Traditional	PCR	POCT
Base case (model A)			
Costs (£)	2327 (1989 to 2664)	1978 (1743 to 2165)	2159 (1828 to 2485)
QALYs	0.007588 (0.006334 to 0.008854)	0.007779 (0.006555 to 0.008983)	0.008035 (0.006772 to 0.009280)
Burn-in/sample			
10k/20k			
Costs (£)	2327 (1992 to 2661)	1977 (1739 to 2216)	2160 (1831 to 2491)
QALYs	0.007596 (0.006337 to 0.008882)	0.007776 (0.006553 to 0.008990)	0.008030 (0.006786 to 0.009286)
50k/100k			
Costs (£)	2326 (1991 to 2663)	1977 (1741 to 2215)	2160 (1833 to 2487)
QALYs	0.007599 (0.006330 to 0.008877)	0.007776 (0.006563 to 0.008988)	0.008033 (0.006789 to 0.009281)
Alternative priors			
Costs (£)	1786 (1478 to 2091)	1724 (1500 to 1947)	1682 (1384 to 1979)
QALYs	0.007322 (0.004132 to 0.010550)	0.007682 (0.004706 to 0.010670)	0.007853 (0.004968 to 0.010750)
Alternative starting values			
Chain 1			
Costs (£)	2327 (1994 to 2664)	1977 (1739 to 2213)	2159 (1834 to 2485)
QALYs	0.007597 (0.006310 to 0.008866)	0.007771 (0.006557 to 0.008987)	0.008037 (0.006787 to 0.009286)
Chain 2			
Costs (£)	2327 (1989 to 2666)	1977 (1741 to 2215)	2160 (1837 to 2485)
QALYs	0.007598 (0.006326 to 0.008882)	0.007770 (0.006568 to 0.008983)	0.008035 (0.006776 to 0.009284)
Chain 3			
Costs (£)	2326 (1990 to 2662)	1978 (1739 to 2216)	2161 (1835 to 2487)
QALYs	0.007602 (0.006330 to 0.008873)	0.007783 (0.006565 to 0.009009)	0.008039 (0.006793 to 0.009295)

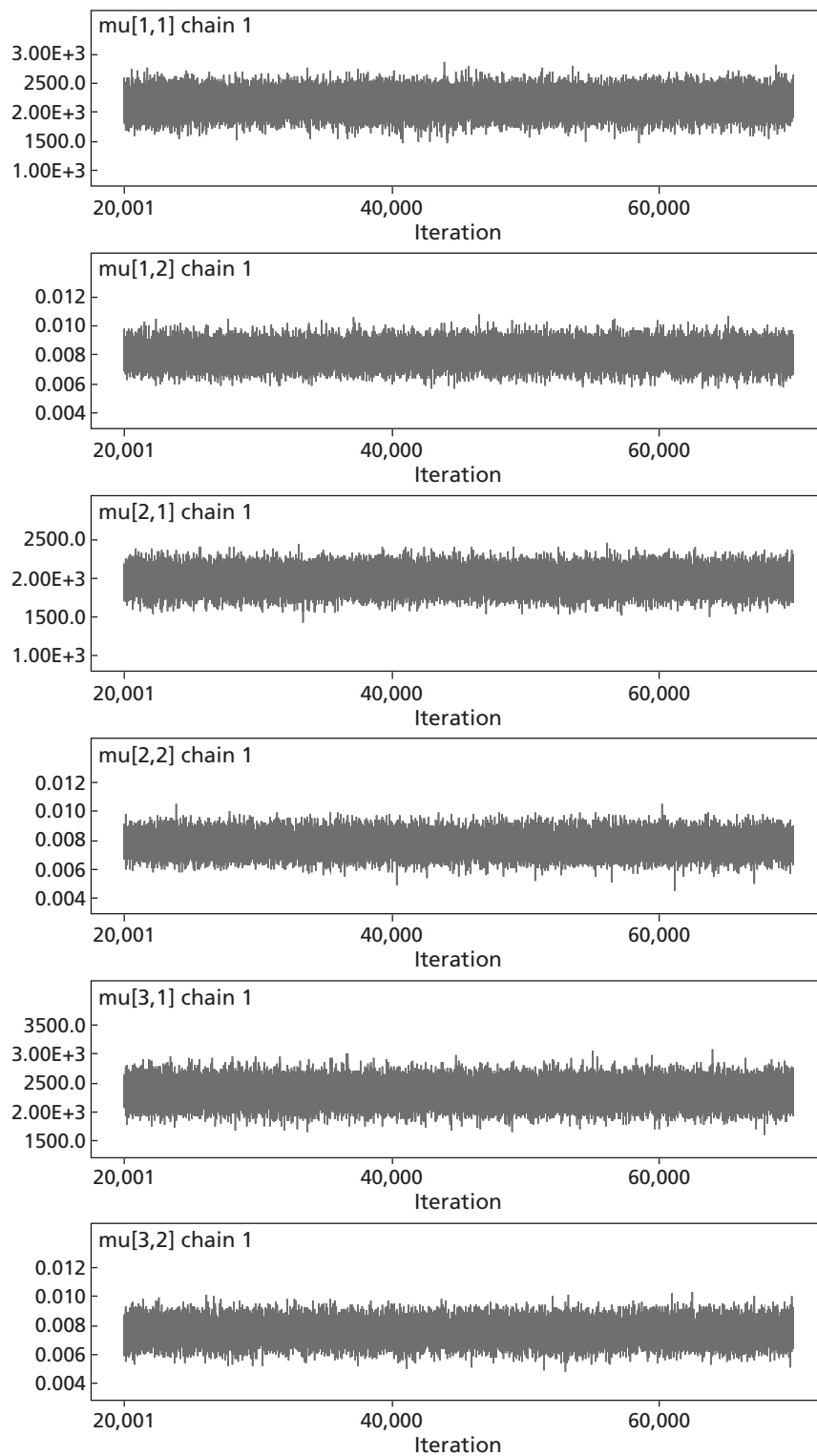


FIGURE 23 Markov chain Monte Carlo history plots for mean costs and QALYs.

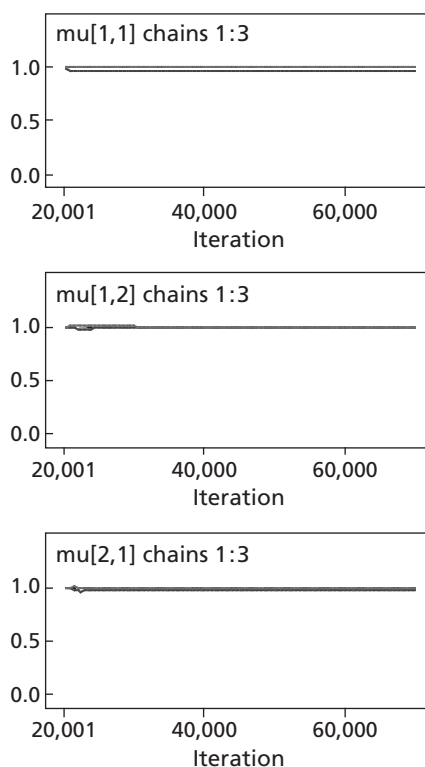


FIGURE 24 Brooks–Gelman–Rubin plots for chains 1, 2 and 3, representing three different sets of starting/initial values.

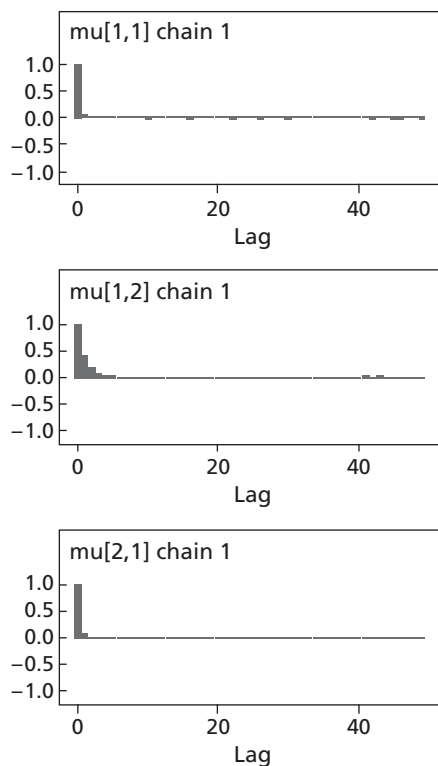


FIGURE 25 Markov chain Monte Carlo autocorrelation plots for mean costs and QALYs.

C. Alternative model (model B) – WinBUGS and R code

WinBUGS code

3 WS – Gamma/Logit cost-effectiveness model

*****1 = costs, 2 = QALYs*****

*****group: 1 = POCT, 2 = PCR, 3 = culture*****

Model

```
model {

  for(j in 1:N) {

    y[j,1] ~ dgamma(eta[group[j]], lambda0[j])

    lambda0[j] <- eta[group[j]]/phi0[j]

    y[j,2] ~ dnorm(mu.e[group[j]],tau[group[j]])

    phi0[j] <- mu.c[group[j]] + beta[group[j]]*(y[j,2] – mu.e[group[j]])

  }

}
```

Priors

```
for (i in 1:3) {

  tau[i] <- pow(sigma.e[i],–2)

  sigma2.e[i] <- pow(sigma.e[i],2)

  eta[i] ~ dunif(1,100)

  mu.c[i] ~ dunif(1,50000)

  mu.e[i] ~ dnorm(0.0,0.001)

  sigma.e[i] ~ dnorm(0.0,1)(0,)

  beta[i] ~ dnorm(0.0,0.001)}

}
```

Data

group[]	y[,1]	y[,2]
1	1042.02	NA
1	8763.113	–5.569660463

2	959.1775	-4.971515961
2	529.565	NA
3	NA	NA
1	1240.867	-5.468461909
3	1011.275	-5.968833489
3	2585.17	-5.38489336
.		
.		
.		
.		
.		
2	NA	-4.763064064
1	NA	-7.291560949
3	NA	-4.089360693

END

Starting values

```
list(beta = c(0,0,0), eta = c(40,40,40), sigma.e = c(0.5,0.5,0.5), mu.c = c(2000,2000,2000),
mu.e = c(-5,-5,-5))
```

R code

Matrices mu.e and sigma.e (which are on the logit(QALY) scale) are obtained from WinBUGS model above using files wb.output and wb2.output.

```
# Read data in
```

```
mu.e <- cbind(wb.output[60001:80000,2],wb.output[80001:100000,2],wb.output[100001:120000,2])
```

```
sigma.e <- cbind(wb.output2[1:20000,2],wb.output2[20001:40000,2],wb.output2[40001:60000,2])
```

```
# Create matrices to store results
```

```
m.e <- array(NA,c(20000,3))
```

```
e.pred <- array(NA,c(1000,20000,3))
```

```
estar.pred <- e.pred
```

```
# Undertake MC simulations

for (t in 1:3) {

  for (s in 1:20000) {

    estar.pred[,s,t] <- rnorm(1000,mu.e[s,t],sigma.e[s,t])

    e.pred[,s,t] <- exp(estar.pred[,s,t])/(1 + exp(estar.pred[,s,t]))

  }

  m.e[,t] <- apply(e.pred[, , t],2,mean)

}

# Calculate means on original scale

mean(m.e[,1])

mean(m.e[,2])

mean(m.e[,3])
```


A decorative graphic consisting of numerous thin, parallel green lines that curve from the left side of the page towards the right, creating a sense of movement and flow.

EME
HS&DR
HTA
PGfAR
PHR

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