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Extended Research Article

Rapid tests to inform triage and antibiotic prescribing decisions for adults presenting with suspected acute respiratory infection: a rapid evidence synthesis of clinical effectiveness and cost–utility studies

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This article

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Abstract

Background: This review assessed the clinical- and cost-effectiveness of point-of-care tests to guide the initial management of people presenting with suspected acute respiratory infection.

Methods: Searches for systematic reviews, randomised controlled trials and cost–utility studies were conducted in May 2023. Sources included MEDLINE, Epistemonikos, EMBASE, Cochrane Central Register of Controlled Trials, the Cost-effectiveness Analysis Registry and reference checking.

Eligible studies included people (≥ 16 years) making initial contact with the health system with symptoms suggestive of acute respiratory infection.

Risk of bias in randomised controlled trials was assessed using the Cochrane risk-of-bias tool. The Drummond checklist was used for cost–utility studies.

Meta-analyses of clinical outcomes were conducted to estimate summary risk ratios with 95% confidence intervals.

Study characteristics and main results were summarised narratively and tabulated.

Results: *Clinical effectiveness:* Fourteen randomised controlled trials were included; all had a high risk of bias. Ten randomised controlled trials analysed point-of-care tests for C-reactive protein. Compared with usual care, the effects on hospital admissions and mortality were highly uncertain due to sparse data. Three randomised controlled trials had heterogeneous findings on the resolution of symptoms/time to full recovery. The risk of re-consultations increased in patients receiving C-reactive protein point-of-care tests (pooled risk ratio 1.61, 95% confidence interval 1.07 to 2.41; four studies). There was a reduction in antibiotics initially prescribed (C-reactive protein point-of-care tests vs. usual care: pooled risk ratio 0.75, 95% confidence interval 0.68 to 0.84; nine studies).

The effects of procalcitonin point-of-care tests compared with usual care on hospital admission, escalation of care, and duration of symptoms were very uncertain as only one randomised controlled trial was included. The study found a large reduction in antibiotic prescriptions within 7 days.

Two studies revealed a large reduction in initial antibiotic prescriptions for Group A streptococcus point-of-care tests versus usual care. Only one study compared an influenza point-of-care test with usual care. The effect of the antibiotics prescribed was very uncertain. No deaths occurred in either treatment group.

Cost-effectiveness: Six of the 17 included cost–utility studies were judged to be directly applicable to our review, 4 of which focused on the C-reactive protein point-of-care test. The results suggested that the C-reactive protein point-of-care test is potentially cost-effective; these studies were generally limited to capturing only short-term costs and consequences.

One study evaluated 14 different point-of-care tests for Group A streptococcus; none were cost-effective compared with usual care.

A further study evaluated two rapid tests (Quidel for influenza [Quidel Corp, San Diego, CA, USA], and BinaxNOW [Binax, Inc., Portland, ME, USA]) for the pneumococcal antigen) compared to culture/serology and found that they were not cost-effective.

Limitations: Rapid synthesis methods were used, so relevant studies may have been missed. No evidence was identified for several review questions.

Conclusion: C-reactive protein point-of-care test may reduce the number of patients given an antibiotic prescription but could increase the rate of re-consultations. C-reactive protein point-of-care test may potentially be cost-effective but existing estimates were based on very small and uncertain gains in quality-adjusted life-years and only accounted for short-term costs and consequences. There was very limited or an absence of evidence for other point-of-care tests.

Future work: Research is needed to explore the impact of point-of-care tests on triaging decisions across different clinical settings and to quantify the longer-term health and cost consequences.

Study registration: This study is registered as PROSPERO CRD42023429515.

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Report Supplementary Material 1	Supplementary material

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/KHGP7129).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer-reviewed.

List of abbreviations

A&E	accident and emergency
AECOPD	acute exacerbation of chronic obstructive pulmonary disease
AMR	antimicrobial resistance
ARI	acute respiratory infection
ARTI	acute respiratory tract infection
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CRQ-SAS	Chronic Respiratory Questionnaire Self-Administered Standardized
CUA	cost–utility analysis
DALY	disability-adjusted life-year
ED	emergency department
EQ-5D	EuroQol-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GAS	group A streptococcus
GP	general practice/general practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IP-10	interferon-γ-induced protein-10
LRTI	lower respiratory tract infection
MxA	Myxovirus resistance protein A
NICE	National Institute for Health and Care Excellence
PCR	polymerase chain reaction
POC	point of care
POCT	point-of-care test
PPI	patient and public involvement
QALY	quality-adjusted life-year
RADT	rapid antigen detection test
RCT	randomised controlled trial
RSV	respiratory syncytial virus
RTI	respiratory tract infection
TRAIL	tumour necrosis factor-related apoptosis-inducing ligand
VAS	visual analogue scale
WTP	willingness to pay

Plain language summary

Acute respiratory infection is a group of common diseases caused by viruses or bacteria. Examples of acute respiratory infections include 'cold' and flu. When people consult a doctor (or other healthcare professionals) for suspected acute respiratory infection, it is not always easy for the doctor to identify what is causing the symptoms. The doctor also needs to assess whether the patient's condition is serious or may become serious. Laboratory tests can provide useful information to help the doctor decide what to do next, but it takes several hours or days to get the test results back. This delay means the doctor cannot use the test results to make a decision while seeing the patient. Rapid tests that can be done and produce results quickly (within 45 minutes) are now available. It is currently unclear whether the use of these rapid tests to assess patients would improve or worsen patient outcomes or increase or decrease costs overall.

We conducted a rapid review (i.e. using systematic but streamlined methods to improve efficiency) of the literature to summarise the best available published evidence to help answer these questions. We found that rapid tests for C-reactive protein (a substance that tends to increase in our blood when we have inflammation caused by an infection or other conditions) may reduce the perceived need for doctors to prescribe antibiotics, but the number of patients who come back to see the doctor again may increase. There is still some uncertainty in this evidence. Our review found that the test may represent good value for money, but the studies were limited as they only considered costs and health implications in the short term. Evidence either is very limited to draw conclusions or did not indicate good value for money for the other rapid tests that we evaluated.

Scientific summary

Background

Acute respiratory infection (ARI) is a group of diseases caused by viruses or bacteria that affect the respiratory tract, such as the common cold and influenza. Rapid testing of biomarkers and microbial pathogens that can return results quickly at the point of care has emerged as potentially useful tools to aid the initial assessment of patients with suspected ARI. The primary objective of this rapid evidence synthesis was to evaluate the clinical effectiveness and cost-effectiveness of different near-patient, rapid point-of-care tests (POCTs) alone or in combination to guide initial assessment and management in people aged 16 and over with suspected ARI. This evidence review was conducted to help inform whether rapid tests should be made available for use at initial patient consultations in various settings to help inform referral of patients to NHS ARI hubs, virtual wards or hospitals.

Methods

This rapid synthesis consists of a review of clinical effectiveness studies with meta-analysis and a review of cost–utility studies. The reviews followed published methods, were registered on PROSPERO (CRD42023429515) and are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance.

Search strategies

Searches were conducted in May 2023. MEDLINE and Epistemonikos databases were searched for systematic reviews with no date limit. Searches for randomised controlled trials (RCTs) were conducted in EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials. Searches for cost–utility studies were conducted in EMBASE, MEDLINE and the Cost-effectiveness Analysis Registry with no date limit. Relevant study design filters were used. Searches combined the concepts of ARI with near-patient, rapid POCTs. For the RCT searches, terms for specific biomarkers and tests in combination with terms for guide or inform were added to capture the concept of biomarker test-guided management. All searches were restricted to English language and humans, and excluded grey literature and non-research articles. References of included studies and relevant reviews were checked.

Eligibility criteria

Systematic reviews of RCTs or economic evaluations, RCTs and cost–utility studies that evaluated near-patient, rapid POCTs (with a turnaround time of 45 minutes or shorter) licensed for use in the UK in people aged 16 years or over with suspected ARI were eligible. In an amendment to the protocol, POCTs no longer available in the UK were also included. The following outcomes were eligible for the review of clinical effectiveness: hospital admission, escalation of care, length of hospital stay, follow-up consultation/ongoing monitoring, antibiotic/antiviral use, time to clinical cure or resolution of symptoms, mortality and health-related quality of life; and for the review of cost-effectiveness: incremental cost, life-years gained, incremental quality-adjusted life-years, incremental disability-adjusted life-years, incremental cost-effectiveness ratio and incremental net health/monetary benefit. Studies concerning patients with confirmed COVID-19, hospital inpatients and children under 16 years were excluded.

Study selection

For the clinical effectiveness review, titles and abstracts were screened by one reviewer with the initial 20% of records screened by two reviewers. At least 90% agreement was achieved before proceeding to single reviewer screening. Relevant full texts were obtained and screened following the same process. For the cost-effectiveness review, both phases of screening were conducted by two independent reviewers. In both reviews, any disagreements were resolved through discussion and with a third reviewer if needed.

Data extraction

Data were extracted by one reviewer using a pre-piloted and standardised form and checked by a second reviewer, with disagreements resolved by discussion.

Risk-of-bias assessment

Systematic reviews were assessed using the JBI Critical Appraisal Checklist. RCTs and cost–utility studies (if not assessed by existing reviews) were assessed using the Cochrane risk-of-bias tool and the Drummond checklist respectively.

Data synthesis

All included studies were tabulated and summarised narratively. Meta-analyses of clinical effectiveness outcomes were conducted to estimate summary risk ratios with 95% confidence intervals (CIs). Meta-analysis using a random-effects model using the DerSimonian and Laird method was undertaken. A sample size adjustment was made to cluster randomised trials. Inconsistency across studies was measured using I^2 statistic and chi-squared test and by assessing study characteristics. Subgroup analyses were planned and sensitivity analyses undertaken.

Assessment of certainty of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to evaluate the certainty of evidence for the key outcomes of 7- or 28-day mortality, escalation of care and hospital admission.

Results

Clinical effectiveness

Eligible trials were identified for C-reactive protein (CRP) POCTs, procalcitonin POCTs, group A streptococcus (GAS) POCTs and influenza POCTs only. No evidence was identified for other types of near-patient rapid POCTs. Outcomes assessed by the included studies varied.

One recent systematic review was included as a source of data for eligible studies. Fourteen RCTs were included; all had a high risk of bias. The setting was mainly primary care; two studies involved outpatient clinics, and one study involved nursing homes. Ten RCTs analysed POCTs for CRP. In five of these studies, the test assessed is currently unavailable in the UK. The effects of CRP tests compared with usual care on hospital admissions, mortality and health-related quality of life were highly uncertain due to sparse data. Three RCTs had heterogeneous findings on resolution of symptoms/time to full recovery. The risk of re-consultations increased in patients receiving CRP POCTs (risk ratio 1.61, 95% CI 1.07 to 2.41; I^2 56.6%; four studies). There was a reduction in antibiotics initially prescribed (CRP POCT vs. usual care: risk ratio 0.75, 95% CI 0.68 to 0.84; I^2 54.7%; nine studies). Subgroup analysis of people with chronic obstructive pulmonary disease and sensitivity analyses excluding studies in a nursing home setting or tests unavailable in the UK did not change the conclusions inferred from the main analyses.

The effects of procalcitonin POCTs compared with usual care on hospital admission, re-consultations, duration of symptoms and mortality were very uncertain as evidence was available from only one RCT with a high risk of bias. The study found a large reduction in initial antibiotic prescriptions within 7 days.

Two RCTs found a large reduction in initial antibiotic prescriptions for GAS POCTs versus usual care. Only one RCT compared an influenza POCT with usual care. The effect on antibiotics prescribed was very uncertain. No deaths occurred in either treatment group. These trials had a high risk of bias.

Cost-effectiveness

Six of the included cost–utility studies were judged to be directly applicable to our review question, four of which focused on CRP POCT. The results suggested that CRP POCT is potentially cost-effective; these studies were generally limited to capturing only short-term costs and consequences.

One study evaluated 14 different POCTs for GAS; none were cost-effective compared with usual care.

A further study evaluated two rapid tests (Quidel for influenza, and BinaxNOW for the pneumococcal antigen) compared to culture/serology and found that they were not cost-effective.

Conclusion

The rapid review of clinical effectiveness identified only a small number of eligible trials covering few relevant POCTs. There was limited evidence of the effectiveness of near-patient rapid POCTs in adults with suspected ARI. CRP POCT may reduce the number of patients given an antibiotic prescription at initial consultation but could increase the rate of re-consultations. The overall certainty of the evidence was very low according to the GRADE assessment. CRP POCT may potentially be cost-effective, but existing estimates were based on very small and uncertain gains in quality-adjusted life-years and only accounted for short-term costs and consequences. There was very limited or an absence of evidence for other POCTs.

Further research is needed to explore the impact of POCTs, used alone or in combination, on triaging decisions across different clinical settings and to quantify the longer-term health and cost consequences of reducing antibiotic prescribing.

Study registration

This study is registered as PROSPERO CRD42023429515.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Evidence Synthesis programme (NIHR award ref: NIHR159946) and is published in full in *Health Technology Assessment*; Vol. 29, No. 13. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction

Acute respiratory infection (ARI) is a common illness caused by a wide variety of viral and bacterial pathogens. In the UK, self-management is encouraged for adults with suspected ARI with minor symptoms. People with more severe symptoms, or ongoing symptoms that do not resolve and worsen over time may contact NHS 111 through a designated website or telephone, seek an appointment with their general practitioner (GP), visit a walk-in centre or request a home visit (including care homes) by a GP. More recently, ARI hubs (which are treatment centres established specifically for ARI to provide new or more integrated services with same-day access in addition to the existing services mentioned above) are being set up through funding provided by NHS England.[1] Patients who are severely unwell suggestive of serious conditions and/or rapid deterioration may call the ambulance service or be self-present to a hospital emergency department (ED). A variety of rapid point-of-care tests (POCTs), defined as any medical device and/or system that enables diagnosis, monitoring or screening of patients at the time and place of care by appropriately trained users,[2] have become available that could help healthcare professionals in the initial assessment of patients with suspected ARI in these settings. Evidence on clinical and cost-effectiveness of these tests is emerging and requires careful evaluation to inform a decision on their adoption in clinical practice. This rapid synthesis of evidence addresses this need.

Two broad types of POCTs are considered:

1. POCTs for determining the possible cause of the acute respiratory symptoms. These can be further categorised into two groups:

    i. POCTs using host biomarkers to detect an inflammatory response and/or distinguish between bacterial and viral infections.

These tests utilise host-response biomarkers that can be potential surrogates for detecting bacterial or viral infections.[3] Many rapid tests targeting different biomarkers have been developed, including those for C-reactive protein (CRP),[3] procalcitonin,[4] Myxovirus resistance protein A (MxA),[5] tumour necrosis factor-related apoptosis-inducing ligand (TRAIL)[5] and interferon-γ-induced protein-10 (IP-10, also known as C-X-C motif chemokine ligand 10).[6] Some POCTs can test more than one biomarker simultaneously.[7]

    ii. POCTs for the detection of specific pathogens.

These tests detect antigens (substances such as nucleic acid or protein) from specific viruses or bacteria that may have caused the symptoms for the suspected ARI, and so are also known as rapid antigen tests. Common targets of rapid antigen tests related to ARI include influenza A and B, respiratory syncytial virus (RSV),[8] group A β-haemolytic streptococcus,[9] and *Streptococcus pneumoniae* and *Legionella pneumophila*.[10]

Given the relatively low cost of COVID-19 lateral flow tests and their wide adoption by the general public with suspected ARI, rapid tests for COVID-19 infection are likely to be used earlier in the diagnostic pathway compared with other POCTs for ARI, and therefore they were not evaluated in this rapid evidence synthesis.

2. POCTs for monitoring the patient's physiological condition and detection of those in unstable or critical condition requiring urgent referral or immediate intervention. These tests have wide clinical applications and are not specifically used for patients with ARI. They include:

Blood gases (arterial blood gas analysis), which may also simultaneously provide blood chemistry/electrolyte analysis, including lactate, sodium and urea. These could alternatively be obtained through blood samples drawn from veins.

Full blood count: this test assesses the number of red blood cells, white blood cells (white blood cell count) and platelets in the blood, measures the size and amount of haemoglobin in the red blood cells and calculates the haematocrit (percentage of red blood cells in terms of volume in the blood).

The objectives of this rapid synthesis were to identify, appraise and synthesise evidence on the clinical effectiveness and cost-effectiveness of different near-patient, rapid microbiological or biomarker tests alone or in combination to guide initial assessment and management in people aged 16 and over with suspected ARI.

Chapter 2 Methods

This research consists of two distinct reviews, conducted in parallel: one focused on clinical effectiveness and one focused on cost-effectiveness. The methods used to conduct these reviews were pre-specified and a protocol was registered on PROSPERO (Registration ID: CRD42023429515). There is synergy between the two methodologies presented. In this section, we first describe the methodology for the clinical effectiveness review. We then detail the methodology for the cost-effectiveness review, highlighting where the methodology differs (to avoid repetition).

Clinical effectiveness review

Search strategy

Searches were developed iteratively and combined the concepts of ARIs and near-patient and rapid tests, with study-type filters being applied where appropriate.

Systematic reviews

The following databases were searched from inception to May 2023 (see *Appendix 1* for exact dates) for systematic reviews:

- MEDLINE via Ovid.
- Epistemonikos.

Search concepts combined ARI and rapid tests (as a broad concept). These elements were based on the draft search strategy developed by Bristol Evidence Synthesis Group for a related review (PROSPERO CRD42023427097), with some terms removed (see excluded conditions listed in *Population*). *Appendix 1* shows our full record of searches. A sensitive systematic review search filter (based on CADTH's SR/MA/HTA/ITC filter[11]) was applied to the MEDLINE search. No date limit was applied. The MEDLINE search was restricted to English language, and comments, editorials, letters and news items were removed.

References identified by the project team via highly targeted searches during the scoping phase were also reviewed.

Randomised controlled trials

Additional searches to find randomised controlled trials (RCTs) were conducted in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL), from inception
- EMBASE (Ovid), from 2022 to May 2023
- MEDLINE (Ovid), from 2022 to May 2023

The same subject search terms as those used for the search for systematic reviews were included, but we broadened this search by adding terms for specific biomarkers and tests in combination with terms for guide or inform. These terms were included in order to additionally capture the concept of biomarker test-guided management. See *Appendix 1* for our full record of searches. As the identified systematic reviews were all limited to specific populations, interventions and outcomes (i.e. none fully addressed our research question), and it was difficult to say whether a combination of reviews would cover our review question, we did not limit the CENTRAL search by date. Based on an understanding of how the CENTRAL database is created[12] and the rapid timescales for this review, we searched MEDLINE and EMBASE for literature published from 2022 to May 2023 only by applying a date limit filter. A sensitive RCT filter was used in MEDLINE and EMBASE (based on the latest versions of Cochrane's sensitivity- and precision-maximising versions[13–15]).

Searches were restricted to English language and humans, and excluded:

- Conference abstracts.
- Editorials, letters, news items and commentaries.

Pre-print sources were not searched.

References of included studies and relevant systematic reviews were checked.

Inclusion and exclusion criteria

Population

Inclusion criteria

People aged 16 years or over with suspected ARI.

Exclusion criteria

People aged 16 years or over:

- With a confirmed COVID-19 diagnosis (patients with known COVID will be triaged in a different way; suspected COVID would be treated as suspected ARI).
- All inpatients in hospital.
- Who have a respiratory infection during end-of-life care.
- With aspiration pneumonia, bronchiectasis, cystic fibrosis or known immunosuppression.
- Who are presenting with ARIs that rarely require or lead to escalation of care to hospital admission such as otitis media and sinusitis.
- Who are presented with suspected tuberculosis.

Children and young people under 16 years were excluded. ARIs mostly found in children and infants such as croup, bronchiolitis and whooping cough are therefore excluded.

Intervention

Inclusion criteria

Near-patient, rapid tests (turnaround time ≤ 45 minutes, also known as point-of-care tests) which are currently licensed and available for use in the UK are as follows:

- rapid antigen tests
- rapid polymerase chain reaction (PCR) tests
- urinary antigen tests
- CRP
- procalcitonin
- serum sodium
- urea nitrogen
- partial pressure O_2
- blood gases
- full blood count
- white blood cell count
- MxA
- TRAIL
- IP-10.

Protocol amendment: where a test is no longer available in the UK and it was unclear whether it has been superseded by a similar version or product, and the study was otherwise eligible, a pragmatic decision was made to include the study with a caveat regarding test availability.

Exclusion criterion

Tests for COVID-19.

Comparator
Current practice.

Outcomes

- Hospital admission (immediately after triage or at 28 days).
- Escalation of care (sometime after initial consultation):
    - re-consultation/appointment (within the infection episode)
    - virtual ward
    - ED visit
    - unplanned hospital admission.
- Hospital length of stay.
- Follow-up consultation/ongoing monitoring.
- Antibiotic/antiviral use.
- Time to clinical cure/resolution of symptoms.
- Mortality.
- Health-related quality of life (HRQoL; using a validated scale).

Study designs
Inclusion criteria

- Systematic reviews of RCTs.
- RCTs.

Exclusion criteria

- Non-systematic reviews.
- Non RCTs.
- Studies not published in English.
- Pre-prints.
- Dissertations and theses.
- Registry entries for ongoing clinical trials.
- Editorials, letters, news items and commentaries.
- Animal studies.
- Conference abstracts and posters.
- Derivation studies.

Screening
Titles and abstracts were reviewed by one reviewer with 20% of the titles and abstracts being reviewed by two reviewers (FW, JC). We aimed to achieve at least 90% agreement before proceeding to single reviewer screening. Any disagreements were resolved by discussion or, if necessary, a third independent reviewer (EL).

The full texts of potentially eligible studies were retrieved and assessed in line with the criteria outlined above by one reviewer (FW, JC or EL). The initial 20% of potentially eligible studies were assessed by two reviewers (FW, JC or EL). At least 90% agreement was achieved before proceeding with single reviewer screening.

Disagreements between reviewers were resolved by discussion, with involvement of a third review author where necessary.

Assessment of identified systematic reviews
Identified systematic reviews were considered for the rapid review both as the primary source of evidence and as a source of RCTs.

Starting with the most recent published reviews, identified systematic reviews were assessed for their applicability, and those eligible were quality assessed using published tools (see *Risk-of-bias assessment*). We planned to extract systematic reviews of good quality that closely matched the review protocol rather than extracting from the primary studies. Where a good-quality review was found, earlier reviews with largely overlapping scopes and RCTs covered by the review were not assessed or extracted.

As no good-quality, applicable systematic reviews were identified for all interventions, and because there were evidence gaps (e.g. missing interventions or outcomes) in the systematic reviews, we conducted searches for RCTs following the methods described above.

All references identified by the searches and from other sources were uploaded into EndNote and deduplicated.

Data extraction

A pre-piloted and standardised form was used to extract data from studies (by JC, EL or FW). All extractions were checked by a second reviewer (JC, EL or FW). Extracted data items included characteristics of included studies (country, study design, study dates, funding sources and duration of follow-up), sample sizes, inclusion and exclusion criteria, key baseline characteristics of participants, interventions and comparator, outcomes (as listed in *Outcomes*) and results.

Disagreements between reviewers were resolved by discussion, with the involvement of a third review author where necessary.

Risk-of-bias assessment

The quality of included studies was assessed by one reviewer (JC, EL or FW), with the initial 20% assessed by a second reviewer to ensure that consistency was achieved (JC, EL or FW). For systematic reviews, we planned to use the tool produced by the Joanna Briggs Institute (https://jbi.global/critical-appraisal-tools); for RCTs, we used the Cochrane risk-of-bias tool consistent with the identified systematic reviews. Risk of bias was assessed for each trial and for individual outcomes of importance to the review question; a summary of the risk-of-bias assessment is presented by the type of intervention. For RCTs included in the Smedemark (2022) Cochrane review,[16] we used the judgements made by the Cochrane review authors for study-level bias and conducted new assessments for outcomes relevant to the present review.

Evidence synthesis

All included RCTs were tabulated and summarised narratively. For binary outcomes, risk ratios (RRs) were calculated and used in meta-analysis. Adjusted odds ratios (ORs) for binary outcomes and hazard ratios (HRs) for time-to-event outcomes, where reported, were also recorded and presented. For continuous outcomes, means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for each treatment arm and differences between treatment arms as reported by the original authors of included studies were recorded and presented.

Meta-analysis of clinical effectiveness outcomes was performed when sufficient data from reasonably homogeneous studies were available. This was guided by study design, population, outcomes and risk-of-bias assessment. A sample size adjustment was made to cluster randomised trials before they were included in a meta-analysis or forest plot with individually randomised trials. We followed methods in the Cochrane Handbook for Systematic Reviews of Interventions for calculating the effective sample size.[17] The adjustment was done by dividing the total numbers in each arm and the event numbers in each arm by the 'design effect'. The design effect for each cluster randomised trial was calculated using the formula:

$$1+(M-1)\times ICC$$

where M is the average cluster size and ICC is the intracluster correlation coefficient.

Random effects models were fitted using the DerSimonian and Laird method in the Metan command in Stata version 17 (StataCorp LP, College Station, TX, USA). Alternative methods for performing random-effects meta-analyses were explored because no single approach is universally preferable.[18] Inconsistency across studies was assessed using the I^2

statistic. Due to insufficient number of studies (< 10) in each meta-analysis, funnel plots were not constructed to assess small study effects. We did not attempt to contact authors to get pertinent missing data due to lack of time.

Analysis of subgroups

We pre-specified the following factors for subgroup analyses irrespective of statistical heterogeneity:

- age of patient (65 years and under, 66–80 years, over 80 years)
- presence of chronic comorbidity [e.g. chronic obstructive pulmonary disease (COPD)]
- pregnancy and post-partum (up to 28 days).

However, only data stratified by the presence or absence of COPD were available in the included studies.

Sensitivity analyses

Sensitivity analyses were undertaken to explore the impact of comorbidity, setting and test availability on the main analyses.

Assessment of certainty of evidence

We assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment (risk of bias, indirectness, inconsistency, imprecision and publication bias) for the key outcomes of:

- 7- or 28-day mortality
- escalation of care (including unplanned admission)
- hospital admission (immediately after triage or at 28 days).

One reviewer undertook the GRADE assessment, and this was checked by a second reviewer.

Cost-effectiveness review

Search strategy

Searches combined the concepts of: (a) ARIs, (b) near-patient, rapid tests (or, more broadly, diagnostics and testing), and (c) cost–utility.

Searches for cost–utility studies were conducted in the following databases in May 2023:

- MEDLINE (Ovid), from inception
- EMBASE (Ovid), from inception
- Cost-effectiveness Analysis Registry, from inception.

A precise, yet highly sensitive cost–utility study filter was used in EMBASE and MEDLINE.[19] See *Appendix 1* for our full record of searches. Our search was developed iteratively in MEDLINE. The final version finds a known systematic review,[20] and 13 studies included in it that were likely to be relevant to our research question. No date limit was applied.

References identified by the project team via highly targeted searches during the scoping phase were also reviewed.

Searches were restricted to English language and humans, and excluded:

- dissertations and theses
- conference abstracts
- editorials, letters, news items and commentaries.

Pre-print sources were not searched.

References of included studies and relevant systematic reviews were checked.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the cost-effectiveness review were the same as the clinical-effectiveness review in terms of the population, intervention and comparator eligible (see *Inclusion and exclusion criteria*). The exclusion criteria in terms of study design were also the same. The inclusion criteria for relevant outcomes and study designs differed and are described here.

Outcomes

Inclusion criteria

- Incremental cost (NHS and Personal Social Services perspective).
- Life-years gained.
- Incremental quality-adjusted life-years (QALYs).
- Incremental disability-adjusted life-years (DALYs).
- Incremental cost-effectiveness ratio (ICER)/cost per QALY.
- Incremental net health/monetary benefit.

Study designs

Inclusion criteria

- Systematic reviews of economic evaluations.
- Economic evaluations which included a cost–utility study.

Screening

Initial screening of titles and abstracts, followed by full-text screening was carried out using Rayyan (www.rayyan.ai/).[21] All records at both phases of screening were assessed by two independent reviewers (BS and KS), blinded to each other's decisions. Any conflicting screening decisions were resolved through discussion, with a third independent reviewer (YFC) if needed.

Data extraction

Data from included studies were extracted using standard forms (in the same formats as those of the summary tables presented in *Cost-effectiveness review results*) by one reviewer (KS) and checked by a second reviewer (BS). Extracted data included patient characteristics, study setting, perspective, time horizon, country, index and comparator testing strategies, target conditions, analytical approaches, key cost results, key effectiveness results, ICER results, headline results of uncertainty analyses and key conclusions.

Applicability and critical appraisal

For systematic reviews of cost-effectiveness studies, we used the tool produced by the Joanna Briggs Institute (https://jbi.global/critical-appraisal-tools) to assess the quality of the review. We then provide a narrative description of their applicability to our review question.

To assess the quality of included cost–utility studies, we used the Drummond checklist.[22] We also used Section 1 of the National Institute for Health and Care Excellence (NICE) appraisal checklist for economic evaluations to assess the applicability of each study to our review question.[23] This was done by one reviewer (KS), and then checked by a second reviewer (BS).

Evidence synthesis

All included systematic reviews and cost–utility studies were tabulated and summarised narratively. For each included cost–utility study, the total costs and total QALYs for each comparator were extracted (using the same denominator reported), as well as the ICER. Details of any uncertainty analyses, such as a one-way sensitivity analysis, probabilistic sensitivity analyses, or scenario analyses were also extracted.

Chapter 3 Results

Clinical effectiveness review results

Results of the search

Systematic reviews

A systematic search carried out to identify potentially relevant systematic reviews found 1355 references (see *Appendix 1* for the literature search strategy). Twenty per cent of references were screened separately by two reviewers with 96.6% agreement. An additional seven references were identified through examining reference lists.

The full texts of 70 systematic reviews were obtained for closer inspection. Five of these systematic reviews[16,24–27] reported synthesised evidence relevant to the review protocol; four of the earlier reviews had largely overlapping scopes and RCTs covered by the most recent review and were not quality assessed or extracted.[24–27] One systematic review was included as a source of data only (*C-reactive protein* and *Procalcitonin*).[16] The selection of systematic reviews is presented in *Figure 1*. Details of reviews excluded at full text are given in *Report Supplementary Material 1*, *Table 1*.

Randomised controlled trials

A systematic search carried out to identify potentially relevant studies found 2341 references (see *Appendix 1* for the literature search strategy). Twenty per cent of references were screened separately by two reviewers with 98.8% agreement. An additional 42 references were identified through examining reference lists of relevant systematic reviews.

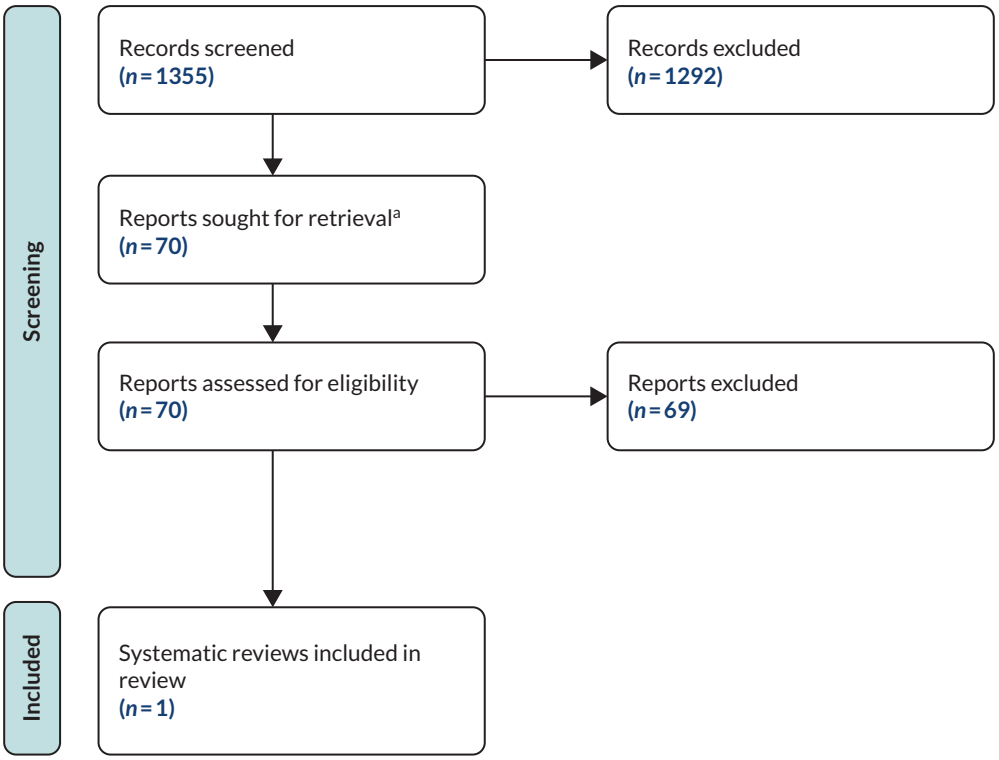

FIGURE 1 Study flow diagram: systematic reviews of clinical effectiveness. a, Includes seven records identified through examining reference lists. Reproduced with permission from Page *et al.*[28] This is an Open Access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. This figure includes minor additions and formatting changes to the original text.

The full texts of 118 records were obtained for closer inspection, and 14 studies (reported in 18 references)[29–46] met the inclusion criteria. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of study selection is presented in *Figure 2*. Key study characteristics and findings are presented in *C-reactive protein* to *Assessment of certainty of evidence* below. Detailed data extractions for individual studies are presented in *Appendix 2*, *Tables 11–14*.

Details of studies excluded in the full text screening stage are given in *Report Supplementary Material 1*, *Table 2*.

Results are discussed according to intervention. No eligible evidence was identified for the following eligible tests:

- rapid PCR tests
- urinary antigen tests
- serum sodium
- urea nitrogen
- partial pressure O_2
- blood gases
- full blood count
- white blood cell count
- MxA
- TRAIL.

C-reactive protein

A recent systematic review[16] assessed point-of-care (POC) biomarker tests to guide antibiotic treatment in people with ARI in primary care settings regardless of age. The scope differed from the present review in terms of patient age, setting, interventions and outcomes, but provided a subgroup meta-analysis for the effect of CRP testing on antibiotic

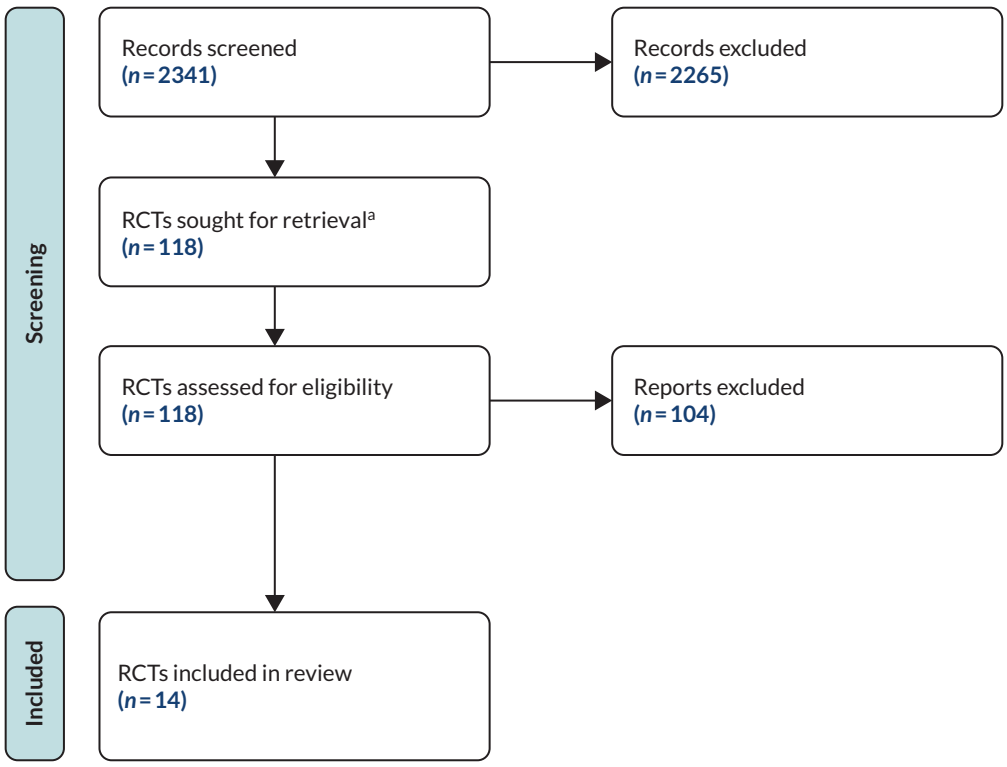

FIGURE 2 Study flow diagram: RCTs. a, Includes 42 records identified through examining reference lists of relevant systematic reviews. Reproduced with permission from Page *et al.*[28] This is an Open Access article distributed under the terms of the Creative Commons Attribution (CC BY 4.0) Licence, which permits unrestricted use, distribution, and reproduction in any medium and for any purpose, provided the original author and source are credited. See: https://creativecommons.org/licenses/by/4.0/. This figure includes minor additions and formatting changes to the original text.

use in adults. On closer inspection, we could not replicate the computation of the effective sample size for some of the cluster RCTs (see *Appendix 3*, *Tables 15* and *16*); therefore, we conducted new meta-analyses of outcomes for this test. The systematic review was used as a source of data for the relevant primary studies, in addition to the primary publications of the studies.

Ten RCTs (four of which were cluster RCTs) compared CRP POCT with usual care to guide antibiotic decisions (see *Table 1* and *Appendix 2*). All 10 RCTs were included in the Smedemark (2022) review.[16] Date of publication ranged from 1995 to 2021, with only three of the primary reports published in the past 5 years. One study was conducted in the UK,[30] and another study was conducted in Europe, including the UK.[41] Three studies were conducted in the Netherlands,[33,38,40] and the remaining studies were conducted in each of Russia,[29] Thailand and Myanmar,[32] Denmark,[35] Norway[37] and North Vietnam.[36] Study sample sizes ranged from 179[29] to 1932 adults.[41]

Five of the studies assessed a test not currently available in the UK (Nycocard II CRP POC testing);[32,33,35–37] however, a pragmatic decision was taken to include these studies. Two tests that are currently available in the UK were assessed: Afinion CRP POC testing (two studies[29,30]) and QuikRead CRP (three studies[38,40,41]).

Eight studies were conducted in a primary care setting,[29,30,33,35–37,40,41] one in primary care and outpatients,[32] and one study was conducted in nursing homes.[38] There were some differences in the populations eligible for inclusion in the studies. Most included people with acute lower respiratory tract infection (RTI) or upper or lower RTI, using slightly differing definitions; however, Butler (2019)[30] limited inclusion to people with acute exacerbation of COPD (AECOPD) (see *Table 1*). Three studies included children in their population; Do (2016)[36] presented subgroup data for adults in their study of non-severe ARI, while Althaus (2019)[32] and Diederichsen (2000)[35] provided raw data for adults with ARI to Smedemark (2022).[16]

Three studies received funding or test kits from the manufacturer.[29,37,40]

The following outcomes specified in our review protocol were not assessed by the included CRP POCT studies:

- escalation of care (some time after initial consultation): virtual ward
- escalation of care (some time after initial consultation): accident and emergency (A&E) visit
- escalation of care (some time after initial consultation): unplanned hospital admission
- antiviral use
- hospital length of stay
- follow-up consultation/ongoing monitoring.

Risk of bias in included C-reactive protein studies

The overall risk of bias was considered high for all 10 studies assessing CRP POCTs because of the lack of blinding of participants and personnel (see *Appendix 4*, *Tables 17* and *18*).[29,30,32,33,35–38,40,41] In addition, six studies were considered to have an unclear risk of selection bias due to unclear allocation concealment,[29,33,35,37,38,41] and four studies were considered to be at high risk of bias because of 'other bias'.[29,33,38,41] One study was at high risk of bias due to lack of blinding in the assessment of 'other outcomes'.[37] Based on the reviewer's judgements, one study was considered at high risk of bias due to incomplete outcome data reporting for 7- or 28-day mortality and hospital admission (immediately after triage or at 28 days).[38] Two studies were at high risk of bias due to incomplete outcome reporting for 'other outcomes' (i.e. antibiotic/antiviral use, hospital length of stay, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms, and HRQoL).[30,36] Risks of bias for other domains (e.g. random sequence generation and selective reporting) were considered to be low or unclear (see *Appendix 4*, *Tables 17* and *18*).

Hospital admission (immediately after triage or at 28 days)

No eligible evidence was identified for hospital admission immediately after triage.

Four cluster RCTs[29,33,38,41] and two individual RCTs[30,40] reported data on hospital admissions at varying time points (where reported), ranging from 2 weeks[29] to 6 months.[30] It was not possible to calculate RRs for two cluster RCTs[29,33] and one individual RCT[40] due to zero events in both intervention arms. Three RCTs provided data allowing calculation

TABLE 1 Characteristics of included studies for CRP POCT

Study details	Participants	Interventions	Outcomes	Comments[a]
Afinion CRP POCT				
Andreeva 2014[29] Russia Open-label cluster RCT GP January–April 2010 Follow-up: 14 days	179 patients: CRP 101, usual care 78 Acute cough/lower RTI for < 28 days	Interventions: single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 14 days • Hospital admission (not stated, assume within 14 days) • Number of re-consultations within 14 days • Number of participants fully or almost recovered within 14 days	Funding: not reported. Test kits provided by manufacturer and CRP readers acquired at reduced prices. Overall risk of bias: high
Butler 2019[30] Francis 2020[31] UK (England and Wales) Open-label RCT General medical practices January 2015–September 2017 Follow-up: 4 weeks and 6 months	649 patients: CRP 325, usual care 324 AECOPD between 24 hours and 21 days duration	Interventions: single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 28 days • Antibiotics prescribed within 4 weeks post-randomisation (patient-reported) • Mortality within 28 days • Hospital admissions within 6 months • Primary and/or secondary care consultations during 6 months follow-up • HRQoL (EQ-5D-5L index value) at 1, 2 and 4 weeks and at 6 months • HRQoL (EQ-5D-5L health status) at 1, 2 and 4 weeks and at 6 months • HRQoL (CRQ-SAS)	Funding: non-commercial Overall risk of bias: high
Nycocard II CRP POCT (not currently available in the UK)				
Althaus 2019[32] Thailand and Myanmar Open-label RCT Public primary care, 1 outpatient setting June 2016–June 2017 Follow-up: Day 5 + 14	937 patients (adults subgroup) CRP 614, usual care 323 Documented fever or chief complaint of fever (< 14 days)	Interventions: single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation	Funding: non-commercial Overall risk of bias: high
Cals 2009[33] Cals 2013[34] The Netherlands Open-label cluster RCT Primary care practices Winter periods June 2005 and July 2006 Follow-up: 28 days	431 patients CRP 227, usual care 204 Suspected lower RTI	Interventions: single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 28 days • Mortality during 28 days • Hospital admissions during 28 days • Number of re-consultations within 28 days • Number of participants substantially improved within 28 days	Funding: non-commercial Overall risk of bias: high
Diederichsen 2000[35] Denmark Open-label RCT Primary care practices January–April 1997 Follow-up: 1 week	673 patients CRP 342, usual care 331 All patients with index case of respiratory infection	Interventions: single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation	Source of funding: not reported Overall risk of bias: high

TABLE 1 Characteristics of included studies for CRP POCT (*continued*)

Study details	Participants	Interventions	Outcomes	Comments[a]
Do 2016[36] Northern Vietnam Open-label RCT Primary healthcare centres March 2014–July 2015 Follow-up: 14 days	1008 patients CRP 507, usual care 501 Non-severe acute RTI	Interventions: single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 14 day (per-protocol analysis) • Subsequent antibiotic use in those without an immediate antibiotic prescription • Antibiotic management change in those without an immediate antibiotic prescription • Time to resolution of symptoms • Mortality within 14 days	Funding: non-commercial Overall risk of bias: high
Melbye 1995[37] Norway Open-label RCT Primary care practices Study dates not reported Follow-up: 3 weeks	239 patients CRP 108, usual care 131 Suspected lower RTI	Interventions: single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 28 days • Number of participants substantially improved within 7 days • Number of participants substantially improved within 28 days	Funding: Nycomed Pharma Study terminated early due to parity at interim analysis and lack of interest in participating practices. Overall risk of bias: high
QuikRead CRP				
Boere 2021[38] Boere 2022[39] The Netherlands Open-label cluster RCT Nursing homes September 2018–March 2020 Follow-up: 3 weeks	241 patients CRP 162, usual care 79 Nursing home residents with suspected lower RTI	Interventions: single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation (including subgroup analysis for COPD) • Antibiotic treatment changes (start, cessation, switch, or prolongation) • Mortality within 3 weeks • Hospital admission within 3 weeks • Hospitalisation at initial consultation • Hospitalisation at 1 and 3 weeks • Number of participants substantially improved within 3 weeks • Number of participants fully recovered at 3 weeks	Funding: non-commercial Overall risk of bias: high
Cals 2010[40] The Netherlands Open-label RCT Primary care practices November 2007–April 2008 Follow-up: 28 days	258 patients CRP 129, usual care 129 Suspected acute lower RTI or rhinosinusitis	Interventions: single POC CRP Comparator: usual care	• Antibiotics use after index consultation (immediate prescription and/or delayed prescription and filled) • Antibiotics prescribed within 28 days • Mortality within 28 days • Hospital admissions within 28 days • Number of re-consultations within 28 days • Number of participants substantially improved within 7 days • Patient-reported time to full recovery	Funding: Orion Diagnostica Espoo, Finland Overall risk of bias: high
Little 2013[41] Little 2019[42] Belgium, UK, Poland, Spain, The Netherlands Open-label cluster RCT Primary care practices February 2011–May 2012 Follow-up: 12 months	1932 patients CRP 1062, usual care 870 Upper or lower RTI	Interventions: single POC CRP Comparator: usual care	• Hospital admissions within 4 weeks • Number of re-consultations within 28 days • Resolution of moderately bad symptoms, • Mortality	Funding: non-commercial Overall risk of bias: high

CRQ-SAS, Chronic Respiratory Questionnaire Self-Administered Standardized; EQ-5D-5L, EuroQol-5 Dimensions, five-level version.
a Overall risk of bias: see *Appendix 4*, *Tables 17* and *18* for details.

of RRs: two cluster RCTs with follow-up between 3 and 4 weeks reported very few events;[38,41] one RCT with follow-up at 6 months showed no difference between CRP and usual care groups, RR 1.02 [95% confidence interval (CI) 0.65 to 1.59; 1 RCT, *n* = 605; very low certainty evidence].[30]

Meta-analysis was not conducted for the studies reporting hospital admissions due to differences in duration of follow-up (*Figure 3*).

Escalation of care (some time after initial consultation): re-consultation/appointment

Three cluster RCTs[29,33,41] and one individual RCT[40] reported data on the number of re-consultations at 14 days,[29] or at 28 days,[33,40] or re-consultations due to 'new or worsening symptoms' within 28 days.[41] The pooled result for all included studies showed that CRP POCT may increase the risk of needing a re-consultation compared to usual care (*Figure 4*): RR 1.61 (95% CI 1.07 to 2.41, I^2 = 56.6%; four RCTs, *n* = 1433; very low certainty evidence).

Antibiotic use

Three cluster RCTs[29,33,38] and six individual RCTs[30,32,35–37,40] provided evidence on the number of antibiotics prescribed at index consultation. The pooled result for all included studies showed CRP POCT may reduce the risk of antibiotic prescribing at index consultation compared with usual care (*Figure 5*): RR 0.75 (95% CI 0.68 to 0.84, I^2 = 54.7%; nine RCTs, *n* = 4027). There was a high level of heterogeneity among estimated effects between individually randomised trials.

In contrast to the Smedemark (2022) review,[16] data on antibiotics prescribed at index consultation for Little (2013)[41] and Little (2019)[42] were excluded from the meta-analysis in the current review because it was clear from Little (2019)[42] that the data related to antibiotics prescribed at 3 months. The data reported at 3 months also appeared to be based on

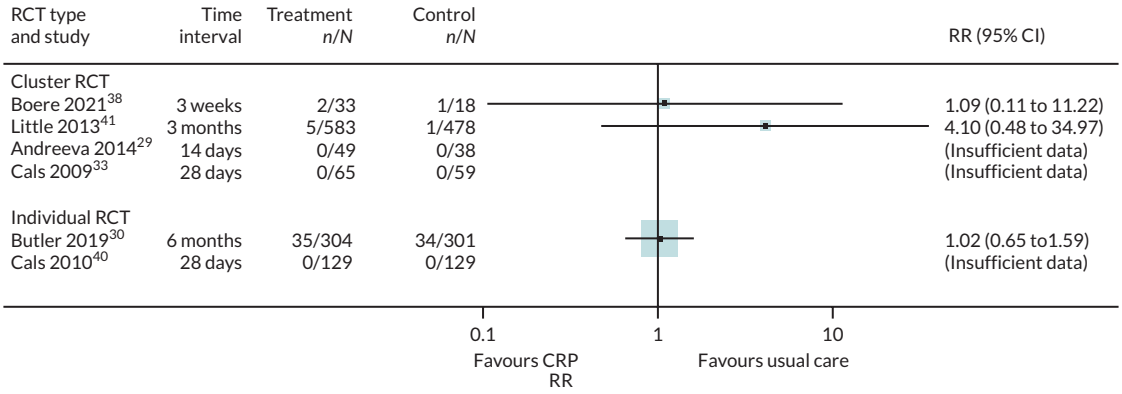

FIGURE 3 C-reactive protein POCT vs. usual care – hospital admission.

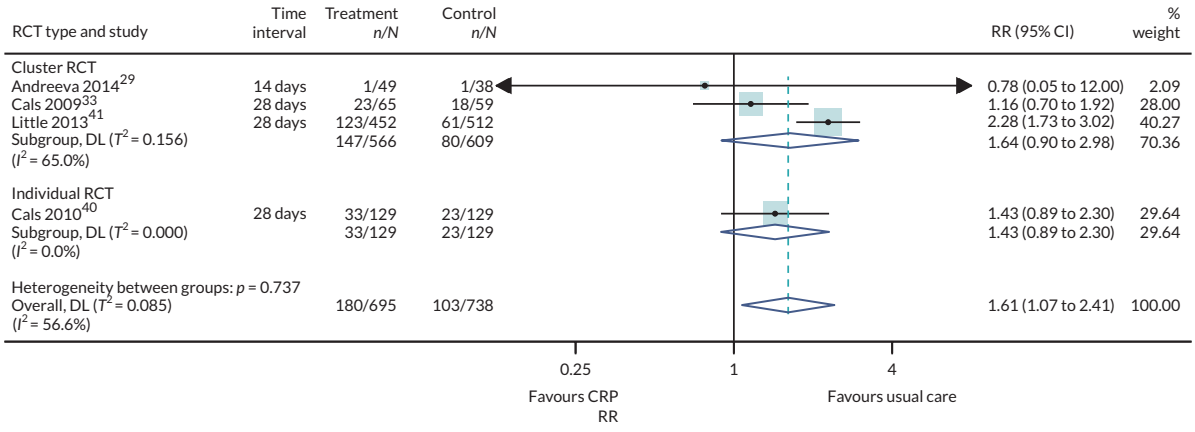

FIGURE 4 C-reactive protein POCT vs. usual care – escalation of care: number of re-consultations.

GP practices, suggesting the data reported were not necessarily follow-up of the same patients initially included in the study (see *Appendix 3*).

Two cluster RCTs[29,33] and four individual RCTs[30,36,37,40] also provided evidence on the number of antibiotics prescribed within 14 or 28 days. The pooled result for all included studies showed that CRP POCT may reduce the risk of antibiotic prescribing within 14 or 28 days compared to usual care (*Figure 6*): RR 0.79 (95% CI 0.73 to 0.85, I^2 = 24.4%; six RCTs, *n* = 2251).

Three studies reported additional data relating to antibiotic use or changes to antibiotic treatment that could not be meta-analysed.[30,31,36,38] Butler (2019)[30,31] assessed patient-reported antibiotic use for an AECOPD within 4 weeks after randomisation and found a reduction in antibiotic consumption in the CRP group (57.0%) compared with the usual care group (77.4%): adjusted OR 0.31 (95% CI 0.20 to 0.47; one RCT, *n* = 537).

Boere (2021)[38] found that antibiotic treatment changes (start, cessation, switch, or prolongation) occurred less frequently in the CRP group during follow-up (12.2%) compared with the usual care group (16.8%), OR 0.53 (95% CI 0.26 to 1.08; one cluster RCT); Do (2016)[36] found a small difference between the CRP group and usual care group in terms of subsequent antibiotic use in those without an immediate antibiotic prescription, 30.0% versus 34.2%,

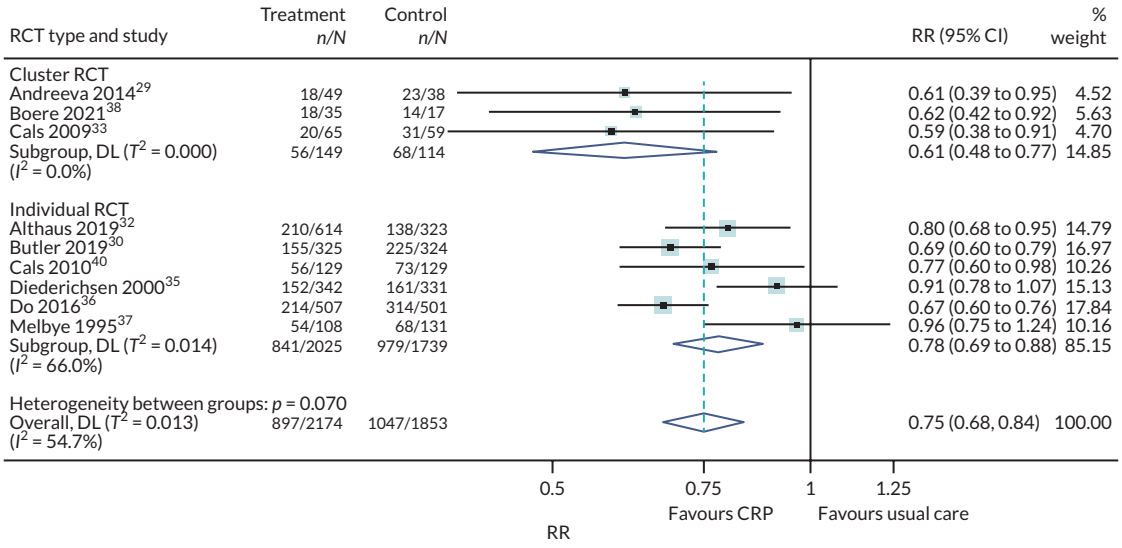

FIGURE 5 C-reactive protein POCT vs. usual care – antibiotics prescribed at index consultation.

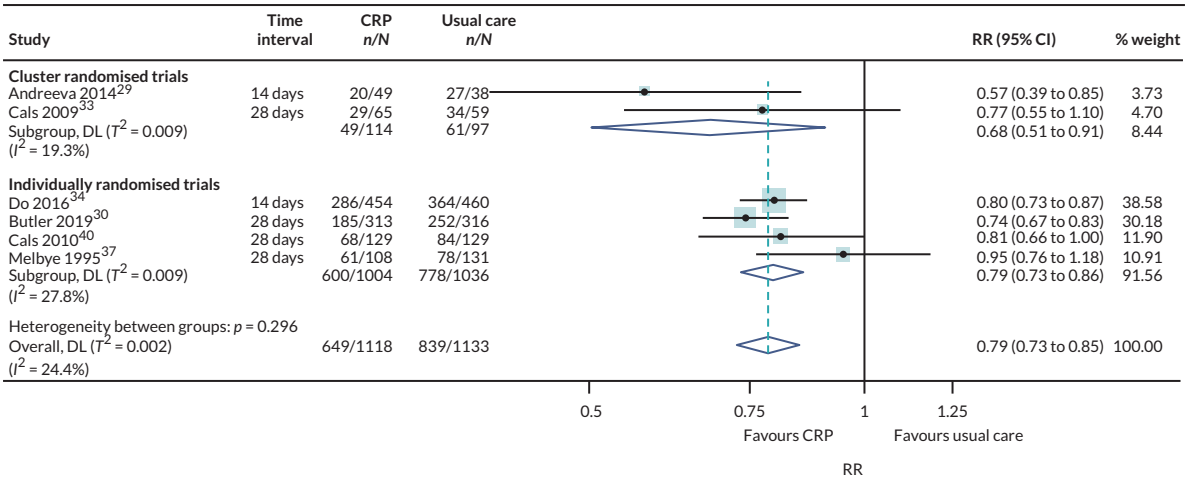

FIGURE 6 C-reactive protein POCT vs. usual care – antibiotics prescribed within 28 days.

TABLE 2 C-reactive protein POCT vs. usual care – time to resolution of symptoms/time to full recovery

Study	Outcome	CRP test	Usual care	Effect size
Cals 2010[40]	Time to full recovery, days	Mean LRTI 17.5 (SD 9.2) Rhinitis 17.3 (SD 9.3)	Mean LRTI 19.8 (SD 9.5) Rhinitis 16.6 (SD 9.9)	–
Do 2016[36]	Time to resolution of symptoms, days	Median 6 (IQR 4–10)	Median 5 (IQR 4–8)	HR 0.89 (95% CI 0.77 to 1.03)
Little 2013[41]	Time to resolution of moderately bad symptoms, days	Median 5 (IQR 3–8)	Median 5 (IQR 3–7)	Adjusted[a] HR 0.87 (95% CI 0.74 to 1.03)

LRTI, lower respiratory tract infection.
a The adjusted model additionally controlled for age, smoking, sex, major cardiovascular or respiratory comorbidity, baseline symptoms, crepitations, wheeze, pulse > 100 beats per minute, temperature > 37.8 °C, respiratory rate, blood pressure, physician's rating of severity and duration of cough.

respectively, OR 0.73 (95% CI 0.45 to 1.17; one RCT, *n* = 386), and an increase in terms of antibiotic management changes in those without an immediate antibiotic prescription between the CRP group (8.6%) and usual care group (4.6%): OR 1.99 (95% CI 0.86 to 4.64; one RCT, *n* = 430).

Time to clinical cure/resolution of symptoms

Three studies provided evidence on time to resolution of symptoms/time to full recovery (*Table 2*).[16,36,40,41]

Do (2016) and Little (2013) found no significant difference between the CRP and usual care groups in time to resolution of symptoms/moderately bad symptoms: HR 0.89 (95% CI 0.77 to 1.03; one RCT)[36] and adjusted HR 0.87 (95% CI 0.74 to 1.03; one cluster RCT).[16,41]

Similarly, Cals (2010) found little difference between the CRP and usual care groups in terms of patient-reported time to full recovery for patients with lower RTI [CRP mean 17.5 days (SD 9.2), usual care mean 19.8 days (SD 9.5); one cluster RCT, *n* = 100] or patients with rhinosinusitis [CRP mean 17.3 days (SD 9.3) and usual care mean 16.6 days (SD 9.9); one cluster RCT, *n* = 143].[40]

In addition, five studies provided evidence on the number of patients substantially improved (*Table 3*). Two studies reported the number of patients substantially improved within 7 days, with both studies showing no significant differences between CRP and usual care groups: RR 0.94 (95% CI 0.75 to 1.18; one RCT, *n* = 230)[16,37] and RR 1.03 (95% CI 0.89 to 1.18; one RCT, *n* = 243)[16,40]

One study reported a similar proportion of patients fully or almost recovered within 14 days between the CRP group (91.1%; *n* = 101, original sample size) and the usual care group (92.3%; *n* = 78, original sample size).[16,29]

One study found no significant difference in the number of patients fully recovered within 3 weeks between the CRP group (86.4%) and the usual care group (90.8%), OR 0.49 (0.21 to 1.12).[38] The sample sizes these proportions were based on were unclear and did not align with the original sample sizes in each group.

Two studies reporting that the number of patients substantially improved at 28 days found no significant difference between the CRP group and usual care group: RR 0.97 [95% CI 0.53 to 1.78; one cluster RCT (modified sample size due to cluster level data), *n* = 124][16,33] and RR 0.85 (95% CI 0.57 to 1.29; one RCT, *n* = 219).[16,37]

Mortality

Three cluster RCTs[33,38,41] and three individual RCTs[30,36,40] provided evidence of mortality rates at varying time points (*Figure 7*). It was not possible to calculate RRs for two cluster RCTs[33,41] and two individual RCTs[36,40] due to zero events in both intervention and usual care arms. Two RCTs provided data to calculate RRs but the event rates were very low.[30,38] Meta-analysis was not conducted.

TABLE 3 C-reactive protein POCT vs. usual care – number of patients substantially improved

Study	Outcome	CRP test *n*/*N*	Usual care *n*/*N*	Effect size
Cals 2010[40]	Substantially improved within 7 days	27/118	31/125	RR 1.03 (95% CI 0.89 to 1.18)
Melbye 1995[37]	Substantially improved within 7 days	46/102	53/128	RR 0.94 (95% CI 0.75 to 1.18)
Melbye 1995[37]	Substantially improved within 28 days	71/98	82/121	RR 0.85 (95% CI 0.57 to 1.29)
Andreeva 2014[29]	Fully or almost recovered within 14 days	92/101	72/78	Not reported
Boere 2021[38]	Substantially improved within 3 weeks	86.4%[a]	90.8%[a]	OR 0.49 (0.21 to 1.12)
Cals 2009[33]	Substantially improved within 28 days	49/65[b]	44/59[b]	RR 0.97 (95% CI 0.53 to 1.78)

RR, relative risk.
a Sample size unclear.
b Modified sample size.

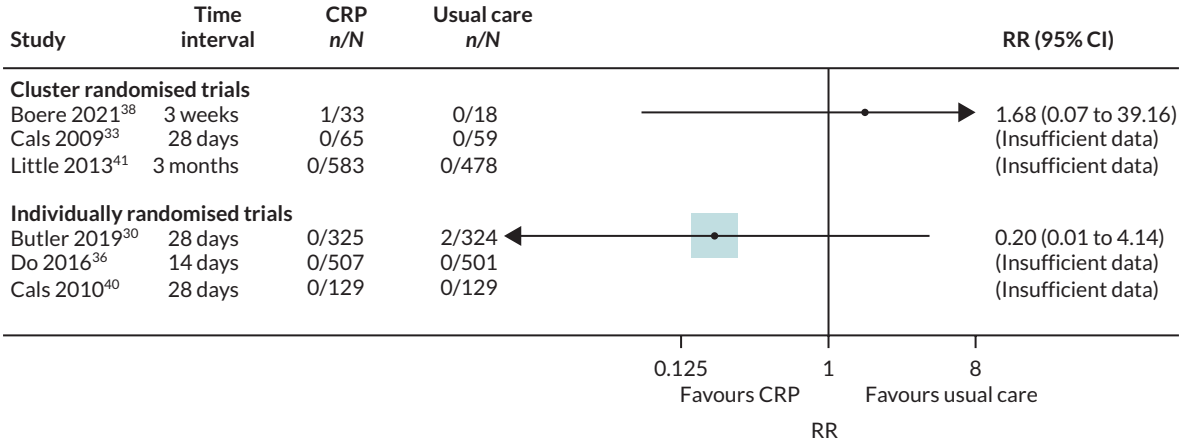

FIGURE 7 C-reactive protein POCT vs. usual care – mortality.

Health-related quality of life

One UK study[30] reported HRQoL (see *Appendix 2*), measured using the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) index value, EuroQol-5 Dimensions (EQ-5D) visual analogue scale (VAS; with scores ranging from 0 to 100 and higher scores indicating better health),[47] and the Chronic Respiratory Questionnaire Self-Administered Standardized (CRQ-SAS) which measures disease-specific HRQoL, including domains for dyspnoea, fatigue, emotional functioning and mastery (scores range from 1 to 7 with higher scores indicating better patient outcomes for each domain).[48]

No differences were found between patients in the CRP group compared with patients in the usual care group for EQ-5D-5L index values measured across different time points (i.e. at weeks 1, 2 and 4, and at 6 months): adjusted mean difference 0.03 (95% CI −0.04 to 0.09; one RCT). By contrast, EQ-5D VAS scores were 3 points higher in the CRP group compared with the usual care group measured across different time points (i.e. at weeks 1, 2 and 4, and at 6 months): adjusted mean difference 3.12 (95% CI 0.50 to 5.74; one RCT).[30]

No significant differences were found between the CRP and usual care groups for any CRQ-SAS domain at 6-month follow-up: adjusted mean difference for dyspnoea domain 0.06 (95% CI −0.20 to 0.33; one RCT, *n* = 399); adjusted mean difference for fatigue domain 0.13 (95% CI −0.12 to 0.38; one RCT, *n* = 436); adjusted mean difference for

emotional function domain 0.15 (95% CI −0.04 to 0.34; one RCT, *n* = 441); adjusted mean difference for mastery domain −0.09 (95% CI −0.18 to 0.01; one RCT, *n* = 435).[30]

Subgroup and sensitivity analyses for clinical effectiveness outcomes

Only one subgroup analysis was performed due to limited data. This subgroup analysis of antibiotics prescribed at index consultation included only patients with COPD.[30,38] Sensitivity analyses were conducted to assess the impact of excluding one study each in patients with AECOPD[30] or in a nursing home setting,[38] on antibiotics prescribed at index consultation or at 28 days. Sensitivity analyses were also conducted to assess the impact of excluding studies using tests that are unavailable in the UK on antibiotics prescribed at index consultation, within 28 days, or on the escalation of care.[32,33,35–37] Findings for subgroup and sensitivity analyses did not change the conclusions inferred from the main analyses (see *Appendix 6*, *Table 25*).

Procalcitonin

The systematic review[16] described above (see *C-reactive protein*) provided data for one included cluster RCT on the effects of procalcitonin testing.[43] The systematic review was used as a source of data for the RCT, in addition to the primary publication of the RCT. No additional RCTs were identified by our searches.

The RCT assessed the use of POC procalcitonin (BRAHMS PCT direct POCT) to guide antibiotic decisions in adults with acute cough in a primary care setting in Switzerland (*Table 4* and see *Appendix 2*, *Table 12*).[43]

Funding was non-commercial, although test kits were provided by the manufacturer.

The following outcomes were not assessed by the included procalcitonin study:

- escalation of care (some time after initial consultation): virtual ward
- escalation of care (some time after initial consultation): A&E visit
- escalation of care (some time after initial consultation): unplanned hospital admission
- antiviral use
- hospital length of stay
- follow-up consultation/ongoing monitoring
- HRQoL.

Risk of bias in included procalcitonin study

Based on the Cochrane Review assessment,[16] the single study assessing procalcitonin[43] was considered to be at high risk of bias due to lack of blinding of participants and personnel, and selection bias due to unclear allocation concealment and lack of individual randomisation. The remaining risk-of-bias domains were considered to be low or unclear risk. Based on the reviewer's judgements, the study was also at high risk of bias due to incomplete outcome reporting for 7- or 28-day mortality (see *Appendix 4*, *Tables 18* and *19*).

TABLE 4 Characteristics of included studies for procalcitonin tests

Study details	Participants	Interventions	Outcomes and results	Comments[a]
BRAHMS PCT procalcitonin				
Lhopitallier 2021[43] Switzerland Open-label cluster RCT Primary care practices September 2018–March 2020 Follow-up: 28 days	469 patients Procalcitonin 195, usual care 122[b] Lower RTI/acute cough	Interventions: POC procalcitonin Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 7 days • Antibiotics prescribed within 28 days • Number of re-consultations within 28 days • Hospital admissions within 7 days • Mortality within 28 days • Duration of symptoms by day 28	Funding: non-commercial. POCT kits were provided by the manufacturer Overall risk of bias: high

a Overall risk of bias: see *Appendix 4*, *Tables 18* and *19* for details.
b The trial included a third arm with 152 patients; this was not presented here as the intervention evaluated in this arm was outside the scope for this synthesis.

Hospital admission (immediately after triage or at 28 days)

No significant difference was found between procalcitonin and usual care in the number of patients in need of hospital admission within 7 days follow-up (RR 1.40, 95% CI 0.26 to 7.51; one cluster RCT, *n* = 277, very low certainty evidence).[16,43]

Escalation of care (some time after initial consultation): re-consultation/appointment

No difference was found between procalcitonin and usual care in the number of adults in need of a re-consultation within 28 days follow-up (RR 1.00, 95% CI 0.69 to 1.46; one cluster RCT, *n* = 317; very low certainty evidence).[16,43]

Antibiotic use

At the index consultation, antibiotic prescriptions were substantially lower in the procalcitonin group compared with the usual care group (RR 0.32, 95% CI 0.23 to 0.44; one cluster RCT, *n* = 317).[16,43]

Similarly, the number of antibiotic prescriptions was substantially lower in the procalcitonin group compared with the usual care group within 7 days (29.7% vs. 61.5%, respectively; one cluster RCT, *n* = 317) and within 28 days follow-up (40.0% vs. 70.5%, respectively; one cluster RCT, *n* = 277).[43]

Time to clinical cure/resolution of symptoms

There was no significant difference in the median duration of symptoms by day 28 between the procalcitonin group (8 days) and usual care group (7 days): HR 0.81 (95% CI 0.62 to 1.04; one cluster RCT, *n* = 261).[43]

Mortality

No deaths occurred in the procalcitonin group (0/163) or usual care group (0/114); one cluster RCT, *n* = 317; very low certainty evidence).[43]

Rapid antigen test – group A streptococcus tests

Two cluster RCTs assessed the effects of rapid antigen detection test (RADT) group A streptococcus (GAS) tests in adults with acute sore throat in primary care settings (RADT OSOM® Strep A[44] and RADT Clearview® Exact Strep A; *Table 5* and see *Appendix 2*, *Table 13*).[45] The studies were conducted in 2011 and 2007, in Spain and Canada, respectively. Sample sizes in the relevant intervention groups were 557[44] and 261.[45] One of the studies included people aged 14 years or over,[44] which is different from the present review criteria, but a pragmatic decision was made to include it as the difference is only slight. Funding was non-commercial in one study[44] and not reported in the other study.[45] Antibiotic use was the only outcome relevant to our review that was reported by these studies.

TABLE 5 Characteristics of included studies for GAS tests

Study details	Participants	Interventions	Outcomes and results	Comments[a]
RADT OSOM® Strep A				
Llor 2011[44] Spain Open-label cluster RCT Primary healthcare centres January to May 2008 Follow-up: NR	557 patients RADT 285, usual care 272 Acute pharyngitis	Interventions: RADT OSOM® Strep A test Comparator: usual care	• Antibiotics prescribed at index consultation	Funding: non-commercial Includes patients aged ≥ 14 years, slight difference to current review criteria. Overall risk of bias: high
RADT Clearview® Exact Strep A				
Worrall 2007[45] Canada Open-label cluster RCT Family doctors' offices February to April 2005 Follow-up: NR	533 patients RADT 120, usual care 141 Acute sore throat as primary symptom	Interventions: RADT Clearview® Exact Strep A dipstick Comparator: usual care	• Antibiotics prescribed at index consultation	Funding: not reported Overall risk of bias: high

NR, not reported.
a Overall risk of bias: see *Appendix 4*, *Tables 18* and *20* for details.

Risk of bias in included of group A streptococcus test studies

The two studies that assessed GAS tests were considered to be at high risk of bias according to reviewers' judgements, due to high risk of selection bias (lack of allocation concealment in both studies and inadequate sequence generation in one study) and high risk for 'other bias' (see *Appendix 4*, *Tables 18* and *20*).[44,45] In addition, one study was at high risk of bias due to a lack of blinding of participants and personnel.[44]

Antibiotic use

Two cluster RCTs found that antibiotic prescriptions were substantially lower in the RADT group compared with the usual care group at the index consultation: 43.8% versus 64.1% in the RADT and usual care groups, respectively; $p < 0.001$ (one cluster RCT, $n = 543$)[44] and 26.7% versus 58.2% in the RADT and usual care groups, respectively; $p < 0.001$ (one cluster RCT, $n = 261$) (*Table 6*).[45] Neither trial reported data allowing for adjustment of sample sizes for clustering effect.

Rapid antigen test – influenza tests

One RCT ($n = 93$) conducted in two hospital outpatient clinics in Switzerland in 2015 assessed the effects of an influenza RADT in adults with an influenza-like illness after returning from a trip abroad (*Table 7* and see *Appendix 2*, *Table 14*). The test used, BD Directigen™ Flu A + B rapid test (Becton and Dickinson, Maryland, USA), is not currently available in the UK.[46]

The source of funding was not reported. The trial was terminated early due to low sensitivity of the intervention. Antibiotic/antiviral use and mortality were the only outcomes relevant to our review that were reported by this study.

Risk of bias in the included study of influenza tests

The single study assessing an influenza test[46] was judged to be at high risk of bias due to selection bias (limitations in methods used for random sequence generation and allocation concealment), the lack of blinding of participants and personnel, and high risk due to 'other bias' (see *Appendix 4*, *Tables 18* and *21*).

Antibiotic/antiviral use

No significant difference was found between RADT and usual care in the number of adults prescribed antibiotics: 23.3% in the RADT group versus 39.4% in the usual care group; $p = 0.15$ (one RCT, $n = 93$).[46] No patient received antiviral treatment.

Mortality

No deaths occurred in the RADT group (0/60) or usual care group (0/33) (one RCT, $n = 93$; very low certainty evidence).[46]

TABLE 6 Rapid antigen detection test vs. usual care – antibiotic prescriptions at index consultation

Study	RADT test *n*/*N*	Usual care *n*/*N*	*p*-value
Llor 2011[44]	123/281 (44%)	168/262 (64%)	< 0.001
Worrall 2007[45]	32/120 (27%)	82/141 (58%)	< 0.001

TABLE 7 Characteristics of included study for influenza tests

Study details	Participants	Interventions	Outcomes and results	Comments[a]
BD Directigen™ Flu A + B rapid test (not currently available in the UK)				
Berthod 2015[46] NCT00821626[49] Switzerland Open-label RCT Hospital outpatient clinics December 2008–November 2012 Follow-up: NR	93 patients RADT 60, usual care 33 Fever or cough or sore throat within 4 days; illness within 14 days of a trip abroad	Interventions: BD Directigen A + B Comparator: usual care	• Antibiotics prescribed at index consultation • Antiviral use • Mortality	Funding: not reported Trial finished early due to low sensitivity of the intervention. Overall risk of bias: high

NR, not reported.
a Overall risk of bias: see *Appendix 4*, *Tables 18* and *21* for details.

Assessment of certainty of evidence

Appendix 5, *Tables 22–24* provide the GRADE summary of the certainty of the evidence for the included tests.

Cost-effectiveness review results

Search results

The titles and abstracts of 1600 records were screened, of which 77 records were identified as potentially meeting the eligibility criteria and were identified for full-text review. The full text for one record[50] could not be retrieved by our library, but we are confident that it is highly unlikely to be relevant given that the title indicates it is an erratum to a previous paper and the page numbers suggest it is just one page long, and thus unlikely to report a full economic evaluation. The reasons for exclusion at full-text stage are described in *Figure 8*, with the full references and reasons available in *Report Supplementary Material 1*, *Table 3*.

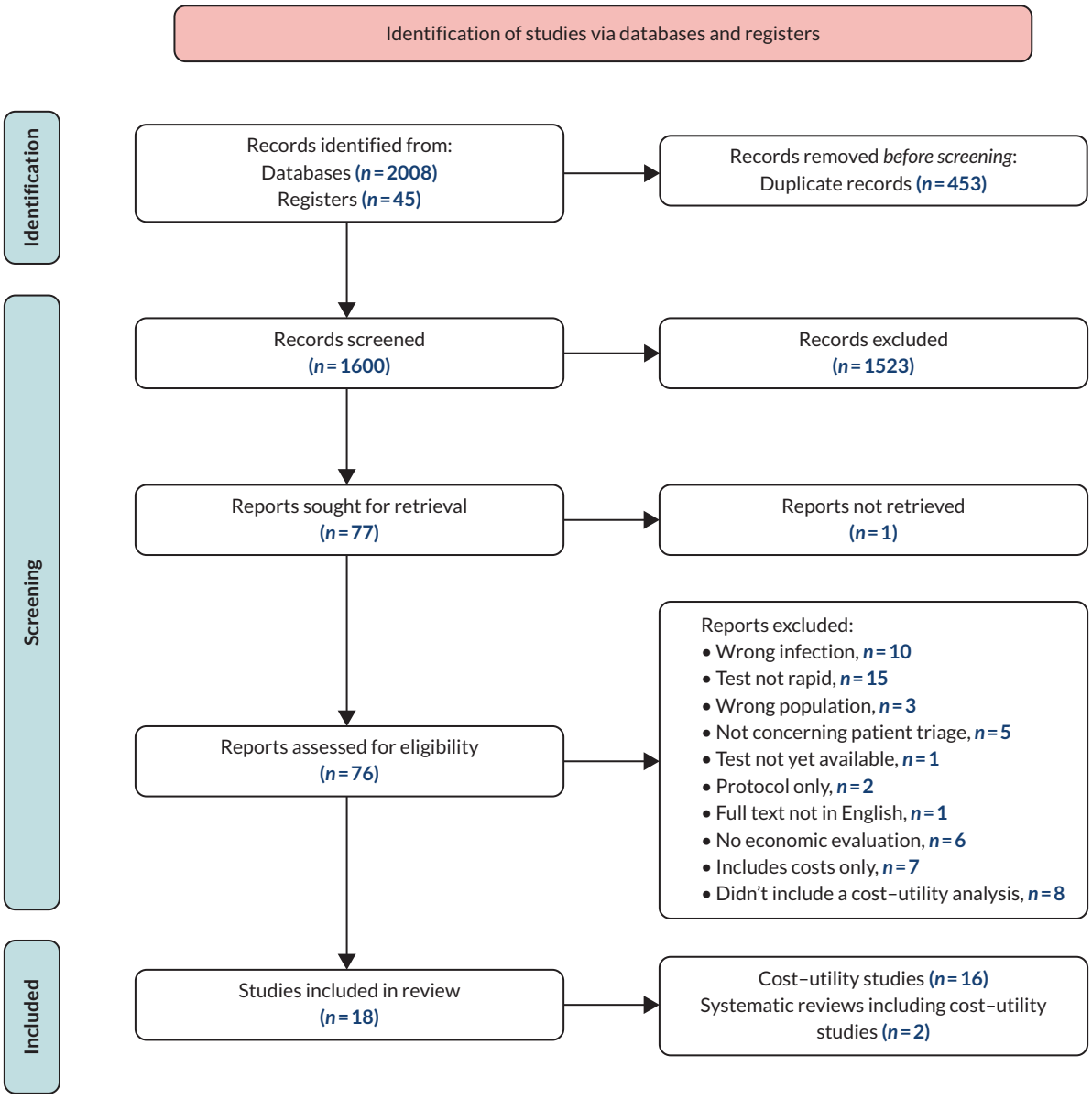

FIGURE 8 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for the selection of systematic reviews and cost–utility studies.

No eligible additional references were identified through examining reference lists.

Two systematic reviews[20,51] and 16 individual cost–utility studies[31,52–66] met the pre-defined eligibility criteria (see *Figure 8*).

Narrative summary, appraisal and applicability – systematic reviews

Two potentially relevant systematic reviews were identified.[20,51] Here we briefly summarise each review, focusing largely on whether these reviews are likely to have captured all the cost–utility studies relevant to our review question.

Van der Pol (2021)

The main objective of this review[20] was 'to review the methods used in economic evaluations of applied diagnostic techniques, for all patients seeking care for infectious diseases of the respiratory tract'. The searches were limited to articles published between January 2000 and May 2020. The review included cost-effectiveness analyses, cost–utility analyses and cost-minimisation analyses, if patient-relevant outcomes were included. Diagnostic strategies were defined as 'identifying the most likely cause of, and optionally optimal treatment for, a previously undetected disease in a clinically suspect patient who is seeking care'. Of the 70 studies included in the review, 23 evaluated rapid diagnostic tests, which included rapid influenza tests, CRP tests and procalcitonin tests. Other strategies evaluated included traditional diagnostics (n = 26), Xpert (n = 19) and clinical rules (n = 9).

The quality of the review was assessed using a critical appraisal checklist (for full details, see *Appendix 7*, *Table 26*). The key issues identified were that (1) the search strategy used terms which are likely to be inconsistently used in the literature, for example 'diagnostic' and was limited in breadth, (2) the grey literature was not searched, (3) the CHEERS checklist[67] was used to create a quality score for the included studies, but this is a reporting checklist rather than a quality appraisal tool and (4) only 10% of the data extraction was done by two independent reviewers.

Data extraction focused on the methodology used in each economic evaluation, in line with the objective of the review. Data relating to study results were not extracted. Given the different review objectives, the wider scope and the issues identified through the quality assessment, it was decided that this review is a useful source of relevant cost–utility studies, but the review itself could not be used in isolation to answer our review question. The findings of the Van der Pol review do however provide useful and very relevant discussion about the methodological strengths and limitations of cost-effectiveness research in this area, which we will refer to in the discussion of this report.[20]

Wubishet (2022)

The main objective of the Wubishet (2022) review[51] was to summarise and critically appraise the quality of published economic evaluations focused on interventions which promote antimicrobial stewardship or aim to reduce inappropriate antimicrobial prescribing in primary care. Full or partial economic evaluations of one or more antimicrobial stewardship interventions evaluated in a primary care setting were included. There were no restrictions on the type of intervention evaluated, the study population or the type of infection under consideration, or the comparator. Twelve studies were included in the review; 10 of which focused on inappropriate prescribing for upper/lower/acute RTI (ARTI). Six of the included studies focused on adults specifically, with a further four studies including both children and adults in their evaluation. Six of the included studies evaluated a strategy which involved the use of POC CRP testing.

The quality of the review was assessed using a critical appraisal checklist (for full details see *Appendix 7*, *Table 26*). The key issues identified were as follows: (1) the inclusion and exclusion criteria for the review were not clearly stated; (2) the search strategy was very limited, particularly with regards to the terms relating to the intervention; (3) it was unclear whether the critical appraisal had been done in duplicate; and (4) the discussion in the review did not discuss the implications of the results on future practice/policy.

The data extraction focused on the methods used in each study and the findings of each study. Given the different review objectives, the different (albeit overlapping) target interventions and the issues identified through the quality assessment, it was decided that this review is a useful source of relevant cost–utility studies, but the review itself could not be used in isolation to answer our review question.

Cost–utility studies – study characteristics

The references for the included studies in the two systematic reviews were checked against our search results to ensure we have captured all relevant studies in our searches for cost–utility studies. Our search identified all of the relevant (i.e. cost–utility studies) in the Van der Pol (2021) review.[20] There were also no additional relevant studies from those included in the Wubishet (2022) review.[51]

Details of the study characteristics for all 16 included cost–utility studies can be found in *Table 8*. Three of the included cost–utility studies were economic evaluations conducted alongside RCTs.[31,57,61] The majority of the remaining studies were model-based evaluations, 11 of which were decision trees,[52–55,58–60,63–66] and 1 study used a combination of a decision tree to capture the short-term diagnostic pathway and a Markov model to capture longer-term outcomes and costs.[56] One study was an economic evaluation based on an observational study.[62] The majority of the studies selected a relatively short time horizon to estimate costs and consequences, four studies adopted a time horizon of 28 days,[55,57,61,62] and two stated that an episode of illness or treatment episode was the time horizon. One study reported a model which had been developed using data largely from a trial, Cals (2013),[34] with 3 years' follow-up.[56]

Seven of the included evaluations were for a UK/England and Wales setting, with a further six developed for a US setting and one in each of Hong Kong, Sweden/Norway, Canada and Thailand. The economic evaluations focused on patients presenting in a range of settings, with many studies (n = 7/16) focusing solely or partially on primary care.[31,53–57,62] There were a further six studies conducted for a US population where the setting was not clearly stated, but looked likely to be focused on a primary care setting.[52,60,63–65] Five studies focused their evaluation either solely or partially on a secondary care setting, including ambulatory care, outpatient, or EDs.[54,58,59,61,66]

A wide range of different rapid tests were evaluated, the most common of which being POCT for CRP (n = 4/17),[31,55,56,62] and rapid tests for influenza (n = 5/17).[61,63–66] A range of different comparators were used across the evaluations, with standard care being the most commonly included.

Six of the included studies evaluated rapid tests for influenza.[58,61,63–66] Three of these studies were conducted for a US population and the focus was mainly on evaluating different antiviral treatments rather than the use of rapid testing (although rapid testing vs. no rapid testing was included as a comparator).[63–65] Nicholson (2014) evaluated multiple tests (rapid molecular and near-patient diagnostic tests for influenza, RSV, and *S. pneumoniae* infections) in a UK RCT to evaluate the impact on prescribing and clinical outcomes and cost-effectiveness.[61]

Four of the included studies focused on the use of rapid tests to manage individuals presenting with symptoms suggestive of GAS pharyngitis.[52,54,57,60] One of these studies was a model, developed for a UK NHS and Personal Social Services perspective, informed by an extensive systematic review of the evidence (diagnostic accuracy, clinical effectiveness and economic evaluations) for 21 different POCTs for detecting GAS bacteria (14 of these tests featured in the economic evaluation).[54] Another of these studies was an economic evaluation alongside a RCT conducted in the UK.[57]

One of the included studies focused specifically on a subgroup of patients, those who are diagnosed with COPD and experiencing an exacerbation.[31] This study was an economic evaluation conducted alongside a RCT.[31]

Cost–utility studies – applicability

The applicability of the included studies was assessed using the first section of the NICE appraisal checklist for economic evaluations (see *Appendix 8*, *Table 27* for details).[23]

Six of the included studies were judged to be directly applicable to our review question, four of which evaluated the cost-effectiveness of POCTs for CRP.[31,54–56,61,62] Fraser 2020 undertook an extensive systematic review of the evidence of 21 different POCTs for GAS.[54] Nicholson (2014) evaluated rapid near-patient tests for influenza A and B and pneumococcal infection.[61]

Two studies were judged to be partially applicable to our review question.[57,59] Little 2014 is a RCT-based economic evaluation focused on a rapid test for A/C/G streptococci in conjunction with the FeverPAIN clinical scoring

TABLE 8 Characteristics of included cost–utility studies

Author, year	Patient characteristics, setting	Perspective, time horizon, country	Index testing strategy	Comparator testing strategy(s)	Target condition	Analytic approach
Time horizon up to 28 days						
Oppong, 2013[62]	Patients aged ≥ 18 years; presenting to GP with acute or worsened cough as the main symptom for up to 28 days, or who had a clinical presentation suggesting LRTI. Primary care	Health service perspective, 28 days, Sweden and Norway	CRP POCT	No POCT CRP available	Community-acquired LRTI	Data from observational study
Nicholson, 2014[61]	Patients aged > 65 or > 18 years with underlying chronic heart or lung disease; has an acute exacerbation of chronic cardio-pulmonary illness or influenza-like illness of < 7 days. Hospital setting (presenting at medical admissions units, or any ward accepting acute medic admissions)	UK NHS perspective, 28 days, UK	POCT (Quidel for influenza, and BinaxNOW for the pneumococcal antigen)	1. Laboratory-based PCRs (for influenza A and B and RSV A and B), plus laboratory pneumococcal antigen testing 2. Conventional laboratory diagnostic assessment (culture/serology)	Influenza A and B, RSV and pneumococcal infection	RCT
Little, 2014[57]	Patients aged ≥ 3 years; acute sore throat. Primary care	UK NHS perspective, 28 days, UK	Clinical scoring algorithm (FeverPAIN) + RADT if score high on algorithm	Clinical scoring algorithm alone (FeverPAIN) and a separate control (delayed prescribing)	Lancefield group A/C/G streptococci	RCT
Holmes, 2018[55]	Adult patients; symptoms of ARI for > 12 hours. Primary care	UK NHS perspective, 28 days, UK	Alere Afinion AS100 CRP POCT	Current standard of care (no POCT)	ARI	Model-based
Time horizon longer than 28 days						
Neuner, 2003[60]	Adults with suspected GAS pharyngitis, within 3 days of symptom onset, patients without a history of acute rheumatic fever or glomerulonephritis, patients with a history of penicillin allergy also not included. Not explicitly stated; assume primary care	Societal, 1 year, US	Optical immunoassay (OIA)	(1) Observation only, (2) antibiotics for all, (3) throat culture + antibiotics for positives and (4) OIA followed by culture to confirm negative results, antibiotic treatment for positive cases	GAS	Model-based
Hunter, 2015[56]	Adult patients; attend primary care with RTI symptoms. Primary care	UK NHS perspective, 3 years, UK	Afinion Analyzer CRP POCT by GP; CRP POCT by nurse; CRP POCT by GP + communication training for GP	Current standard of care (no test)	RTI	Model-based
Francis, 2020[31]	Patients aged ≥ 40 years; has exacerbation that has lasted at least 24 hours and no longer than 21 days; COPD diagnosis in clinical record/on COPD practice register. Primary care	UK NHS perspective, 6 months, Wales and England.	Alere Afinion CRP POCT	No test (current standard of care)	Bacterial COPD Exacerbation	RCT

TABLE 8 Characteristics of included cost–utility studies (*continued*)

Author, year	Patient characteristics, setting	Perspective, time horizon, country	Index testing strategy	Comparator testing strategy(s)	Target condition	Analytic approach
Time horizon longer than 28 days						
Fraser, 2020[54]	Adults and children who present with an acute sore throat. Primary and secondary care (urgent care/walk-in centres and EDs, modelled separately)	UK NHS and Personal Social Services, 1 year, UK.	POCT (14 tests evaluated) in conjunction with clinical scoring tools, for example Centor and FeverPAIN score for strep A	Current standard of care: clinical assessment incorporating clinical scoring tools (no POCT)	GAS	Model-based
Mac, 2020[58]	Patients aged 65 years; signs of symptoms suggestive of influenza. ED	Single healthcare payer, Lifetime, Canada	RIDTs; digital immunoassays (DIA); rapid NAAT	(1) Do not treat, (2) treat everyone, (3) clinical judgement, (4) batch PCR test, treat until results available and (5) batch PCR test, do not treat until results available	Influenza-like illness	Model-based
Bilir, 2021[52]	Age reflects US population distribution (mean age 38, 22.4% < 18); patients presenting with pharyngitis with sore throat who are tested for GAS. Not stated; assume primary care	US payer, 1 year, USA	POC NAAT	RADTs + culture confirmation of negative results (current standard of care)	GAS	Model-based
Chew, 2022[53]	Patients (any age): systemic antibiotic prescription; ICD 10 code for infection; fever as the chief complaint; documented temperature > 37.5°C. Patients with chronic respiratory infections or bronchitis of unknown acuity were excluded. Government funded primary care units in Mueang Chiang Rai	Health system, 1 year, Thailand	Pulse oximetry-aided ARI management	Standard of care (no pulse oximetry device)	ARI	Model-based; population data from retrospective review
Time horizon unclear						
Smith, 2002[65]	Patients aged 32 years; influenza-like symptoms and a fever ≥ 37.8 °C; different ages included in sensitivity analyses. Not stated; assume primary care	Societal, Unclear, US	Rapid test; followed by different antiviral therapies	No test followed by different antiviral therapies (including no therapy)	Influenza A and B	Model-based
Rothberg, 2003[64]	Unvaccinated, healthy, working adults between 20 and 50 years of age presenting with influenza-like illness during the influenza season. Setting not stated; assume primary care	Societal, Unclear, US	Rapid antigen tests (Directigen A/B; Flu OIA; QuickVue; ZstatFlu); followed by different antiviral therapies	No test followed by different antiviral therapies	Influenza A and B	Model-based

TABLE 8 Characteristics of included cost–utility studies (*continued*)

Author, year	Patient characteristics, setting	Perspective, time horizon, country	Index testing strategy	Comparator testing strategy(s)	Target condition	Analytic approach
Rothberg, 2003[63]	Non-institutionalised patients aged > 65 years; influenza-like illness; separate analyses for vaccinated vs. unvaccinated. Primary care	Societal, Unclear, US	Rapid antigen test QuickVue; followed by different antiviral therapies	No test followed by different antiviral therapies (including no therapy)	Influenza A and B	Model-based
Michaelidis, 2014[59]	(1) Adults; ARTI judged by their doctor to require antibiotics (2) Adults; ARTI prior to any decision about antibiotics. Outpatient clinic	Healthcare system, ARTI treatment episode, US	POC procalcitonin-guided antibiotic therapy	Usual care (no POC procalcitonin)	ARIs	Model-based using two real trial cohorts
You, 2017[66]	Elderly patients (65–90 years); influenza-like symptoms. Patients with symptoms > 7 days or previously treated were excluded. Ambulatory setting (outpatient)	Health service perspective, Not stated, Hong Kong	Rapid molecular PCR to inform antiviral therapy	No test; clinical judgement	Influenza A and B	Model-based

ICD 10, *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision LRTI, lower respiratory tract infection; NAAT, nucleic acid amplification tests; RIDT, rapid influenza diagnostic test.

algorithm.[57] The trial included both adults and children which deviates from our review question, but the results may still be relevant. Michaelidis (2012) evaluated the cost-effectiveness of point-of-care procalcitonin (POC PCT) in a US outpatient setting from a healthcare system perspective.[59] Despite the difference in country, as the only economic evaluation focused on this test in a relevant setting to our review question, we assessed this study as potentially providing some useful evidence.

The remaining studies were scored as being not applicable to our review question.[52,53,58,60,63–66] These studies were all focused on non-UK settings.

Results of included cost–utility studies

The main results of the included cost–utility studies are presented in *Table 9*. Here we will focus on the studies assessed as being either directly or partially applicable to our review question.

Three directly applicable studies evaluated the cost-effectiveness of POCTs for CRP in patients presenting to primary care with symptoms suggestive of ARI. The authors of all three studies concluded that POCTs for CRP are likely to be cost-effective.[55,56,62] Oppong (2013) caveated this conclusion with a warning about the potential resource implications of the widespread use of POCTs for CRP. Holmes (2018) addresses this issue in their evaluation by comparing POCT for CRP use and treatment in line with NICE CG191 clinical recommendations, that test only when clinical assessment is not conclusive and do not routinely offer antibiotics if CRP is < 20 mg/l, and offer a delayed prescription if CRP is between 20 and 100 mg/l, compared to pragmatic use of POC CRP.[68] They found that allowing POCTs for CRP to be used pragmatically in primary care led to it being borderline cost-effective, but by adhering to guidelines around usage, the model predicted a far lower ICER. A further study evaluated POCTs for CRP specifically in patients experiencing a COPD exacerbation and concluded that POCT for CRP was cost-effective at a willingness to pay (WTP) threshold £20,000 per QALY.[31]

Michaelidis (2014) conducted a model-based economic evaluation of POCTs for PCT focusing on an outpatient clinic population, concluding that they had the potential to be cost-effective if the cost of antimicrobial resistance (AMR) was factored into the analysis and if the test is only used in those judged to require antibiotics. The authors attempt to estimate the cost of antibiotic resistance per antibiotic prescribed for outpatient management of ARI in adults, but in the absence of methodological guidance on this issue, the validity of these estimates is unclear.[59]

Fraser (2020) evaluated 14 different POCTs for GAS and found that none of the POCTs evaluated were cost-effective compared with usual care in both a primary care and secondary settings.[54] Little (2014) conducted a RCT-based economic evaluation of a rapid antigen test (IMI TestPack Plus Strep A, Inverness Medical, Bedford, UK) for A/C/G streptococci and concluded that the use of a clinical algorithm alone is most likely to be cost-effective compared to using the rapid test in combination with the clinical algorithm.

Nicholson (2014) evaluated two POCTs (Quidel for influenza, and BinaxNOW for the pneumococcal antigen) in a hospital-based (medical admissions units, or any ward accepting acute medic admissions) RCT compared to laboratory-based PCR and traditional culture/serology and found that, although the POCTs had the highest gain in terms of QALYs, it did not fall below a cost-effectiveness threshold of £30,000 compared to laboratory-based PCR.

Critical appraisal of included cost–utility studies

The results of the critical appraisal using the Drummond (2015) checklist[22] can be found in *Table 10*. We adapted question 4 of the appraisal tool slightly (Were all the important and relevant costs and consequences for each alternative identified?) to allow us to answer this question separately for short-term, long-term and AMR-related costs. We felt this was an important additional detail for these studies given that the majority had a short-term time horizon.

TABLE 9 Data extraction for cost–utility studies – results

Author, year	Index testing strategy	Target condition	Key costs results	Key effectiveness results	ICER results	Headline results of uncertainty analyses	Key conclusions
CRP tests[a]							
Oppong, 2013[62]	CRP POCT	Community-acquired LRTI	Test increases health-care costs by €11.27 per patient (28-day time horizon)	QALY gain of 0.0012 with test per patient (28-day time horizon)	€9391	At a WTP threshold of €30,000, the probability of POC CRP being cost-effective is approxi-mately 70%.	Results provide evidence of cost-effectiveness of testing in terms of cost per QALY and cost per unit reduction in antibiotic prescribing. There are however resource implications from wide-spread use of the test.
Hunter, 2015[56]	Afinion Analyzer CRP POCT by GP; CRP POCT by nurse; CRP POCT by GP + communication training for GP	RTI	Cost per 100 patients (3-year time horizon): GP + CRP: £18,039 Nurse + CRP: £17,401 GP + CRP + training: £18,431 No test: £18,081	QALYs per 100 patients (3-year time horizon) GP + CRP: 255.764 Nurse + CRP: 255.761 GP + CRP + training: 255.588 No test: 255.630	GP + CRP and nurse + CRP are dominant over current practice.	GP + CRP is dominant compared to current practice in 50% of simulations, in 65% the nurse + CRP is dominant and in 19% the GP + CRP + training is dominant. Nurse + CRP has the highest NMB in CEAC. Changing most model parameters has little impact on conclusions.	GP + CRP and nurse + CRP are dominant over current practice. The GP plus CRP testing and communication training strategy is associated with increased costs and reduced QALYs These strategies are associated with reduced risks of infection and rates of antibiotic prescribing.
Holmes, 2018[55]	Alere Afinion AS100 CRP POCT	ARI	Costs per patient (28-day time horizon): Pragmatic use of testing: Test £52.35 No test £40.41 Adhering to guidelines (NICE CG191): Test £48.79 No test £39.48	QALYs per patient (28-day time horizon): Pragmatic use of testing: Test 0.0615 No test 0.0609 Adhering to guidelines (NICE CG191): Test 0.0577 No test 0.0556	Pragmatic use of testing: £19,705 Adhering to guidelines (NICE CG191): £4390	*Pragmatic use of testing* The probability that test is cost-effective at £20,000 per QALY threshold is 49.06%, and 62.82% at £30,000 per QALY threshold. *Adhering to guidelines* Probability test is cost-effective at £20,000/QALY threshold is 84.10%, and 86.33% at £30,000. If the test cost 18p more, or test use fell by 5%, the ICER exceeds £20,000. Test results in higher utility but at a higher cost in 75% of simulations.	POC CRP is borderline cost-effective. Closer adherence to guidelines (by restricting CRP testing to adults with symptoms of LRTI and prescribing appropriate courses of antibiotics) results in a more favourable ICER. The test must cost below £9.67 to be cost-effective. Including the cost of AMR improves the cost-effectiveness of the test.

TABLE 9 Data extraction for cost–utility studies – results (*continued*)

Author, year	Index testing strategy	Target condition	Key costs results	Key effectiveness results	ICER results	Headline results of uncertainty analyses	Key conclusions
Tests for COPD exacerbation							
Francis, 2020[31]	Alere Afinion CRP POCT	Bacterial exacerbation of COPD	Costs per patient (6-month time horizon): Test: £759.35 No test: £629.72	QALYs per patient (6-month time horizon): Test: 0.3 No test: 0.2915	£15,251	Results remained reasonably robust when cost inputs were changed but were sensitive to changes in QALY inputs. The ICER would reduce to £1054 if COPD-related costs only were included. Most results found CRP POCT to be more costly but more effective. The cost–utility analysis (using imputation and an intention-to-treat approach) gave an ICER of £14,334.	The use of CRP POCT in primary care reduces both antibiotic consumption and costs, without significantly affecting other COPD medication costs, health-care resource use and HRQoL.
GAS tests (including Group C/G)							
Bilir, 2021[52]	POC NAAT	GAS pharyngitis	Costs per patient (1-year time horizon): POC NAAT: $44 RADT + culture: $78	QALDs lost per patient (1-year time horizon): POC NAAT 0.0413 RADT + culture 0.0451	POC NAAT dominant	Model results relatively insensitive to 20% variation across parameters. The most sensitive were test sensitivity and specificity. The different scenario analyses (including a GAS outbreak) also showed robust results.	Use of POC NAAT is slightly more effective than RADT + culture without incurring additional costs. POC NAAT also reduces unnecessary antibiotic use.
Little, 2014[57]	Clinical scoring algorithm (FeverPAIN) + RADT if score high on algorithm	Lancefield group A/C/G streptococci	Costs per patient (28-day time horizon): RADT £48.50 Clinical algorithm: £45.90 Control: £49.70	QALYs per patient (28-day time horizon): RADT 0.018 Clinical algorithm: 0.017 Control 0.017	£74,286 (14 day) £24,528 (28 day)	At threshold of £30,000/QALY, the probabilities of cost-effectiveness are 25%, 40% and 35%, for the delayed control, clinical algorithm and RADT groups, respectively (14-day results). For the 28-day QALY gain, the same values are 28%, 38% and 35%.	Differences in QALYs generated were very small with wide CIs, and therefore there were no statistically significant differences between any groups. The CEACs indicate that the clinical algorithm is the most likely to be cost-effective.

continued

TABLE 9 Data extraction for cost–utility studies – results (*continued*)

Author, year	Index testing strategy	Target condition	Key costs results	Key effectiveness results	ICER results	Headline results of uncertainty analyses	Key conclusions
Fraser, 2020[54]	POCT (14 tests evaluated) in conjunction with clinical scoring tools, for example Centor and FeverPAIN score for strep A	GAS	Costs per 1000 patients in primary care (1-year time horizon): NADAL Strep A–test (cheapest test): £54,394 Cobas Liat Strep A Assay (most expensive test): £71,277 No test: £49,147 Costs per 1000 patients in secondary care (1-year time horizon): NADAL Strep A test (cheapest test): £49,318 Cobas Liat Strep A Assay (most expensive): £65,186 No test £49,147	QALYs per 1000 patients in primary care (1-year time horizon): Abbott Clearview Exact Strep A cassette or test strip (lowest QALYs): 859.821 Cepheid's Xpert Xpress Strep A test (highest QALYs): 895.829 No test: 859.825 QALYs per 1000 patients in secondary care (1-year time horizon): Abbott Clearview tests generated fewer QALYs than usual care; remaining tests all generated more QALYs than usual care	Usual care dominant over Abbott Clearview Exact Strep A cassette or test strip; ICERs for remaining tests suggest testing is more costly but more effective than usual care (primary and secondary care)	*Primary care* Results were similar to the base-case results, with ICERs indicating that usual care dominated two (the Abbott Clearview Strep A tests) of the 14 tests. The probability for testing to be cost-effective was zero at a cost-effectiveness threshold of £20,000 per QALY in all scenarios, regardless of the test used. The base-case ICERs are highly sensitive to model assumptions and inputs. *Secondary care* Results mirrored the primary care model.	POCT is not cost-effective compared with usual care across all populations evaluated. Important uncertainties in the model include parameter inputs and assumptions that increase the cost of testing (acquisition cost of test, additional clinician time for administering and processing test results, cost of throat culture for those testing negative) and the penalty for antibiotic over-prescription (acquisition cost of antibiotic and probabilities for penicillin-induced anaphylaxis and rash).
Neuner, 2003[60]	Optical immunoassay (OIA)	GAS pharyngitis	Costs per patient (1-year time horizon): OIA test: $11.73 Observation: $9.84 Culture: $6.66 Empirical therapy: $12.74 OIA + culture: $15.15	QALDs lost per patient (1-year time horizon): OIA test: 0.272 Observation: 0.275 Culture: 0.267 Empirical therapy: 0.404 OIA + culture: 0.272	OIA test dominated by culture	Results unchanged by most sensitivity analyses; they generally made observation more cost-effective. If the probability of side effects is higher, observation is preferred. OIA was only more cost-effective than culture when its cost was greatly reduced. Culture remained the cheapest strategy at all ranges of OIA characteristics tested.	Culture was by a slight margin the most cost-effective in the base-case analysis. Empirical treatment was less effective than the remaining strategies (including OIA), which were all similar in terms of cost-effectiveness. Analyses do not support guideline recommendations for eliminating the use of culture to diagnose GAS.

TABLE 9 Data extraction for cost–utility studies – results (*continued*)

Author, year	Index testing strategy	Target condition	Key costs results	Key effectiveness results	ICER results	Headline results of uncertainty analyses	Key conclusions
Influenza tests							
Mac, 2020[58]	Rapid influenza diagnostic tests (RIDTs); digital immunoassays (DIA); rapid NAAT; followed by antiviral therapy	Influenza-like illness	Costs per patient (lifetime time horizon): RIDT: $622.52 DIA: $618.99 NAAT: $636.75 No test (no treatment): $608.19 No test (treat everyone): $630.01; Batch PCR (treat)[b]: $661.19; Batch PCR (wait)[c]: $661.30 Clinical judgement: $611.02	QALYs per patient (lifetime time horizon): RIDT 15.0175 DIA 15.0338 NAAT 15.0404 No test (no treatment): 14.9961 No test (treat everyone): 15.0470 Batch PCR (treat)[b]: 15.0450 Batch PCR (wait)[c]: 15.0241 Clinical judgement: 15.0145	*N*/A	Costs of treatment and diagnostics had little impact on the cost-effectiveness compared to diagnostic test parameters, treatment benefits and the seasonal prevalence of influenza. If upper limits for sensitivity and specificity are used, batch PCR (treat)[b] was the most cost-effective.	Treating everyone in a high-risk population without a rapid test provides the highest NHB. Of the three rapid tests, NAAT to inform treatment was the most cost-effective. Difference in QALYs between the strategies is minimal.
Rothberg, 2003[64]	Rapid antigen tests (Directigen A/B; Flu OIA; QuickVue; ZstatFlu); followed by different antiviral therapies	Influenza A and B	Exact figures not stated for all strategies (presented as a figure); all testing strategies increase costs	Exact figures not stated for all strategies (presented as a figure); all testing strategies led to negative QALYs	*N*/A	Results sensitive to efficacy of the drugs and the cost of a workday. Decreasing the utility of influenza slightly improved cost-effectiveness of NAI. The lowest priced test is preferred with a slight preference for Directigen. The preferred strategy is affected by the prevalence of influenza.	All of the cost-effective strategies involve treatment based on clinical diagnosis. We did find a limited role for testing when the probability of influenza infection is low, as in the peri-influenza season, and most cases are caused by influenza B.
Rothberg, 2003[63]	Rapid antigen test QuickVue; followed by different antiviral therapies	Influenza A and B	Costs for unvaccinated patient aged 75 years Test + antiviral treatment: $137.35–$147.94 No test, no antiviral treatment: $118.86 No test antiviral treatment: $120.43–$155.56	QALEs for unvaccinated patient aged 75 years Test + antiviral treatment: 9.9794–9.9833 No test no antiviral treatment: 9.9783 No test antiviral treatment: 9.9797–9.9849	Test + antiviral treatment dominated by no test antiviral treatment	Only vaccination status, the probability that the patient has influenza, the patient's risk of hospitalisation, and the efficacy of oseltamivir in preventing hospitalisations affected the choice of treatment. The model is insensitive to all other parameters.	Rapid testing followed by oseltamivir treatment, although less effective than empirical treatment, is cost-effective for low-risk patients and vaccinated patients, especially during the peri-influenza season. Vaccinated low-risk patients should be tested before receiving a NAI.

continued

TABLE 9 Data extraction for cost–utility studies – results (*continued*)

Author, year	Index testing strategy	Target condition	Key costs results	Key effectiveness results	ICER results	Headline results of uncertainty analyses	Key conclusions
Smith, 2002[65]	Rapid test; followed by different antiviral therapies	Influenza A and B	Costs per patient Test + antiviral treatment: $115–$134.30 No test, no antiviral treatment: $92.50 No test, antiviral treatment: $97.50–$137.10	QALDs lost per patient: Test + antiviral treatment 1.59–1.75 No test, no antiviral treatment: 2.11 No test, antiviral treatment: 1.47–1.69	Test + antiviral treatment dominated by no test antiviral treatment	Results for treatment with NAI were sensitive to the probability of influenza, influenza A likelihood, influenza utility, untreated influenza duration, rimantadine cost, therapy effect on utility, treated influenza duration, medication side-effect utility, probability of complications and side-effect costs. At a WTP threshold of $100 per QALD, then amantadine or no treatment was favoured. At a WTP threshold of $200–$300, NAIs are favoured in younger patients and rimantadine in older patients. At a WTP of $500, NAIs are favoured.	Analysis did not favour rapid testing unless the influenza probability is < 30%. The rapid test was more costly and less effective than treatment without testing. In unvaccinated patients, antiviral therapy without testing is economically reasonable compared with rapid testing or no intervention.
You, 2017[66]	Rapid molecular PCR to inform antiviral therapy	Influenza A and B	Costs per patient: Test: $116.60 No test: $83.40	QALYs lost per patient: Test: 0.00139 No test: 0.00251	$29,582	Rapid PCR group remained QALY-saving at a higher cost throughout all sensitivity analyses. Cost-effectiveness of rapid PCR is affected most by hospitalisation rate in elderly without oseltamivir therapy; OR of hospitalisation with oseltamivir therapy; prevalence of influenza and the age and mortality rate of patients admitted to non-ICU ward. ICERs were above the WTP threshold in 39.5% of simulations.	Using rapid PCR for the detection of influenza in elderly patients with influenza-like illness at outpatient clinics appears to be a cost-effective option to reduce hospitalisation and mortality rate. This strategy also saves QALYs from the healthcare provider perspective in Hong Kong. The prevalence of influenza should be higher than 14.3% for the rapid PCR to be effective.

TABLE 9 Data extraction for cost–utility studies – results (*continued*)

Author, year	Index testing strategy	Target condition	Key costs results	Key effectiveness results	ICER results	Headline results of uncertainty analyses	Key conclusions
Other							
Chew, 2022[53]	Pulse oximetry-aided ARI management	ARI	Cost savings per year with pulse oximetry were $52,944	DALYs averted per year with pulse oximetry were 0.9	*N*/A	Cost savings robust across all sensitivity analyses. Where pulse oximetry had only a slight increase in sensitivity and specificity over clinical judgement there were still cost savings.	Supplementing standard care with pulse oximetry is a cost-effective way of saving lives in Northern Thailand and reducing antibiotic overuse. The WHO guideline could be extended to cover all ages.
Michaelidis, 2014[59]	POC procalcitonin-guided antibiotic therapy	ARTIs	Costs per patient: Patients judged to require antibiotics: Test $51 No test $29 Prior to any antibiotic decision: Test: $49 No test: $15	QALYs per patient: Patients judged to require antibiotics: Test: 0.00746 No test: 0.00765 Prior to any antibiotic decision: Test: 0.00743 No test: 0.00749	Patients judged to require antibiotics: $118,828 Prior to any antibiotic decision: $575,249	None conducted for cost–utility analyses.	Testing is unlikely to be preferred over usual care based on cost alone. However, it is likely to be cost-effective when the costs of antibiotic resistance are considered and if the test is only used in those judged to require antibiotics as testing becomes more favoured as antibiotic costs increase, test costs decrease and physician adherence increases.
Nicholson, 2014[61]	Rapid near-patient diagnostic tests (Quidel for influenza, and BinaxNOW for the pneumococcal antigen)	Influenza A and B, RSV and pneumococcal infection	Cost per patient (28-day time horizon): PCR: £1978 Traditional: £2327 POCT: £2159	QALYs per patient (28-day time horizon) PCR: 0.007779 Traditional: 0.007588 POCT: 0.008035	Traditional laboratory culture was dominated. POCT compared to PCR: £734,717	Price reduction of the tests has a relatively small impact on results. Ranking of the strategies remains the same as the base case. Probabilities (of error) of being cost-effective at WTP thresholds of £20,000 and £30,000 respectively are 0.183 and 0.186 for the POCT; 0.783 and 0.781 for PCR and 0.034 and 0.033 for the traditional strategy.	There is relatively little difference in the cost distributions or QALYs gained between the three diagnostic strategies. Using traditional laboratory culture is the most expensive and is also associated with the lowest gain in terms of QALYs. 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 WTP.

CEAC, cost-effectiveness acceptability curve; LRTI, lower respiratory tract infection; NAAT, nucleic acid amplification tests; NAI, neuraminidase inhibitors; NMB, net monetary benefit; QALDs, quality-adjusted life days; QALEs, quality-adjusted life expectancy.
a See Francis *et al.* (2020) who also focused on POC CRP but specifically for COPD exacerbation.
b Batch PCR and treat everyone until results become available.
c Batch PCR and wait until results are available before making treatment decisions.

TABLE 10 Critical appraisal of included cost–utility studies

Author, Year	1. Was a well-defined question posed in answerable form?	2. Was a comprehensive description of the competing alternatives given?	3. Was the effectiveness of the programmes or services established?	4. Were all the important and relevant costs and consequences for each alternative identified?	5. Were costs and consequences measured accurately in appropriate physical units?	6. Were the costs and consequences valued credibly?	7. Were costs and consequences adjusted for differential timings?	8. Was an incremental analysis of costs and consequences of alternatives performed?	9. Was uncertainty in the estimates of costs and consequences adequately characterised?	10. Did the presentation and discussion of study results include all issues of concern to users?
Bilir, 2021[52]	✔	X	?	Short? Long X AMR X	✔	?	N/A	✔	✔	✔
Chew, 2022[53]	✔	✔	X	Short X Long X AMR ✔	✔	?	N/A	✔	X	✔
Francis, 2020[31]	✔	✔	✔	Short ✔ Long X AMR X	✔	✔	N/A	✔	✔	✔
Fraser, 2020[54]	✔	✔	✔	Short ✔ Long X AMR X	✔	✔	N/A	✔	✔	✔
Holmes, 2018[55]	✔	✔	✔	Short ✔ Long X AMR ✔	✔	✔	N/A	✔	✔	✔
Hunter, 2015[56]	✔	✔	✔	Short ✔ Long ✔ AMR X	✔	✔	✔	✔	✔	✔
Little, 2014[57]	✔	✔	X	Short ✔ Long X AMR X	✔	✔	N/A	✔	X	✔
Mac, 2020[58]	✔	✔	?	Short? Long? AMR X	X	?	✔	✔	✔	✔
Michaelidis, 2013[59]	✔	✔	X	Short X Long X AMR X	?	?	N/A	✔	X	✔
Neuner, 2003[60]	✔	✔	✔	Short ✔ Long X AMR X	✔	✔	N/A	✔	✔	✔
Nicholson, 2014[61]	✔	✔	?	Short ✔ Long X AMR X	?	?	N/A	✔	X	✔

TABLE 10 Critical appraisal of included cost–utility studies (*continued*)

Author, Year	1. Was a well-defined question posed in answerable form?	2. Was a comprehensive description of the competing alternatives given?	3. Was the effectiveness of the programmes or services established?	4. Were all the important and relevant costs and consequences for each alternative identified?	5. Were costs and consequences measured accurately in appropriate physical units?	6. Were the costs and consequences valued credibly?	7. Were costs and consequences adjusted for differential timings?	8. Was an incremental analysis of costs and consequences of alternatives performed?	9. Was uncertainty in the estimates of costs and consequences adequately characterised?	10. Did the presentation and discussion of study results include all issues of concern to users?
Oppong, 2013[62]	?	?	X	Short Long X AMR X	X	?	N/A	X	✔	X
Rothberg, 2003[64]	?	?	X	Short Long X AMR X	X	?	?	✔	✔	X
Rothberg, 2003[63]	?	?	X	Short Long X AMR X	✔	✔	N/A	✔	✔	✔
Smith, 2002[65]	?	?	?	Short Long X AMR	X	X	N/A	✔	✔	✔
You, 2017[66]	✔	?	X	Short? Long? AMR X	✔	?	✔	✔	✔	✔

N/A, not applicable.

The short time horizon of many of the studies was consistently highlighted as a limitation, specifically the lack of robust data to inform longer-term projections. Despite concluding that POCTs for CRP are cost-effective, three of the four economic evaluations focused on this test were limited to capturing short-term costs and consequences.[31,55,62] Hunter *et al*. (2015) however did base their analysis on longer-term (3 years) data from a RCT and also found it to be cost-effective.[56] It should be noted for the four studies evaluating the cost-effectiveness of POCTs for CRP,[31,55,56,62] the incremental benefit in terms of QALYs was very marginal and based on highly uncertain evidence.

A key motivation for rapid testing is to reduce future AMR associated with unnecessary antibiotic prescribing to limit, yet there is no standardised, recommended methodology for estimating the costs and consequences associated with AMR in an economic evaluation. Logically, this is an oversight of a key potential benefit, both in terms of reducing long-term costs and improving patient outcomes (or avoiding patient harm). Two studies did make some attempts to incorporate an estimated cost associated with AMR into their sensitivity analyses, but the validity of their calculations was unclear.[53,55]

Another key potential benefit or harm of rapid, POC testing is the potential effect it has on patient behaviour over time. Patients may be discouraged from attending their GP in future, having received a POCT for CRP if they feel they are less likely to be prescribed antibiotics. Conversely, the ability to get a 'quick answer' may actually result in more patients with ARI symptoms presenting to their GP over time. Cals *et al.* (2013), a pragmatic cluster-randomised trial, is the only trial in the UK with long enough follow-up and the appropriate study design to assess this longer-term implication.[34] Although the mean number of episodes of RTIs during follow-up was lower for the POCT for the CRP arm, the difference was not statistically significant. Hunter *et al.* (2015) was the only study to incorporate this data into their evaluation, noting that any harms associated with reduced attendance will not have been captured in their analysis.[56]

Many of the other studies lacked robust underpinning evidence on effectiveness. Adjustment for differential timing was rarely an applicable problem for these studies due to the short-term nature (1 year or less) of most evaluations.

The critical appraisal checklist shown in this table was adapted from Drummond *et al.* (2015).[22]

Chapter 4 Discussion/interpretation

Statement of principal findings

Clinical effectiveness review

We identified a large number of systematic reviews that were then excluded, mainly due to lack of synthesised evidence in adults relevant to the present review. One systematic review[16] was used only as a source of data for relevant primary studies because we were unable to replicate their synthesised evidence for the effect of CRP testing in the adult subgroup for some of the cluster RCTs. We also searched for additional relevant primary publications.

Overall, this rapid review found limited evidence on the use of POCTs at initial contact with the health system for people over 16 years with suspected ARI. The studies were conducted mainly in primary care, with two studies involving outpatient clinics and one study conducted in nursing homes. No studies were conducted in an ED. The majority of evidence was for CRP POCT with limited evidence on procalcitonin, GAS and influenza POCTs. No evidence was identified on other POCTs, such as full blood count or blood gases. The studies included in the clinical effectiveness review were all judged to have a high risk of bias overall, so we cannot be confident in their findings.

In people presenting with symptoms of ARI, CRP POCTs may reduce the number of antibiotic prescriptions given at index consultation by 25%, with similar reductions within 14 days or 28 days' follow-up. However, people who had CRP POCT were 1.61 times as likely to need further consultations. There was considerable heterogeneity across the included studies and the effect estimates should be viewed with caution. The effects of CRP POCT on hospital admissions, resolution of symptoms, mortality or HRQoL were also uncertain.

No evidence for any POCT was identified on escalation of care to a virtual ward, ED visit or unplanned hospital admission, or on hospital length of stay or follow-up consultation/ongoing monitoring.

Our findings regarding the effect of CRP POCT on antibiotic use align with those in other systematic reviews. Many of the studies included in previous systematic reviews overlap with those in our review; however, our review reports outcomes in adults only. Systematic reviews in adults only[26] or presenting subgroup analyses of adults[16,24,25] also found CRP POCT reduced the number of antibiotic prescriptions at index consultation. However, our finding that antibiotic prescriptions at 14- or 28-day follow-up continued to be lower in the CRP POCT groups compared with usual care aligns with findings from two of the reivews[16,26] but not others.[24,25] This may be due to differences in the inclusion of children[16,24,25] or other differences in eligibility criteria or analytical approaches. Other interventions to reduce antibiotic use, such as clinician communication skills training, were beyond the scope of our review.

For other outcomes such as recovery rates, resolution of symptoms and mortality, our findings for CRP POCT also align with these previous reviews.

Cohen (2020)[69] assessed the safety and efficacy of GAS RADT for sore throat in primary care settings. Studies in adults and/or children were included, but data were too scarce to permit subgroup analysis in adults only. The review found RADTs probably reduce antibiotic prescriptions rates by 25%, which is in line with our findings. Cohen (2020)[69] also found re-consultation was increased after RADT, but this was not reported by the studies included in our review.

Cost-effectiveness review

We identified two relevant systematic reviews, but the focus and the scope of these reviews differed from our review question and therefore they were used solely as a source of data for relevant primary studies. We conducted a separate search for cost–utility studies and identified 16 studies which met our pre-specified eligibility criteria. We used the first section of the NICE appraisal checklist for economic evaluations to assess the applicability of these studies to our review question;[23] six studies were judged to be directly applicable[31,54–56,61,62] and two further studies were judged to be partially applicable.[57,59]

Four of the directly applicable cost–utility studies evaluated the cost-effectiveness of POCTs for CRP.[31,55,56,62] All of these studies concluded that POCTs for CRP are likely to be cost-effective, although they were generally limited in that they only captured short-term costs and health consequences. Across all four evaluations, an overall incremental benefit in terms of QALYs associated with POCT for CRP compared to usual care was estimated, although this difference was very small and highly uncertain. In three evaluations, POCTs for CRP were associated with an overall increase in costs, largely driven by the additional cost of the test itself.[31,55,62] Hunter (2015) conducted a cost–utility analysis over a longer time horizon (3 years) and estimated that POCTs for CRP were likely to be cost-saving overall. This reduction in costs was driven by a reduced risk of RTI for which patients consulted their doctor per person per year, a finding observed in a cluster-randomised trial, although this difference was not statistically significant.[34]

There was very limited evidence available for POCTs for other biomarkers. Fraser (2020) conducted a cost–utility analysis of 14 different POCTs for GAS based on an extensive systematic review of the evidence, concluding that none of the POCTs were cost-effective.[54]

Nicholson (2014) evaluated a strategy which involved the use of two POCTs (Quidel for influenza, and BinaxNOW for the pneumococcal antigen) in a RCT and found that it was not cost-effective compared to laboratory-based PCR.[61]

The remaining studies were scored as being not applicable to our review question.[52,53,58,60,63–66] These studies were all focused on non-UK settings.

Strengths of the review

Methods of the review were specified a priori in the published review protocol.[70] Extensive searches of electronic databases for both systematic reviews, RCTs and cost–utility studies were conducted, and reference lists of all relevant systematic reviews were examined.

Limitations of the review

Clinical effectiveness review

Rapid evidence synthesis methods were employed for this review. The list of sources searched was not exhaustive. Further limitations may include the exclusion of non-English language publications and difficulty in searching for evidence in this topic area due to the lack of standardisation in search terms to cover the interventions of interest. We mitigated this by using a reasonable variety of concepts, terms and search approaches. It is therefore possible that relevant evidence may have been missed. The screening processes may also have introduced errors in the selection of evidence, as one reviewer screened all studies and the initial 20% were screened by two reviewers. However, we mitigated this by achieving over 90% agreement before proceeding with single-reviewer screening. The limited timescale meant we were unable to contact the authors of studies for clarification or additional data.

It was intended that good-quality, applicable systematic reviews would be utilised in this review for all interventions, and where there were evidence gaps (e.g. missing outcomes) in the systematic reviews, searches would be conducted to identify relevant RCTs. One systematic review[16] was initially considered a source of synthesised evidence and data extractions were based on this review. However, as the analyses in the systematic review could not be replicated, we changed to using this as a source of data for the relevant primary studies and our data extractions were updated using the primary publications of the studies. Judgements for study-level risk of bias of relevant studies were obtained from the systematic review and not checked by our reviewers.

Cost-effectiveness review

Rapid evidence synthesis methods were employed for this review. The list of sources searched was not exhaustive. A further limitation may include the exclusion of non-English language publications. It is therefore possible that relevant evidence may have been missed.

Many of the cost–utility studies included in the review were decision-analytic models and therefore had many parameters feeding into the analyses. Although a standardised risk-of-bias tool was used to critically appraise all the cost–utility studies included in our review, it was not feasible to appraise the evidence that underpinned each model parameter. This may have provided more insight into the validity of the overall results, model assumptions and the extent to which the results of the uncertainty analyses undertaken reflect the uncertainties and potential biases in the underlying evidence.

Our review focused on cost-effectiveness analyses which included a cost–utility analysis. While this aligns with NICE's preferred form of economic evaluation,[71] studies which have only evaluated cost-effectiveness using a different measure of clinical effectiveness (e.g. cost per antibiotic prescription avoided) will not be included in this review. This approach overcomes one of the limitations identified by the van der Pol (2021) review,[20] where the majority of studies were found to have used non-generalisable clinical outcome measures, but it also sets the evidence bar higher as comparative evidence on the impact of rapid testing on QALYs is required which can be challenging to obtain or estimate in the context of diagnostic testing.

Limitations of the evidence base

Clinical effectiveness review

It was not possible to answer the review questions for many of the interventions stated in the review protocol (e.g. full blood count, blood gases) as no evidence was identified. Similarly, it was not possible to answer the review questions for many of the pre-specified outcomes for included interventions. Outcomes relating to escalation of care to the virtual ward, ED visits and unplanned hospital admission, and other outcomes including hospital length of stay and follow-up consultation/ongoing monitoring were not reported. The most commonly reported outcome in the studies related to antibiotic practices; however, definitions varied with a number of studies reporting antibiotic prescriptions and other studies reporting antibiotic use. While these have been combined in our review, they may not be fully interchangeable as we have no information about whether all prescriptions were fulfilled. Only a single study assessed HRQoL, and none of the studies included in our reviews evaluated the impact of POCTs on subsequent infection transmissions or estimated other cases prevented.

The main limitations of the included studies were poor methodological quality and reporting. Issues may arise when using an individual RCT design to assess the use of POCTs versus usual care in these settings. Allocating POCTs versus usual care within the same primary care setting at the patient level may introduce contamination with the risk of underestimating the outcomes. Andreeva (2014),[29] for example, used a cluster design to ensure consecutive recruitment of patients and to avoid potential contamination from the GPs' experience gained through the use of the test affecting those receiving usual care. However, disadvantages of cluster RCTs include selection bias due to the inclusion of participants post randomisation and the need for large sample sizes to ensure adequate power. Some of the cluster RCTs included in our review did not achieve the anticipated sample size. Furthermore, in some studies, it was unclear how intracluster correlation coefficients were calculated or whether they were estimated reliably.

There was considerable heterogeneity across the studies, which may be partly explained by differences in inclusion criteria and design (individual RCT or cluster RCT), and differences in CRP algorithm thresholds used to guide antibiotic decisions. For example, one study used thresholds at < 11 and > 50 mg/l, while other studies used values at < 20 mg/l and > 100 mg. The settings (e.g. primary care practices, outpatient clinics and nursing homes) varied between studies. There are also issues around generalisability of the findings of our review to the UK population due to different healthcare systems from a variety of countries. There was very limited evidence in adults aged above 80 years or those with severe comorbidities because of either exclusion from the included studies or under-representation.

The certainty of the evidence for CRP POCTs, procalcitonin POCTs and RADTs for influenza was very low according to our GRADE assessment. This was mainly due to very serious limitations in the quality of the evidence because of a lack of blinding, unclear allocation concealment, and sometimes incomplete reporting of outcome data. The evidence on CRP POCTs was also downgraded due to serious indirectness and due to serious inconsistency. GRADE assessment was not performed for GAS tests as data were not reported for the key outcomes.

Cost-effectiveness review

There was limited or no evidence of cost-effectiveness identified for most of the rapid tests identified in our inclusion criteria.

The main limitation of the cost–utility studies included in this review was the time horizon of the analyses; the vast majority of the studies only estimated short-term costs and health consequences. One of the main motivations for POCTs for suspected ARI is to reduce the number of unnecessary antibiotic prescriptions, given the longer-term repercussions on AMR. There is currently no guidance on how to incorporate the costs and health consequences of AMR into economic evaluations, although some studies did attempt to incorporate estimates of the societal cost of AMR avoided by reducing antibiotic prescribing.[53,55] Despite evidence of a significant reduction in antibiotic prescribing, there remains a cost imbalance when trading off the short-term additional costs associated with testing with the short-term reduced cost of treatment, given the generally low cost of antibiotics. The majority of studies included in this review therefore concluded that using rapid tests was more costly overall compared to current practice. Interestingly, there was one study which found POCTs for CRP cost saving overall and this analysis had a longer time horizon of 3 years.[56] This reduction in costs was based on an observed reduction in the rate of individuals presenting with RTIs during follow-up in a cluster-randomised trial, but this difference was not statistically significant and therefore would require further validation.

Where cost–utility studies concluded that POCTs for CRP were cost-effective, the incremental benefits in terms of QALYs were very small and based on highly uncertain evidence. While clinical effectiveness studies in this clinical context are unlikely to be powered to show a statistically significant difference in HRQoL, the differences incorporated in these cost–utility studies were so small and with such wide CIs, that they could be more reasonably interpreted as providing no evidence of any short-term harms in terms of HRQoL associated with POCTs for CRP. Again, however, by only focusing on the short-term health impacts and failing to incorporate the potential health benefits of reducing antibiotic treatment, there is a risk of underestimating the cost-effectiveness of rapid tests which provide health benefits over a longer time horizon.

Chapter 5 Patient and public involvement

We recognised the importance of patient and public involvement (PPI) in ensuring that the evidence synthesis addressed issues relevant to patients and service users. However, as the rapid evidence synthesis needed to be completed within a very tight schedule of 3 months to help inform the development of clinical guidelines by NICE,[72] it was agreed between NICE, the NIHR and the Evidence Synthesis Groups involved in producing relevant reviews that the timelines were too short to allow meaningful PPI activities to take place and to directly inform the review process. Nevertheless, NICE has standard procedures in place to facilitate PPI during its guideline production, which were also applicable here.

Chapter 6 Equality, diversity and inclusion

Acute respiratory infection affects the whole population, although its health impact might be greater in people with certain characteristics, such as people of older ages, people with comorbidities and women who are pregnant or in the post-partum period. We set out to evaluate evidence related to whether POCTs are effective and cost-effective among patients with these characteristics and whether there is evidence of differential effectiveness and cost-effectiveness between patients with and without these characteristics. However, few studies reported relevant evidence. Our analysis using limited evidence from two studies[30,38] showed that the effect of CRP POCT among patients with COPD was similar to those observed in other patient populations.

Chapter 7 Impact and Learning

This rapid evidence synthesis was undertaken within a tight timeline in order to provide timely support for the development of clinical guidelines by NICE. Although a large number of POCTs were potentially eligible, we found only limited RCT evidence of generally low certainty for a relatively small number of such tests. The findings indicate that while POCTs may hold promise in improving patient care, more effort is still needed to generate evidence on clinical and cost-effectiveness that can directly inform clinical practice and service delivery.

Chapter 8 Implications for decision-makers

The use of CRP POCTs for adults presenting with suspected ARI at initial contact with the health system may reduce antibiotic prescription at initial consultation and in the short-term period following the consultation. However, a firm conclusion on their clinical and cost-effectiveness and hence on their adoption in clinical practice cannot be drawn based on currently available evidence due to the many uncertainties identified. These included:

- Whether the use of CRP POCT increases re-consultation for the current episode of suspected ARI and affects care-seeking behaviours for future episodes.
- Whether the use of CRP POCT impacts on referral to virtual wards and admission to hospital.
- The potential benefits of reduced antibiotic prescribing on AMR.

National Institute for Health and Care Excellence Clinical Guidelines CG191 suggested considering CRP POCT 'if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed' for people presenting with symptoms of lower respiratory traction infection in primary care.[68] Although more evidence was found in this rapid evidence synthesis compared to that was reviewed in CG191, there does not appear to be strong justification for changing the recommendation based on currently available evidence.

The evidence on the use of other POCTs is very limited. Technologies related to POCTs are undergoing rapid development. Decision-makers may wish to consider acquisition and maintenance costs (where relevant) for the new technologies and their impact on clinical processes and patient flow. Some platforms allow POCTs related to different disease conditions. They may require evaluations with a broader scope than the current evaluation which only focused on suspected ARI.

Chapter 9 Research recommendations

The limited evidence precludes conclusions on the effects of POCTs to inform referral and treatment decisions in people over 16 years with suspected ARI at initial contact with the health system. Further research is needed to evaluate potential biomarkers such as POCTs used in health settings to guide the treatment pathway in people with symptoms of ARI. Priority research recommendations are:

Adequately powered, good-quality RCTs are needed to assess the clinical and cost-effectiveness of rapid, near-patient POCTs (used alone or in combination, e.g. with full blood count) to inform triage and antibiotic decisions for adults presenting with suspected ARI at initial contact with the health system, both in primary care and in ED settings. Research is needed on the impact of reduced antibiotic prescription on the need for re-consultation, referral to virtual wards and admission to hospital for the current infection episode, and the impact of POCTs on care-seeking behaviours for future infection episodes.

Methods for exploring the implications of reduced antibiotic prescribing on long-term costs and health consequences of AMR in economic evaluations are needed.

Algorithms and thresholds for CRP POCTs to guide antibiotic prescribing decisions should be relevant for use in the UK. Change in actual antibiotic use, as well as antibiotic prescribing only, may be useful.

Limited evidence was identified in people with chronic comorbidities (e.g. COPD) and no evidence was identified to enable comparisons between different age groups (i.e. people aged 65 years and under, 66–80 years, and over 80 years) or to assess outcomes in pregnancy and postpartum (up to 28 days). Therefore, research is needed in specific groups of people at greater risk of harm from ARIs.

Chapter 10 Conclusions

The evidence suggests the use of CRP POCTs reduce antibiotic prescribing at first presentation to the health system but may increase the need for further consultations. However, the certainty of the evidence was very low. The effects on mortality and hospital admission were highly uncertain due to sparse data. The effects of procalcitonin POCTs and influenza POCTs were very uncertain as evidence was available from only one study at high risk of bias on each. A large reduction in initial antibiotic prescriptions was found with GAS POCT, but evidence on other key outcomes was lacking. No evidence was found for other eligible POCTs.

C-reactive protein POCT may potentially be cost-effective but existing estimates were based on very small and uncertain gains in QALYs and only accounted for short-term costs and consequences. There was very limited or an absence of evidence for other POCTs.

Further studies are needed to evaluate the effects of POCTs used alone or in combination to guide the treatment pathway for patients with suspected ARI.

Additional information

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Data-sharing statement

All data collected during the rapid synthesis concerning characteristics of included studies, risk-of-bias assessment and meta-analyses have been presented in the main text, appendices and supplementary material. Requests for additional information should be addressed to the corresponding author.

Ethics statement

This rapid evidence synthesis evaluated evidence from publicly accessible literature. No ethical approval was required as the project did not involve primary data collection.

Information governance statement

This was an evidence synthesis project which did not involve collection and handling of personal information.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/KHGP7129.

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Appendix 1 Literature search strategies

Searches for systematic reviews

MEDLINE (Ovid)

Searched: 4 May 2023

Ovid MEDLINE(R) ALL <1946–3 May 2023>

1 Respiratory Tract Infections/42594
2 exp Bronchitis/or Common Cold/or Infectious Mononucleosis/ or Influenza, Human/ or Laryngitis/ or exp Pharyngitis/ or exp Pneumonia/ or Severe Acute Respiratory Syndrome/433538
3 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (infect* or coinfect* or inflamm*)).tw,kf. 122465
4 ((chest or lung? or lobar or pleura?) adj3 (absces* or infect* or coinfect* or inflamm*)).tw,kf.44681
5 (bronchit* or bronchopneumon* or common cold* or glandular fever or infectious mononucleosis or flu or influenza or laryngit* or laryngotracheobronchit* or laryngo tracheo bronchit* or laryngo tracheobronchit* or laryngotracheit* or nasopharyngit* or parainfluenza or pharyngit* or pneumoni* or pleuropneumoni* or rhinopharyngit* or severe acute respiratory syndrome or SARS or sore throat* or throat infection* or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit*).tw,kf.520988
6 ((acute* or exacerbat* or flare*) adj3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).mp. 10264
7 ((acute* or subacute* or exacerbat* or prolonged) adj3 cough*).mp. 1542
8 (RTI or LRTI or URTI or ARTI or AURI or ALRI).tw,kf. 6290
9 exp Respiratory System/ and (exp Viruses/ or exp Virus Diseases/)34955
10 exp pneumonia, viral/ or *orthomyxoviridae infections/ or influenza, human/288725
11 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (nonbacter* or viral* or virus* or adenovir*)).tw,kf. 35760
12 (rhinovir* or rhino* vir* or coryzavir* or coryza* vir* or influenzavir* or influenza* vir* or (H1N1 or H3N2) or parainfluenzavir* or parainfluenza* vir* or pneumovir* or pneumo* vir* or human metapneumovir* or human metapneumovir* or HMPV or respiratory syncytial vir*).mp. or RSV.tw,kf. 138771
13 exp Respiratory System/ and (exp Bacteria/ or exp Bacterial Infections/)48045
14 pneumonia, bacterial/ or chlamydial pneumonia/ or pneumonia, mycoplasma/ or pneumonia, pneumococcal/ or pneumonia, staphylococcal/22808
15 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir* or pathogen*)).tw,kf. 22594
16 (strep* pneumon* or diplococ* pneumon* or pneumococ* or staph* pneumon* or chlamyd* pneumon* or myco* pneumon* or influenza bacil* or bacteri* influenza* or h?emophil* influenza*).mp. 80712
17 ((strep* adj3 (throat* or pharyn* or tonsil*)) or (strep* and (airway* or pulmonary or brochopulmonar* or brocho-pulmonar* or respiratory*))).mp.22142
18 (GABHS or ("group a" adj3 strep*)).tw,kf. 10718
19 strep* pyogen*.mp. 18532
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection]957868
21 Point-of-Care Systems/16336
22 (POCT or POCTs or (((point adj2 care) or poc) adj3 (analys* or antigen? or assay* or device? or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or platform? or predict* or rapid or routine* or screen* or system* or technique* or test* or (cassette? or dipstick? or film* or stick or strip or fluorescent antibod*))))).tw,kf. 21606

23 (point adj2 care).ti,kf. 14978
24 (((near adj2 patient) or nearpatient or rapid* or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 (analys* or antigen? or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test* or fluorescent antibod*)).tw,kf. 204252
25 (((near adj2 patient) or nearpatient or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 rapid*).tw,kf. 635
26 Rapid Diagnostic Tests/35
27 (rapid* adj3 (detect* or diagnos* or screen*)).tw,kf. 71578
28 (time-to-result? or ((quick* or rapid* or short* or time*) adj3 (turnaround or turn-around))).tw,kf. 8081
29 (antigen? adj3 (analys* or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf. 90702
30 (RADT or RADTs or RDT or RDTs).tw,kf. 3308
31 (rapid molecular or multiplex*).mp. 72823
32 lab-on-a-chip.tw,kf. 3494
33 ((lateral flow adj (assay* or immunoassay* or test*)) or LFA or LFIA).tw,kf. 9954
34 (immunochromatograph* or immuno-chromatograph* or immuno-chromato-graph* or direct immunofluorescence or direct immuno-fluorescence or enzym* immunoassay* or enzym* immuno-assay* or fluorescence immunoassay* or fluorescence immuno-assay* or optical immunoassay* or optical immuno-assay*).mp. or (ICA or EIA or FIA or OIA).tw,kf. 60364
35 ((chemiluminescen* or chemi-luminescen*) adj (immunoassay* or immuno-assay* or assay*)).mp. 4693
36 (((mobile or portable or handheld or hand-held) adj3 (analy#er? or device? or meters or metres)) and (blood? or plasma or saliva or sputum or spit or mucus or urine or urea or urinalys* or fluids or gas or gases)).mp. 2602
37 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 [Rapid Tests]452888
38 20 and 37 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection AND Rapid Tests]33006
39 (systematic review or meta-analysis).pt. 309240
40 meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)" / or "systematic review (topic)" / or exp technology assessment, biomedical/ or network meta-analysis/347218
41 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf. 313541
42 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf. 15381
43 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf. 38276
44 (data synthes* or data extraction* or data abstraction*).ti,ab,kf. 39706
45 (handsearch* or hand search*).ti,ab,kf. 11062
46 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf. 35169
47 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf. 11998
48 (meta regression* or metaregression*).ti,ab,kf. 14264
49 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw. 459155
50 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.335245
51 (cochrane or (health adj2 technology assessment) or evidence report).jw. 21350
52 (comparative adj3 (efficacy or effectiveness)).ti,ab,kf. 17353
53 (outcomes research or relative effectiveness).ti,ab,kf. 11149
54 ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf. 4285
55 (multi* adj3 treatment adj3 comparison*).ti,ab,kf. 291
56 (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf. 178
57 umbrella review*.ti,ab,kf. 1411
58 (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf. 14
59 (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf. 18
60 (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf. 12

61 or/39-60 [CADTH SR filter]672225
62 38 and 61 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection AND Rapid Tests AND CADTH SR filter]901
63 (metaanalys* or meta analys* or NMA* or MAIC* or indirect comparison* or mixed treatment comparison*).mp. 303671
64 (systematic* adj3 (review* or overview* or search or literature)).mp. 351213
65 63 or 64 [in-house SR filter]485892
66 38 and 65 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection AND Rapid Tests AND in-house SR filter]642
67 62 or 66 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection AND Rapid Tests AND either SR filter]906
68 limit 67 to english language 875
69 limit 68 to (comment or editorial or letter or news)19
70 68 not 69856

Total after seven duplicates identified in EndNote removed: 849

Epistemonikos

Searched: 11 May 2023

title:((((airway* OR bronchopulmonar* OR broncho-pulmonar* OR tracheobronch* OR tracheo-bronch* OR pulmonary OR respiratory OR chest OR lung* OR lobar OR pleura*) AND (infect* OR coinfect* OR inflamm* OR nonbacter* OR viral* OR virus* OR adenovir* OR bacter* OR bacilli* OR bacili* OR corynebac* OR mycobac* OR nonvir* OR pathogen*)) OR (bronchit* OR bronchopneumon* OR "common cold" OR "glandular fever" OR "infectious mononucleosis" OR flu OR influenza OR laryngit* OR laryngotracheobronchit* OR "laryngo tracheo bronchitis" OR "laryngo tracheobronchitis" OR laryngotracheit* OR nasopharyngit* OR parainfluenza OR pharyngit* OR pneumoni* OR pleuropneumoni* OR rhinopharyngit* OR "severe acute respiratory syndrome" OR SARS OR "sore throat" OR "throat infection" OR supraglottit* OR supraglotit* OR tonsillit* OR tonsilit* OR tracheit*) OR ((acute* OR exacerbat* OR flare*) AND (copd OR coad OR "chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "chronic obstructive lung disease")) OR ("acute cough" OR "subacute cough" OR "exacerbated cough" OR "prolonged cough" OR "acute coughing" OR "subacute coughing" OR "exacerbated coughing" OR "prolonged coughing") OR (RTI OR LRTI OR URTI OR ARTI OR AURI OR ALRI) OR (rhinovir* OR "rhino virus" OR coryzavir* OR "coryza virus" OR influenzavir* OR "influenza virus" OR H1N1 OR H3N2 OR parainfluenzavir* OR "parainfluenza virus" OR pneumovir* OR "pneumo virus" OR "human metapneumovirus" OR "human meta-pneumovirus" OR HMPV OR "respiratory syncytial virus" OR RSV) OR (((strep* OR diplococ* OR pneumococ* OR staph* OR chlamyd* OR myco*) AND pneumon*) OR ((bacil* OR bacteri* OR haemophil* OR hemophil*) AND influenza*)) OR ((strep* AND (throat* OR pharyn* OR tonsil* OR airway* OR pulmonary OR brochopulmonar* OR brocho-pulmonar* OR respiratory* OR pyogen*))) OR (GABHS OR ("group a" AND strep*)))) AND (title:((POCT OR POCTs OR (("point of care" OR "near patient" OR near-patient OR nearpatient OR bedside* OR bed-side* OR extra-laboratory OR extralaboratory OR time-to-result* OR quick* OR rapid* OR short* OR antigen*) AND (analys* OR assay* OR immunoassay* OR classif* OR detect* OR determin* OR diagnos* OR differenti* OR identif* OR method* OR kit OR kits OR panel* OR predict* OR routine* OR screen* OR system* OR technique* OR test*)) OR (RADT OR RADTs OR RDT OR RDTs OR "rapid molecular" OR multiplex* OR "lab-on-a-chip") OR (((mobile OR portable OR handheld OR hand-held) AND (analyser* OR analyzer* OR device* OR meters OR metres)) AND (blood* OR plasma OR saliva OR sputum OR spit OR mucus OR urine OR urea OR urinalys* OR fluids OR gas OR gases)))) OR abstract:((POCT OR POCTs OR (("point of care" OR "near patient" OR near-patient OR nearpatient OR bedside* OR bed-side* OR extra-laboratory OR extralaboratory OR time-to-result* OR quick* OR rapid* OR short* OR antigen*) AND (analys* OR assay* OR immunoassay* OR classif* OR detect* OR determin* OR diagnos* OR differenti* OR identif* OR method* OR kit OR kits OR panel* OR predict* OR routine* OR screen* OR system* OR technique* OR test*)) OR (RADT OR RADTs OR RDT OR RDTs OR "rapid molecular" OR multiplex* OR "lab-on-a-chip") OR (((mobile OR portable OR handheld OR hand-held) AND (analyser* OR analyzer* OR device* OR meters OR metres)) AND (blood* OR plasma OR saliva OR sputum OR spit OR mucus OR urine OR urea OR urinalys* OR fluids OR gas OR gases)))))

Limited to:

Publication Type: Systematic Reviews

Total: 617

Searches for RCTs

CENTRAL (Wiley)

Search Name: Acute Respiratory Infections RCTs

Date Run: 26 May 2023 22:22:45

Comment: 26 May 2023

ID Search Hits

#1 [mh ^"Respiratory Tract Infections"]2777
#2 [mh Bronchitis] OR [mh ^"Common Cold"] OR [mh ^"Infectious Mononucleosis"] OR [mh ^"Influenza, Human"] OR [mh ^Laryngitis] OR [mh Pharyngitis] OR [mh Pneumonia] OR [mh ^"Severe Acute Respiratory Syndrome"]17706
#3 ((airway* OR bronchopulmonar* OR broncho-pulmonar* OR tracheobronch* OR tracheo-bronch* OR (pulmonar* NEXT tract) OR pulmonary OR (respirat* NEXT tract) OR respiratory) NEAR/3 (infect* OR coinfect* OR inflamm*)):ti,ab,kw 18614
#4 ((chest OR lung? OR lobar OR pleura?) NEAR/3 (absces* OR infect* OR coinfect* OR inflamm*)):ti,ab,kw 4150
#5 (bronchit* OR bronchopneumon* OR (common NEXT cold*) OR "glandular fever" OR "infectious mononucleosis" OR flu OR influenza OR laryngit* OR laryngotracheobronchit* OR ("laryngo tracheo" NEXT bronchit*) OR (laryngo NEXT tracheobronchit*) OR laryngotracheit* OR nasopharyngit* OR parainfluenza OR pharyngit* OR pneumoni* OR pleuropneumoni* OR rhinopharyngit* OR "severe acute respiratory syndrome" OR SARS OR (sore NEXT throat*) OR (throat NEXT infection*) OR supraglottit* OR supraglotit* OR tonsillit* OR tonsilit* OR tracheit*):ti,ab,kw51341
#6 ((acute* OR exacerbat* OR flare*) NEAR/3 (copd OR coad OR "chronic obstructive pulmonary disease" OR ("chronic obstructive" NEXT airway* NEXT disease) OR "chronic obstructive lung disease")):ti,ab,kw 4040
#7 ((acute* OR subacute* OR exacerbat* OR prolonged) NEAR/3 cough*):ti,ab,kw 525
#8 (RTI OR LRTI OR URTI OR ARTI OR AURI OR ALRI):ti,ab,kw 1399
#9 [mh "Respiratory System"] AND ([mh Viruses] OR [mh "Virus Diseases"])453
#10 [mh "pneumonia, viral"] OR [mh ^"orthomyxoviridae infections"] OR [mh ^"influenza, human"]7578
#11 ((airway* OR bronchopulmonar* OR broncho-pulmonar* OR tracheobronch* OR tracheo-bronch* OR (pulmonar* NEXT tract) OR pulmonary OR (respirat* NEXT tract) OR respiratory) NEAR/3 (nonbacter* OR viral* OR virus* OR adenovir*)):ti,ab,kw 2500
#12 (rhinovir* OR (rhino* NEXT vir*) OR coryzavir* OR (coryza* NEXT vir*) OR influenzavir* OR (influenza* NEXT vir*) OR (H1N1 OR H3N2) OR parainfluenzavir* OR (parainfluenza* NEXT vir*) OR pneumovir* OR (pneumo* NEXT vir*) OR (human NEXT metapneumovir*) OR (human NEXT meta-pneumovir*) OR HMPV OR ("respiratory syncytial" NEXT vir*) OR RSV):ti,ab,kw 4910
#13 [mh "Respiratory System"] AND ([mh Bacteria] OR [mh "Bacterial Infections"])874
#14 [mh ^"pneumonia, bacterial"] OR [mh ^"chlamydial pneumonia"] OR [mh ^"pneumonia, mycoplasma"] OR [mh ^"pneumonia, pneumococcal"] OR [mh ^"pneumonia, staphylococcal"]946
#15 ((airway* OR bronchopulmonar* OR broncho-pulmonar* OR tracheobronch* OR tracheo-bronch* OR (pulmonar* NEXT tract) OR pulmonary OR (respirat* NEXT tract) OR respiratory) NEAR/3 (bacter* OR bacilli* OR bacili* OR corynebac* OR mycobac* OR nonvir* OR pathogen*)):ti,ab,kw1072
#16 ((strep* NEXT pneumon*) OR (diplococ* NEXT pneumon*) OR pneumococ* OR (staph* NEXT pneumon*) OR (chlamyd* NEXT pneumon*) OR (myco* NEXT pneumon*) OR (influenza NEXT bacil*) OR (bacteri* NEXT influenza*) OR (hemophil* NEXT influenza*) OR (haemophil* NEXT influenza*)):ti,ab,kw 5166
#17 ((strep* NEAR/3 (throat* OR pharyn* OR tonsil*)) OR (strep* AND (airway* OR pulmonary OR brochopulmonar* OR brocho-pulmonar* OR respiratory*))):ti,ab,kw 1729
#18 (GABHS OR ("group a" NEAR/3 strep*)):ti,ab,kw 496
#19 (strep* NEXT pyogen*):ti,ab,kw 494

#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #1974475
#21 [mh ^"Point-of-Care Systems"]575
#22 (POCT OR POCTs OR (((point NEAR/2 care) OR poc) NEAR/3 (analys* OR antigen? OR assay* OR device? OR immunoassay* OR classif* OR detect* OR determin* OR diagnos* OR differenti* OR identif* OR method* OR kit OR kits OR panel? OR platform? OR predict* OR rapid OR routine* OR screen* OR system* OR technique* OR test* OR cassette? OR dipstick? OR film* OR stick OR strip OR (fluorescent NEXT antibod*)))):ti,ab,kw 2015
#23 (point NEAR/2 care):ti,kw 1372
#24 (("near patient" OR "near-patient" OR nearpatient OR rapid* OR bedside? OR bed-side? OR extra-laboratory OR extralaboratory) NEAR/3 (analys* OR antigen? OR assay* OR immunoassay* OR classif* OR detect* OR determin* OR diagnos* OR differenti* OR identif* OR method* OR kit OR kits OR panel? OR predict* OR screen* OR system* OR technique* OR test* OR (fluorescent NEXT antibod*))):ti,ab,kw 6530
#25 (("near patient" OR "near-patient" OR nearpatient OR bedside? OR bed-side? OR extra-laboratory OR extralaboratory) NEAR/3 rapid*):ti,ab,kw 39
#26 [mh ^"Rapid Diagnostic Tests"]0
#27 (rapid* NEAR/3 (detect* OR diagnos* OR screen*)):ti,ab,kw 1611
#28 (time-to-result? OR ((quick* OR rapid* OR short* OR time*) NEAR/3 (turnaround OR turn-around))):ti,ab,kw 314
#29 (antigen? NEAR/3 (analys* OR assay* OR immunoassay* OR classif* OR detect* OR determin* OR diagnos* OR differenti* OR identif* OR method* OR kit OR kits OR panel? OR predict* OR rapid OR routine* OR screen* OR system* OR technique* OR test*)):ti,ab,kw 4499
#30 (RADT OR RADTs OR RDT OR RDTs):ti,ab,kw 485
#31 ("rapid molecular" OR multiplex*):ti,ab,kw 1767
#32 lab-on-a-chip:ti,ab,kw 0
#33 (("lateral flow" NEXT (assay* OR immunoassay* OR test*)) OR LFA OR LFIA):ti,ab,kw 206
#34 (immunochromatograph* OR immuno-chromatograph* OR immuno-chromato-graph* OR "direct immunofluorescence" OR "direct immuno-fluorescence" OR (enzym* NEXT immunoassay*) OR (enzym* NEXT immuno-assay*) OR ("fluorescence" NEXT immunoassay*) OR ("fluorescence" NEXT immuno-assay*) OR ("optical" NEXT immunoassay*) OR ("optical" NEXT immuno-assay*)) OR (ICA OR EIA OR FIA OR OIA):ti,ab,kw 2911
#35 ((chemiluminescen* OR chemi-luminescen*) NEXT (immunoassay* OR immuno-assay* OR assay*)):ti,ab,kw 500
#36 (((mobile OR portable OR handheld OR hand-held) NEAR/3 (analyser? OR analyzer? OR device? OR meters OR metres)) AND (blood? OR plasma OR saliva OR sputum OR spit OR mucus OR urine OR urea OR urinalys* OR fluids OR gas OR gases)):ti,ab,kw 546
#37 ((biomarker* OR procalcitonin* OR PCT OR "c reactive protein" OR "c-reactive protein" OR "C-reactive protein" OR CRP OR leucocyte OR leukocyte OR neutrophil* OR ("white blood cell" NEXT count*) OR wbc OR wbcc OR sodium OR "partial pressure of oxygen" OR "partial pressure O2" OR PaO2 OR "blood count" OR "platelet count" OR CBC OR FBC OR ("blood" NEXT exam*) OR (blood NEXT test*) OR (blood NEXT draw*) OR haematolog* OR hematolog* OR haemoglobin OR hemoglobin OR haematocrit OR hematocrit OR "white blood cell" OR "red blood cell" OR "mean platelet volume" OR "mean corpuscular volume" OR "mean corpuscular haemoglobin" OR "mean corpuscular hemoglobin" OR platelet* OR basophil* OR eosinophil* OR lymphocyte* OR monocyte* OR erythrocyte*) NEAR/3 (guid* OR direct* OR steer* OR inform* OR algorithm-guided OR algorithm-directed OR algorithm-steered OR algorithm-informed)):ti,ab,kw 1968
#38 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #3720117
#39 #20 AND #382081

CDSR: 37

Protocols: 3

CENTRAL: 2035

Editorials: 1

Clinical Answers: 5

MEDLINE (Ovid)

Searched: 26 May 2023

Ovid MEDLINE(R) ALL <1946–25 May 2023>

1 Respiratory Tract Infections/42643
2 exp Bronchitis/ or Common Cold/ or Infectious Mononucleosis/ or Influenza, Human/ or Laryngitis/ or exp Pharyngitis/ or exp Pneumonia/ or Severe Acute Respiratory Syndrome/436904
3 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (infect* or coinfect* or inflamm*)).tw,kf. 122877
4 ((chest or lung? or lobar or pleura?) adj3 (absces* or infect* or coinfect* or inflamm*)).tw,kf. 44844
5 (bronchit* or bronchopneumon* or common cold* or glandular fever or infectious mononucleosis or flu or influenza or laryngit* or laryngotracheobronchit* or laryngo tracheo bronchit* or laryngo tracheobronchit* or laryngotracheit* or nasopharyngit* or parainfluenza or pharyngit* or pneumoni* or pleuropneumoni* or rhinopharyngit* or severe acute respiratory syndrome or SARS or sore throat* or throat infection* or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit*).tw,kf. 523527
6 ((acute* or exacerbat* or flare*) adj3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).mp. 10315
7 ((acute* or subacute* or exacerbat* or prolonged) adj3 cough*).mp. 1549
8 (RTI or LRTI or URTI or ARTI or AURI or ALRI).tw,kf. 6320
9 exp Respiratory System/ and (exp Viruses/ or exp Virus Diseases/)35017
10 exp pneumonia, viral/ or *orthomyxoviridae infections/ or influenza, human/291951
11 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (nonbacter* or viral* or virus* or adenovir*)).tw,kf. 35921
12 (rhinovir* or rhino* vir* or coryzavir* or coryza* vir* or influenzavir* or influenza* vir* or (H1N1 or H3N2) or parainfluenzavir* or parainfluenza* vir* or pneumovir* or pneumo* vir* or human metapneumovir* or human metapneumovir* or HMPV or respiratory syncytial vir*).mp. or RSV.tw,kf. 139001
13 exp Respiratory System/ and (exp Bacteria/ or exp Bacterial Infections/)48085
14 pneumonia, bacterial/ or chlamydial pneumonia/ or pneumonia, mycoplasma/ or pneumonia, pneumococcal/ or pneumonia, staphylococcal/22815
15 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir* or pathogen*)).tw,kf.22660
16 (strep* pneumon* or diplococ* pneumon* or pneumococ* or staph* pneumon* or chlamyd* pneumon* or myco* pneumon* or influenza bacil* or bacteri* influenza* or h?emophil* influenza*).mp. 80816
17 ((strep* adj3 (throat* or pharyn* or tonsil*)) or (strep* and (airway* or pulmonary or brochopulmonar* or brocho-pulmonar* or respiratory*))).mp. 22180
18 (GABHS or ("group a" adj3 strep*)).tw,kf. 10737
19 strep* pyogen*.mp. 18547
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection]962908
21 Point-of-Care Systems/16388
22 (POCT or POCTs or (((point adj2 care) or poc) adj3 (analys* or antigen? or assay* or device? or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or platform? or predict* or rapid or routine* or screen* or system* or technique* or test* or (cassette? or dipstick? or film* or stick or strip or fluorescent antibod*)))).tw,kf.21789
23 (point adj2 care).ti,kf. 15117
24 (((near adj2 patient) or nearpatient or rapid* or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 (analys* or antigen? or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or

identif* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test* or fluorescent antibod*)).tw,kf. 204945
25 (((near adj2 patient) or nearpatient or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 rapid*).tw,kf. 639
26 Rapid Diagnostic Tests/43
27 (rapid* adj3 (detect* or diagnos* or screen*)).tw,kf. 71887
28 (time-to-result? or ((quick* or rapid* or short* or time*) adj3 (turnaround or turn-around))).tw,kf. 8134
29 (antigen? adj3 (analys* or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf. 90890
30 (RADT or RADTs or RDT or RDTs).tw,kf. 3331
31 (rapid molecular or multiplex*).mp. 73203
32 lab-on-a-chip.tw,kf. 3512
33 ((lateral flow adj (assay* or immunoassay* or test*)) or LFA or LFIA).tw,kf. 9990
34 (immunochromatograph* or immuno-chromatograph* or immuno-chromato-graph* or direct immunofluorescence or direct immuno-fluorescence or enzym* immunoassay* or enzym* immuno-assay* or fluorescence immunoassay* or fluorescence immuno-assay* or optical immunoassay* or optical immuno-assay*).mp. or (ICA or EIA or FIA or OIA).tw,kf. 60476
35 ((chemiluminescen* or chemi-luminescen*) adj (immunoassay* or immuno-assay* or assay*)).mp. 4716
36 (((mobile or portable or handheld or hand-held) adj3 (analy#er? or device? or meters or metres)) and (blood? or plasma or saliva or sputum or spit or mucus or urine or urea or urinalys* or fluids or gas or gases)).mp. 2614
37 ((biomarker* or procalcitonin* or PCT or "c reactive protein" or "c-reactive protein" or "C-reactive protein" or CRP or leucocyte or leukocyte or neutrophil* or white blood cell count* or wbc or wbcc or sodium or partial pressure of oxygen or partial pressure O2 or PaO2 or blood count or platelet count or CBC or FBC or blood exam* or blood test* or blood draw* or haematolog* or hematolog* or haemoglobin or hemoglobin or haematocrit or hematocrit or white blood cell or red blood cell or mean platelet volume or mean corpuscular volume or mean corpuscular haemoglobin or mean corpuscular hemaglobin or platelet* or basophil* or eosinophil* or lymphocyte* or monocyte* or erythrocyte*) adj3 (guid* or direct* or steer* or inform* or algorithm-guided or algorithm-directed or algorithm-steered or algorithm-informed)).tw,kf. 18753
38 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 [Rapid Tests/ biomarker guided management]472216
39 20 and 38 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection AND Rapid Tests/ biomarker guided management]34240
40 exp randomized controlled trial/594769
41 controlled clinical trial.pt. 95314
42 randomized.ab. 604126
43 placebo.ab. 238387
44 clinical trials as topic/200976
45 randomly.ab. 408822
46 trial.ti. 285699
47 40 or 41 or 42 or 43 or 44 or 45 or 461525057
48 exp animals/ not humans/5123796
49 47 not 481403647
50 randomized controlled trial.pt.593242
51 (random* or "controlled trial*" or "clinical trial*" or rct).tw. 1746752
52 50 or 51 1865978
53 39 and 49 1204
54 39 and 52 1917
55 53 or 54 2039
56 limit 55 to english language1959
57 limit 56 to yr="2022 -Current"418
58 limit 57 to (comment or editorial or letter or news)2
59 57 not 58416

EMBASE (Ovid)

Searched: 28 May 2023

EMBASE Classic + EMBASE <1947–25 May 2023>

1 respiratory tract infection/ or lower respiratory tract infection/ or chest infection/ or exp lung infection/360091
2 exp bronchitis/ or common cold/ or mononucleosis/ or exp influenza/ or laryngitis/ or laryngotracheobronchitis/ or exp pharyngitis/ or exp pneumonia/ or severe acute respiratory syndrome/ or parainfluenza virus infection/ or sore throat/ or supraglottitis/ or tonsillitis/ or exp tracheitis/644599
3 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (infect* or coinfect* or inflamm*)).tw,kf. 187030
4 ((chest or lung or lobar or pleura?) adj3 (absces* or infect* or coinfect* or inflamm*)).tw,kf. 62884
5 (bronchit* or bronchopneumon* or common cold* or glandular fever or infectious mononucleosis or flu or influenza or laryngit* or laryngotracheobronchit* or laryngo tracheo bronchit* or laryngo tracheobronchit* or laryngotracheit* or nasopharyngit* or parainfluenza or pharyngit* or pneumoni* or pleuropneumoni* or rhinopharyngit* or severe acute respiratory syndrome or SARS or sore throat* or throat infection* or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit*).tw,kf.731512
6 ((acute* or exacerbat* or flare*) adj3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).mp. 19358
7 ((acute* or subacute* or exacerbat* or prolonged) adj3 cough*).mp. 2539
8 (RTI or LRTI or URTI or ARTI or AURI or ALRI).tw,kf. 9587
9 exp respiratory system/ and (exp virus/ or exp virus infection/)61576
10 exp virus pneumonia/ or exp *orthomyxovirus infection/ or exp influenza/146440
11 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (nonbacter* or viral* or virus* or adenovir*)).tw,kf. 48349
12 (rhinovir* or rhino* vir* or coryzavir* or coryza* vir* or influenzavir* or influenza* vir* or (H1N1 or H3N2) or parainfluenzavir* or parainfluenza* vir* or pneumovir* or pneumo* vir* or human metapneumovir* or human metapneumovir* or HMPV or respiratory syncytial vir*).mp. or RSV.tw,kf. 147895
13 exp respiratory system/ and (exp bacterium/ or exp bacterial infection/)92509
14 exp bacterial pneumonia/38087
15 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir* or pathogen*)).tw,kf. 31985
16 (strep* pneumon* or diplococ* pneumon* or pneumococ* or staph* pneumon* or chlamyd* pneumon* or myco* pneumon* or influenza bacil* or bacteri* influenza* or h?emophil* influenza*).mp. 134619
17 ((strep* adj3 (throat* or pharyn* or tonsil*)) or (strep* and (airway* or pulmonary or brochopulmonar* or brocho-pulmonar* or respiratory*))).mp. 48594
18 (GABHS or ("group a" adj3 strep*)).tw,kf. 14181
19 strep* pyogen*.mp. 22698
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 191474981
21 point of care system/3810
22 (POCT or POCTs or (((point adj2 care) or poc) adj3 (analys* or antigen or assay* or device? or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or platform? or predict* or rapid or routine* or screen* or system* or technique* or test* or (cassette? or dipstick? or film* or stick or strip or fluorescent antibod*)))).tw,kf. 29715
23 (point adj2 care).ti,kf. 20377
24 (((near adj2 patient) or nearpatient or rapid* or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 (analys* or antigen? or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test* or fluorescent antibod*)).tw,kf. 265872

25 (((near adj2 patient) or nearpatient or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 rapid*).tw,kf. 961
26 rapid test/ or influenza A rapid test/ or streptococcus group A rapid test/8381
27 (rapid* adj3 (detect* or diagnos* or screen*)).tw,kf. 90602
28 (time-to-result? or ((quick* or rapid* or short* or time*) adj3 (turnaround or turn-around))).tw,kf. 14966
29 (antigen? adj3 (analys* or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf. 123967
30 (RADT or RADTs or RDT or RDTs).tw,kf. 5327
31 (rapid molecular or multiplex*).mp. 115336
32 lab-on-a-chip.tw,kf. 3683
33 ((lateral flow adj (assay* or immunoassay* or test*)) or LFA or LFIA).tw,kf. 11987
34 (immunochromatograph* or immuno-chromatograph* or immuno-chromato-graph* or direct immunofluorescence or direct immuno-fluorescence or enzym* immunoassay* or enzym* immuno-assay* or fluorescence immunoassay* or fluorescence immuno-assay* or optical immunoassay* or optical immuno-assay*).mp. or (ICA or EIA or FIA or OIA).tw,kf. 111334
35 ((chemiluminescen* or chemi-luminescen*) adj (immunoassay* or immuno-assay* or assay*)).mp. 18319
36 (((mobile or portable or handheld or hand-held) adj3 (analy#er? or device? or meters or metres)) and (blood? or plasma or saliva or sputum or spit or mucus or urine or urea or urinalys* or fluids or gas or gases)).mp. 4058
37 ((biomarker* or procalcitonin* or PCT or "c reactive protein" or "c-reactive protein" or "C-reactive protein" or CRP or leucocyte or leukocyte or neutrophil* or white blood cell count* or wbc or wbcc or sodium or partial pressure of oxygen or partial pressure O2 or PaO2 or blood count or platelet count or CBC or FBC or blood exam* or blood test* or blood draw* or haematolog* or hematolog* or haemoglobin or hemoglobin or haematocrit or hematocrit or white blood cell or red blood cell or mean platelet volume or mean corpuscular volume or mean corpuscular haemoglobin or mean corpuscular hemaglobin or platelet* or basophil* or eosinophil* or lymphocyte* or monocyte* or erythrocyte*) adj3 (guid* or direct* or steer* or inform* or algorithm-guided or algorithm-directed or algorithm-steered or algorithm-informed)).tw,kf. 29271
38 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37682176
39 37 and 201955
40 exp randomized controlled trial/790418
41 controlled clinical trial/469623
42 random$.ti,ab.1981362
43 randomization/99460
44 intermethod comparison/297400
45 placebo.ti,ab.371225
46 (compare or compared or comparison).ti,ab. 7771662
47 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]2981040
48 (open adj label).ti,ab. 109052
49 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 280099
50 double blind procedure/213168
51 parallel group$1.ti,ab. 32267
52 (crossover or cross over).ti,ab. 125950
53 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 417487
54 (assigned or allocated).ti,ab.491973
55 (controlled adj7 (study or design or trial)).ti,ab. 454826
56 (volunteer or volunteers).ti,ab. 288594
57 human experiment/651776
58 trial.ti.411431
59 or/40-5810289233

60 (random$ adj sampl$ adj7 (“cross section$” or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomied controlled.ti,ab. or randomly assigned.ti,ab.) 9599
61 cross-sectional study/ not (exp randomized controlled trial/ or controlled clinical trial/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) 347803
62 ((case adj control$).mp. and random$.ti,ab.) not randomi?ed controlled.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]26076
63 systematic review.ti,ab. not (trial or study).ti. 326205
64 (nonrandom$ not random$).ti,ab. 19058
65 ’random field$’.ti,ab.2951
66 (random cluster adj3 sampl$).ti,ab. 1542
67 (review.ab. and review.pt.) not trial.ti. 1117857
68 “we searched”.ab. and (review.ti. or review.pt.) 49790
69 “update review”.ab. 138
70 (databases adj4 searched).ab. 62434
71 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/1227348
72 animal experiment/ not (human experiment/ or human/)2581423
73 or/60-724378964
74 59 not 738989986
75 39 and 74681
76 limit 75 to english language672
77 limit 76 to yr=“2022 -Current”89
78 limit 77 to (conference abstract or conference paper or “conference review” or editorial or letter)20
79 77 not 7869

Searches for cost-effectiveness

MEDLINE (Ovid)

Searched: 16 May 2023

Ovid MEDLINE(R) ALL <1946–15 May 2023>

1 Respiratory Tract Infections/42626
2 exp Bronchitis/ or Common Cold/ or Infectious Mononucleosis/ or Influenza, Human/ or Laryngitis/ or exp Pharyngitis/ or exp Pneumonia/ or Severe Acute Respiratory Syndrome/435829
3 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (infect* or coinfect* or inflamm*)).tw,kf. 122748
4 ((chest or lung? or lobar or pleura?) adj3 (absces* or infect* or coinfect* or inflamm*)).tw,kf. 44790
5 (bronchit* or bronchopneumon* or common cold* or glandular fever or infectious mononucleosis or flu or influenza or laryngit* or laryngotracheobronchit* or laryngo tracheo bronchit* or laryngo tracheobronchit* or laryngotracheit* or nasopharyngit* or parainfluenza or pharyngit* or pneumoni* or pleuropneumoni* or rhinopharyngit* or severe acute respiratory syndrome or SARS or sore throat* or throat infection* or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit*).tw,kf. 522522
6 ((acute* or exacerbat* or flare*) adj3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).mp. 10295
7 ((acute* or subacute* or exacerbat* or prolonged) adj3 cough*).mp. 1546
8 (RTI or LRTI or URTI or ARTI or AURI or ALRI).tw,kf. 6307
9 exp Respiratory System/ and (exp Viruses/ or exp Virus Diseases/)35000
10 exp pneumonia, viral/ or *orthomyxoviridae infections/ or influenza, human/290911

11 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (nonbacter* or viral* or virus* or adenovir*)).tw,kf. 35861
12 (rhinovir* or rhino* vir* or coryzavir* or coryza* vir* or influenzavir* or influenza* vir* or (H1N1 or H3N2) or parainfluenzavir* or parainfluenza* vir* or pneumovir* or pneumo* vir* or human metapneumovir* or human metapneumovir* or HMPV or respiratory syncytial vir*).mp. or RSV.tw,kf. 138900
13 exp Respiratory System/ and (exp Bacteria/ or exp Bacterial Infections/)48073
14 pneumonia, bacterial/ or chlamydial pneumonia/ or pneumonia, mycoplasma/ or pneumonia, pneumococcal/ or pneumonia, staphylococcal/22813
15 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir* or pathogen*)).tw,kf. 22642
16 (strep* pneumon* or diplococ* pneumon* or pneumococ* or staph* pneumon* or chlamyd* pneumon* or myco* pneumon* or influenza bacil* or bacteri* influenza* or h?emophil* influenza*).mp. 80781
17 ((strep* adj3 (throat* or pharyn* or tonsil*)) or (strep* and (airway* or pulmonary or brochopulmonar* or brocho-pulmonar* or respiratory*))).mp. 22162
18 (GABHS or ("group a" adj3 strep*)).tw,kf. 10727
19 strep* pyogen*.mp. 18540
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection]961136
21 Point-of-Care Systems/16387
22 (POCT or POCTs or (((point adj2 care) or poc) adj3 (analys* or antigen? or assay* or device? or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or platform? or predict* or rapid or routine* or screen* or system* or technique* or test* or (cassette? or dipstick? or film* or stick or strip or fluorescent antibod*))))).tw,kf.21725
23 (point adj2 care).ti,kf. 15063
24 (((near adj2 patient) or nearpatient or rapid* or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 (analys* or antigen? or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test* or fluorescent antibod*)).tw,kf. 204660
25 (((near adj2 patient) or nearpatient or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 rapid*).tw,kf. 637
26 Rapid Diagnostic Tests/43
27 (rapid* adj3 (detect* or diagnos* or screen*)).tw,kf. 71754
28 (time-to-result? or ((quick* or rapid* or short* or time*) adj3 (turnaround or turn-around))).tw,kf. 8119
29 (antigen? adj3 (analys* or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf. 90810
30 (RADT or RADTs or RDT or RDTs).tw,kf. 3318
31 (rapid molecular or multiplex*).mp. 73027
32 lab-on-a-chip.tw,kf. 3504
33 ((lateral flow adj (assay* or immunoassay* or test*)) or LFA or LFIA).tw,kf. 9974
34 (immunochromatograph* or immuno-chromatograph* or immuno-chromato-graph* or direct immunofluorescence or direct immuno-fluorescence or enzym* immunoassay* or enzym* immuno-assay* or fluorescence immunoassay* or fluorescence immuno-assay* or optical immunoassay* or optical immuno-assay*).mp. or (ICA or EIA or FIA or OIA).tw,kf. 60440
35 ((chemiluminescen* or chemi-luminescen*) adj (immunoassay* or immuno-assay* or assay*)).mp. 4700
36 (((mobile or portable or handheld or hand-held) adj3 (analy#er? or device? or meters or metres)) and (blood? or plasma or saliva or sputum or spit or mucus or urine or urea or urinalys* or fluids or gas or gases)).mp. 2611
37 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 [Rapid Tests]453799
38 20 and 37 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection AND Rapid Tests]33110
39 exp Diagnosis/9337079
40 di.fs. 2925815
41 diagnos*.ti,ab,kf. 3041447

42 (test or tests or testing).ti,ab,kf. 2837989
43 39 or 40 or 41 or 42 [Diagnosis/ Testing (broad)]12968950
44 20 and 43 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection AND Diagnosis/ Testing (broad)]420239
45 Cost-Benefit Analysis/92348
46 (cost* and (((qualit* adj2 adjust*) and life*) or qaly*)).tw,kf. 17443
47 ((incremental* adj2 cost*) or ICER).tw,kf. 17647
48 (cost adj2 utilit*).tw,kf. 7139
49 (cost* and ((net adj benefit*) or ((net adj monetary) and benefit*) or ((net adj health) and benefit*))).tw,kf. 2345
50 ((cost adj2 effect*) and ((quality adj of) and life)).tw,kf. 12651
51 (cost and (effect* or utilit*)).ti. 38213
52 45 or 46 or 47 or 48 or 49 or 50 or 51113868 [cost-utility filter – precise version - based on Hubbard et al 2022]
53 38 and 52203
54 44 and 521292
55 53 or 541301
56 limit 55 to english language1238
57 limit 56 to (comment or editorial or letter or news or newspaper article)56
58 56 not 571182

EMBASE (Ovid)

Searched: 18 May 2023

EMBASE Classic + EMBASE <1947–17 May 2023>

1 respiratory tract infection/ or lower respiratory tract infection/ or chest infection/ or exp lung infection/359718
2 exp bronchitis/ or common cold/ or mononucleosis/ or exp influenza/ or laryngitis/ or laryngotracheobronchitis/ or exp pharyngitis/ or exp pneumonia/ or severe acute respiratory syndrome/ or parainfluenza virus infection/ or sore throat/ or supraglottitis/ or tonsillitis/ or exp tracheitis/643746
3 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (infect* or coinfect* or inflamm*)).tw,kf. 186780
4 ((chest or lung or lobar or pleura?) adj3 (absces* or infect* or coinfect* or inflamm*)).tw,kf. 62801
5 (bronchit* or bronchopneumon* or common cold* or glandular fever or infectious mononucleosis or flu or influenza or laryngit* or laryngotracheobronchit* or laryngo tracheo bronchit* or laryngo tracheobronchit* or laryngotracheit* or nasopharyngit* or parainfluenza or pharyngit* or pneumoni* or pleuropneumoni* or rhinopharyngit* or severe acute respiratory syndrome or SARS or sore throat* or throat infection* or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit*).tw,kf. 730007
6 ((acute* or exacerbat* or flare*) adj3 (copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).mp. 19331
7 ((acute* or subacute* or exacerbat* or prolonged) adj3 cough*).mp. 2536
8 (RTI or LRTI or URTI or ARTI or AURI or ALRI).tw,kf. 9584
9 exp respiratory system/ and (exp virus/ or exp virus infection/)61466
10 exp virus pneumonia/ or exp *orthomyxovirus infection/ or exp influenza/146242
11 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (nonbacter* or viral* or virus* or adenovir*)).tw,kf. 48279
12 (rhinovir* or rhino* vir* or coryzavir* or coryza* vir* or influenzavir* or influenza* vir* or (H1N1 or H3N2) or parainfluenzavir* or parainfluenza* vir* or pneumovir* or pneumo* vir* or human metapneumovir* or human metapneumovir* or HMPV or respiratory syncytial vir*).mp. or RSV.tw,kf. 147754
13 exp respiratory system/ and (exp bacterium/ or exp bacterial infection/)92429
14 exp bacterial pneumonia/38054
15 ((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory) adj3 (bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir* or pathogen*)).tw,kf. 31947

16 (strep* pneumon* or diplococ* pneumon* or pneumococ* or staph* pneumon* or chlamyd* pneumon* or myco* pneumon* or influenza bacil* or bacteri* influenza* or h?emophil* influenza*).mp. 134532
17 ((strep* adj3 (throat* or pharyn* or tonsil*)) or (strep* and (airway* or pulmonary or brochopulmonar* or brocho-pulmonar* or respiratory*))).mp. 48553
18 (GABHS or ("group a" adj3 strep*)).tw,kf. 14167
19 strep* pyogen*.mp. 22673
20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection]1472567
21 point of care system/3800
22 (POCT or POCTs or (((point adj2 care) or poc) adj3 (analys* or antigen or assay* or device? or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or platform? or predict* or rapid or routine* or screen* or system* or technique* or test* or (cassette? or dipstick? or film* or stick or strip or fluorescent antibod*))))).tw,kf.29627
23 (point adj2 care).ti,kf. 20316
24 (((near adj2 patient) or nearpatient or rapid* or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 (analys* or antigen? or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test* or fluorescent antibod*)).tw,kf. 265505
25 (((near adj2 patient) or nearpatient or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 rapid*).tw,kf. 957
26 rapid test/ or influenza A rapid test/ or streptococcus group A rapid test/8357
27 (rapid* adj3 (detect* or diagnos* or screen*)).tw,kf. 90455
28 (time-to-result? or ((quick* or rapid* or short* or time*) adj3 (turnaround or turn-around))).tw,kf. 14929
29 (antigen? adj3 (analys* or assay* or immunoassay* or classif* or detect* or determin* or diagnos* or differenti* or identif* or method* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf. 123850
30 (RADT or RADTs or RDT or RDTs).tw,kf. 5314
31 (rapid molecular or multiplex*).mp. 115150
32 lab-on-a-chip.tw,kf. 3675
33 ((lateral flow adj (assay* or immunoassay* or test*)) or LFA or LFIA).tw,kf. 11972
34 (immunochromatograph* or immuno-chromatograph* or immuno-chromato-graph* or direct immunofluorescence or direct immuno-fluorescence or enzym* immunoassay* or enzym* immuno-assay* or fluorescence immunoassay* or fluorescence immuno-assay* or optical immunoassay* or optical immuno-assay*).mp. or (ICA or EIA or FIA or OIA).tw,kf. 111218
35 ((chemiluminescen* or chemi-luminescen*) adj (immunoassay* or immuno-assay* or assay*)).mp. 18247
36 (((mobile or portable or handheld or hand-held) adj3 (analy#er? or device? or meters or metres)) and (blood? or plasma or saliva or sputum or spit or mucus or urine or urea or urinalys* or fluids or gas or gases)).mp. 4050
37 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 [Rapid Tests]653734
38 20 and 37 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection AND Rapid Tests]53242
39 exp diagnosis/8484048
40 di.fs. 3725926
41 diagnos*.ti,ab,kf. 4672696
42 (test or tests or testing).ti,ab,kf. 4221212
43 39 or 40 or 41 or 42 [Diagnosis/ Testing (broad)]13703963
44 20 and 43 [RTIs/ RTI Viral Infection/ RTI Bacterial Infection AND Diagnosis/ Testing (broad)]649809
45 cost utility analysis/12221
46 (cost* and (((qualit* adj2 adjust*) and life*) or qaly*)).tw,kf. 30502
47 ((incremental* adj2 cost*) or ICER).tw,kf. 30673
48 (cost adj2 utilit*).tw,kf. 11663
49 (cost* and ((net adj benefit*) or ((net adj monetary) and benefit*) or ((net adj health) and benefit*))).tw,kf. 3360
50 ((cost adj2 effect*) and ((quality adj of) and life)).tw,kf. 19438
51 (cost and (effect* or utilit*)).ti. 57091
52 45 or 46 or 47 or 48 or 49 or 50 or 51 [cost-utility filter – precise version – based on Hubbard et al 2022]91298

53 38 and 52 186
54 44 and 521108
55 53 or 541121
56 limit 55 to english language1087
57 limit 56 to (conference abstract or conference paper or "conference review" or editorial or letter)261
58 56 not 57826

Cost-effectiveness Analysis Registry

https://cear.tuftsmedicalcenter.org/

Searched: 18 May 2023

Methods tab selected

#1 Keyword is: rapid and Disease (ICD-10) is: 10 [Diseases of the respiratory system (J00-J99)] = 19 articles
#2 Keyword is: point-of-care and Disease (ICD-10) is: 10 [Diseases of the respiratory system (J00-J99)] = 6 articles
#3 Keyword is: point of care and Disease (ICD-10) is: 10 [Diseases of the respiratory system (J00-J99)] = 15 articles
#4 Keyword is: bedside and Disease (ICD-10) is: 10 [Diseases of the respiratory system (J00-J99)] = 1 article
#5 Keyword is: near-patient and Disease (ICD-10) is: 10 [Diseases of the respiratory system (J00-J99)] = 1 article
#6 Keyword is: near patient and Disease (ICD-10) is: 10 [Diseases of the respiratory system (J00-J99)] = 3 articles
#7 Keyword is: extra-laboratory and Disease (ICD-10) is: 10 [Diseases of the respiratory system (J00-J99)] = 0 articles
#8 Keyword is: extra laboratory and Disease (ICD-10) is: 10 [Diseases of the respiratory system (J00-J99)] = 0 articles

Total: 45

Total after duplicates removed: 35

Total after duplicates found in MEDLINE or EMBASE removed: 17

Appendix 2 Studies included in the clinical effectiveness review

TABLE 11 Included studies of CRP tests

Study details	Participants	Interventions	Outcomes and results	Comments
Afinion CRP POC testing				
Andreeva 2014[29] From Smedemark 2022[16] Russia Open-label cluster RCT, 17 GP offices Study dates: January 2010–April 2010 Funding: not reported. Test kits provided by manufacturer and CRP readers acquired at reduced prices. Follow-up: 14 days	Sample size: 179 patients (17 GPs) CRP 101 (8 offices), usual care 78 (9 offices) Inclusion criteria: Age > 18 years with index case of acute cough/lower RTI (including acute bronchitis, pneumonia, infectious exacerbations of COPD or asthma) for < 28 days Exclusion criteria: previously seen by GP for infection in question, immunocompromised, oral corticosteroid treatment Key characteristics CRP; usual care Mean age, years: 50.8, 50.8 Any comorbidity, %: 54, 50 Pulmonary diseases, %: 15, 18 Heart diseases, %: 17, 4 Diabetes, %: 5, 4	Interventions: Single POC CRP to guide antibiotic decisions (< 20 mg/l antibiotics not needed; > 50 mg/l antibiotics may be indicated accounting for duration of illness) Afinion test system (Axis-Shield, Norway) Comparator: usual care	*Data from Smedemark 2022 (modified sample size)* Hospital admission (not stated, assume within 14 days) (number of events/number of participants) CRP: 0/49 Usual care: 0/38 Number of re-consultations within 14 days (number of events/number of participants) CRP: 1/49 Usual care: 1/38 RR 0.78 (95% CI 0.05 to 12.00) *Data from Andreeva 2014 (original sample size)* Antibiotics prescribed at index consultation (number of events/number of participants) CRP: 38/101 Usual care: 46/78, $p = 0.006$ Antibiotics prescribed within 14 days (number of events/number of participants) CRP: 41/101 Usual care: 56/78 Number of participants fully or almost recovered within 14 days (number of events/number of participants) CRP: 92/101 Usual care: 72/78	Cluster RCT therefore modified sample size used in Smedemark 2022 analysis. Referred to as Andreeva 2013 in Smedemark 2022. Smedemark 2022 reports published and unpublished data for Andreeva 2014; hospital admission and re-consultation data could not be checked.

continued

TABLE 11 Included studies of CRP tests (*continued*)

Study details	Participants	Interventions	Outcomes and results	Comments
Butler 2019[30] From Smedemark 2022[16] Francis 2020[31] UK (England and Wales) Open-label RCT, 86 general medical practices Study dates: January 2015–September 2017 Source of funding: non-commercial Follow-up: 4 weeks and 6 months	Sample size: 649 patients with AECOPD CRP 325, usual care 324 Inclusion criteria: ≥ 40 years; diagnosis of COPD in primary care clinical record; presenting with an AECOPD with at least one of AECOPD criteria (with at least one of: increased dyspnoea, increased sputum volume, increased sputum purulence), between 24 hours and 21 days duration Exclusion criteria: urgent hospital admission; severe illness (e.g. suspected pneumonia, tachypnoea > 30 breaths per minute); concurrent infection at another site (e.g. urinary tract infection); past history of respiratory failure or mechanical ventilation; currently taking antibiotics or had already taken antibiotics for this AECOPD; active inflammatory condition; cystic fibrosis, tracheostomy, or bronchiectasis; immunocompromised; pregnancy	Interventions: single POC CRP to guide antibiotic decisions: ≤ 20 mg/l, 20–40 mg/l, ≥ and 40 mg/l Afinion desktop devices for CRP POC testing (Alere, now Abbott) Comparator: usual care	*Data from Smedemark 2022* Antibiotics prescribed at index consultation (number of events/number of participants) CRP: 155/325 Usual care: 225/324 RR 0.69 (95% CI 0.60 to 0.79) Antibiotics prescribed within 28 days (number of events/number of participants) CRP: 185/313 Usual care: 252/316 RR 0.74 (95% CI 0.67 to 0.83) Mortality within 28 days (number of events/number of participants) CRP: 0/325 Usual care: 2/324 RR 0.20 (95% CI 0.01 to 4.14) Hospital admissions within 6 months (number of events/number of participants) CRP: 35/304 Usual care: 34/301 RR 1.02 (95% CI 0.65 to 1.59) *Data from Butler 2019* Primary and secondary care consultations during 6 months follow-up (number of events/number of participants) CRP: 299/305 Usual care: 294/302 Adjusted OR 1.39 (95% CI 0.46 to 4.15)[a] HRQoL (EQ-5D-5L index value) at 1 week (mean, SE) CRP: 0.6 (0.01) Usual care: 0.6 (0.01) HRQoL (EQ-5D-5L index value) at 2 weeks (mean, SE) CRP: 0.6 (0.01) Usual care: 0.6 (0.01) HRQoL (EQ-5D-5L index value) at 4 weeks (mean, SE) CRP: 0.7 (0.01) Usual care: 0.6 (0.01) HRQoL (EQ-5D-5L index value) at 6 months (mean, SE) CRP: 0.6 (0.01) Usual care: 0.6 (0.01) Adjusted mean difference (averaged across time points): 0.03 (95% CI −0.04 to 0.09)[b] HRQoL (EQ-5D-5L health status) at 1 week (mean, SE) CRP: 57.8 (1.26) Usual care: 54.7 (1.24) HRQoL (EQ-5D-5L health status) at 2 weeks (mean, SE) CRP: 60.7 (1.25) [a]	Follow-up consultation/ongoing monitoring defined as patients who had primary care consultations (i.e. consultation with a primary care clinician outside a hospital) or secondary care consultations (i.e. planned consultation with a specialist in a hospital)during 6 months of follow-up Clustering of responses of participants within practices for EQ-5D accounted for by fitting a three-level linear regression model Clustering of participants within practices for CRQ-SAS accounted for by fitting a two-level linear regression model

TABLE 11 Included studies of CRP tests (*continued*)

Study details	Participants	Interventions	Outcomes and results	Comments
	Key characteristics CRP; usual care Mean age (SD; range), years: 67.8 (9.53; 41–90); 68.3 (9.31; 40–92) Heart failure, %: 4.9, 4.6 COPD, %: 100, 100 Coronary heart disease, %: 16.9, 18.2 Diabetes, %: 15.4, 16.7 Chronic kidney disease, %: 8.3, 9.9 Hypertension, %: 38.2, 44.1 Other chronic disease, %: 28.5, 24.1		*Data from Smedemark 2022* Usual care: 57.6 (1.24) HRQoL (EQ-5D-5L health status) at 4 weeks (mean, SE) CRP: 63.0 (1.27) Usual care: 59.9 (1.25) HRQoL (EQ-5D-5L health status) at 6 months (mean, SE) CRP: 62.9 (1.32) Usual care: 59.8 (1.31) Adjusted mean difference (averaged across time points): 3.12 (95% CI 0.50 to 5.74)[b] HRQoL (CRQ-SAS dyspnoea domain) (mean, SE) CRP (*n* = 206): 4.3 (0.10) Usual care (*n* = 193): 4.2 (0.10) Adjusted mean difference (averaged across time points): 0.06 (95% CI −0.20 to 0.33)[a] HRQoL (CRQ-SAS fatigue domain) (mean, SE) CRP (*n* = 221): 3.6 (0.11) Usual care (*n* = 215): 3.5 (0.11) Adjusted mean difference (averaged across time points): 0.13 (95% CI −0.12 to 0.38)[a] HRQoL (CRQ-SAS function domain) (mean, SE) CRP (*n* = 225): 4.4 (0.08) Usual care (*n* = 216): 4.3 (0.08) Adjusted mean difference (averaged across time points): 0.15 (95% CI −0.04 to 0.34)[a] HRQoL (CRQ-SAS mastery domain) (mean, SE) CRP (*n* = 221): 4.2 (0.03) Usual care (*n* = 214): 4.3 (0.03) Adjusted mean difference (averaged across time points): −0.09 (95% CI −0.18 to 0.01)[a] *Data from Francis 2020*[c] Antibiotics prescribed within 4 weeks post randomisation, patient-reported: (number of events/number of participants) CRP: 150/263 Usual care: 212/274 Adjusted OR 0.31 (95% CI 0.20 to 0.47)[a] Primary care consultations during 6 months follow-up (mean, SE) CRP (*n* = 304): 6.6 (0.29) Usual care (*n* = 301): 6.3 (0.28) Adjusted incidence rate ratio 1.04 (95% CI 0.92 to 1.18)[a] Secondary care consultations during 6 months follow-up (mean, SE) CRP (*n* = 305): 1.6 (1.1) Usual care (*n* = 302): 1.7 (0.12) Adjusted incidence rate ratio 0.96 (95% CI 0.79 to 1.17)[a] Primary and secondary care consultations during 6 months follow-up (mean, SE) CRP (*n* = 305): 8.2 (0.35) Usual care (*n* = 302): 7.9 (0.34) Adjusted incidence RR: 1.02 (95% CI 0.91 to 1.15)[a]	

continued

TABLE 11 Included studies of CRP tests (*continued*)

Study details	Participants	Interventions	Outcomes and results	Comments
Nycocard II CRP POC testing (not currently available in the UK)				
Althaus 2019[32] From Smedemark 2022[16] Thailand and Myanmar Open-label RCT, nine centres in public primary care, and one outpatient setting Study dates: June 2016–June 2017 Funding: non-commercial Follow-up Day 5 and 14	Sample size: 937 (adults with ARI subgroup) CRP 614, usual care 323 Inclusion criteria: age > 1 year; documented fever or chief complaint of fever (< 14 days), regardless of previous antibiotic intake, and comorbidities other than malignancies (specific details and raw data to differentiate participants with symptoms of ARIs provided to SR authors). Exclusion criteria: symptoms requiring hospital referral (impaired consciousness, inability to take oral medication, convulsions) Key characteristics NR for relevant subgroup	Interventions: single POC CRP to guide antibiotic decisions at thresholds: (a) Low 20 mg/l (b) High 40 mg/l NycoCard II Reader, Axis Shield, Oslo, Norway Comparator: usual care	*Data from Smedemark 2022* Antibiotics prescribed at index consultation (number of events/number of participants) CRP: 210/614 Usual care: 138/323 RR 0.80 (95% CI 0.68 to 0.95)	Smedemark 2022 reports published and unpublished data for Althaus 2019. Study population is patients with fever attending primary care; specific details and raw data to differentiate participants with symptoms of ARIs provided to Smedemark 2022. Baseline characteristics of subgroup not reported.

TABLE 11 Included studies of CRP tests (*continued*)

Study details	Participants	Interventions	Outcomes and results	Comments
Cals 2009[33] From Smedemark 2022[16] Cals 2013[34] The Netherlands Open-label cluster RCT, 20 primary care practices Study dates: Winter periods June 2005 and July 2006 Source of funding: non-commercial Follow-up: 28 days	Sample size: 431 patients with lower RTI CRP 227 (10 practices, 20 GPs), usual care 204 (10 practices, 20 GPs) Inclusion criteria: adults (> 18 years) with suspected lower RTI (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign) Exclusion criteria: current antibiotic use or usage within previous 2 weeks Hospitalisation in past 6 weeks, or need for immediate hospitalisation Key characteristics CRP; usual care Mean age (SD), years: 49.4 (14.7), 47.0 (9.9) COPD, %: 7.5, 6.9 Asthma, %: 10.1, 7.8 Diabetes, %: 4.0, 4.4 Heart disease, %: 4.8, 4.4	Interventions: single POC CRP to guide antibiotic decisions: < 20 mg/l, 20–99 mg/l, > and 100 mg/l Nycocard II Reader (Axis-Shield, Norway) Comparator: usual care	*Data from Smedemark 2022 (modified sample size)* Number of participants substantially improved within 28 days (number of events/number of participants) CRP: 49/65 Usual care: 44/59 RR 0.97 (95% CI 0.53 to 1.78) *Data from Cals 2009* Antibiotics prescribed at index consultation (number of events/number of participants) CRP: 70/227; 30.8% (crude 95% CI 21.8 to 39.8[c]) Usual care: 108/204; 52.9% (crude 95% CI 43.0 to 62.8[c]) Antibiotics prescribed within 28 days (number of events/number of participants) CRP: 102/227; 44.9% (crude 95% CI 35.2 to 54.6[c]) Usual care: 119/204; 58.3% (crude 95% CI 48.5 to 68.1[c]) Number of re-consultations within 28 days (number of events/number of participants) CRP: 79/227; 34.8% (crude 95% CI 28.3 to 41.3[c]) Usual care: 62/204; 30.4% (crude 95% CI 23.9 to 37.0[c]) Mortality during 28 days (number of events/number of participants) CRP: 0/227 Usual care: 0/204 Hospital admissions during 28 days (number of events/number of participants) CRP: 0/227 Usual care: 0/204 *CRP test alone vs. usual care alone (excluding communication skills training groups)* Antibiotics prescribed at index consultation (number of events/number of participants) CRP: 39/110; 43.0% (crude 95% CI 25. to 52.6[c]) Usual care: 67/120; 80% (crude 95% CI 53.9 to 79.5[c])	Cluster RCT therefore modified sample size used in Smedemark 2022 analysis. Source of data for 'substantial improvement' reported in Smedemark 2022 unclear. Originally 2 x 2 factorial design: CRP includes CRP test group + CRP test and training in communication skills group; usual care includes usual care group + training in enhanced communication skills group.

continued

TABLE 11 Included studies of CRP tests (*continued*)

Study details	Participants	Interventions	Outcomes and results	Comments
Diederichsen 2000[35] From Smedemark 2022[16] Denmark Open-label RCT, 35 primary care practices Study dates: January 1997–April 1997 Source of funding: not reported Follow-up: 1 week	Sample size: 673 (adults with respiratory infection) CRP 342, usual care 331 Inclusion criteria: all patients with index case of respiratory infection Exclusion criteria: previously seen by GP for infection in question, patients who had streptococcal rapid testing performed, patients with chronic inflammatory diseases Key characteristics NR for adults	Interventions: single POC CRP to guide antibiotic decisions: < 10 mg/l and < 50 mg/l. Nycocard II Reader (Axis-Shield, Norway) Comparator: usual care	*Data from Smedemark 2022* Antibiotics prescribed at index consultation (number of events/number of participants) CRP: 152/342 Usual care: 161/331 RR 0.91 (95% CI 0.78 to 1.07)	Specific details and raw data to differentiate adult participants provided to Smedemark 2022. Baseline characteristics of adults not reported.
Do 2016[36] From Smedemark 2022[16] Northern Vietnam Open-label RCT, 10 primary healthcare centres Study dates: March 2014–July 2015 Source of funding: non-commercial Follow-up: 14 days	Sample size: 1008 (adults with non-severe ARI) CRP 507, usual care 501 Inclusion criteria: patients aged 1–65 years presenting with non-severe ARTI (at least one focal and one systemic sign or symptom by the treating physician) Exclusion criteria: sign of severe ARI Key characteristics NR for adults	Interventions: single POC CRP to guide antibiotic decisions: < 20 mg/l and > 100 mg/l. Nycocard analyser (Nycocard II Reader, Alere Technologies, Norway) Comparator: usual care	*Data from Smedemark 2022* Antibiotics prescribed at index consultation (number of events/number of participants) CRP: 214/507 Usual care: 314/501 RR 0.67 (95% CI 0.60 to 0.76) *Data from Do 2016* Antibiotics prescribed within 14 days, per-protocol analysis (number of events/number of participants) CRP: 286/454 Usual care: 364/460 OR 0.41 (95% CI 0.30 to 0.56) Subsequent antibiotic use in those without an immediate antibiotic prescription (number of events/number of participants) CRP: 72/240 Usual care: 50/146 OR 0.73 (95% CI 0.45 to 1.17) Antibiotic management change in those without an immediate antibiotic prescription (number of events/number of participants) CRP: 22/255 Usual care: 8/175 OR 1.99 (95% CI 0.86 to 4.64) Time to resolution of symptoms, days (median, IQR) CRP: 6 (4–10) Usual care: 5 (4–8) HR 0·89 (95% CI 0.77 to 1.03)[d] Mortality within 14 days CRP: 0/507 Usual care: 0/501	Baseline characteristics of adults not reported. Subsequent antibiotic use and antibiotic management change are in patients without immediate antibiotic prescription, that is they refer to non-randomised comparisons because the denominator population depends on the treatment group

TABLE 11 Included studies of CRP tests (*continued*)

Study details	Participants	Interventions	Outcomes and results	Comments
Melbye 1995[37] From Smedemark 2022[16] Norway Open-label RCT, 10 primary care practices Study dates: NR Source of funding: Nycomed Pharma Follow-up: 3 weeks	Sample size: 239 patients with suspected lower RTI CRP 108, usual care 131 Inclusion criteria: adults (> 18 years) with subjective complaint of (i) pneumonia, bronchitis, or asthma or (ii) one of the following symptoms: cough, shortness of breath, chest pain on deep inspiration or cough Exclusion criteria: patients with sore throat, blocked nose, pain in ears or sinuses; patients with angina-like chest pain Key characteristics CRP; usual care Median age (range), years: 50.0 (18–83); 44 (18–82)	Interventions: single POC CRP to guide antibiotic decisions: < 11 mg/l, 11–49 mg/l and > 50 mg/l. Nycocard II Reader (Axis-Shield, Norway) Comparator: usual care	*Data from Smedemark 2022* Antibiotics prescribed at index consultation (number of events/number of participants) CRP: 54/108 Usual care: 68/131 RR 0.96 (95% CI 0.75 to 1.24) Antibiotics prescribed within 28 days (number of events/number of participants) CRP: 61/108 Usual care: 78/131 RR 0.95 (95% CI 0.76 to 1.18) Number of participants substantially improved within 7 days (number of events/number of participants) CRP: 46/102 Usual care: 53/128 RR 0.94 (95% CI 0.75 to 1.18) Number of participants substantially improved within 28 days (number of events/number of participants) CRP: 71/98 Usual care: 82/121 RR 0.85 (95% CI 0.57 to 1.29)	Number of patients not reported for primary diagnosis of total upper ARI, pneumonia, exacerbations of COPD or asthma, other respiratory diseases. Study terminated early due to interim analysis showing no difference between groups and lack of interest in participating practices. Original data from Melbye 1995 not presented here as the full text is not English language.

continued

TABLE 11 Included studies of CRP tests (*continued*)

Study details	Participants	Interventions	Outcomes and results	Comments
QuikRead CRP				
Boere 2021[38] From Smedemark 2022[16] Boere 2022[39] The Netherlands Open-label cluster RCT, 11 nursing homes Study dates: September 2018–March 2020 Source of funding: non-commercial Follow-up: 3 weeks	Sample size: 241 CRP 162 (6 nursing homes), usual care 79 (5 nursing homes) Inclusion criteria: somatic, psychogeriatric, and short-stay nursing home residents with suspected LRTI Exclusion criteria: current or recent infection or use of antibiotics Key characteristics CRP; usual care Mean age (SD), years: 84.3 (8.1); 84.5 (8.4) Cerebrovascular accident, %: 20, 19 Congestive heart failure, %: 31, 24 COPD, %: 30, 37 Dementia, %: 28, 32 Diabetes, %: 18, 23 Kidney failure, %: 2, 3	Interventions: single POC CRP to guide antibiotic decisions. Dutch LRTI guideline recommendations: < 20 mg/l, 20–60 mg/l and > 60 mg/l. QuikRead Go CRP, Aidian, Espoo, Finland Comparator: usual care	*Data from Boere 2021* Antibiotics prescribed at index consultation (number of events/number of participants) CRP: 84/162 Usual care: 65/79 Mortality within 3 weeks (number of events/number of participants) CRP: 5 (3.5%) Usual care: 1 (1.3%) OR 2.76 (0.32 to 24.04) Hospital admission within 3 weeks (number of events/number of participants) CRP: 10 (7.2%) Usual care: 5 (6.5%) OR 1.12 (0.37 to 3.39) Number of participants fully recovered at 3 weeks (number of events/number of participants) CRP: 121 (86.4%) Usual care: 69 (90.8%) OR 0.49 (0.21 to 1.12) Hospitalisation at initial consultation CRP: 1 (1%) Usual care: 0 Hospitalisation at 1 week CRP: 3 (2%) Usual care: 4 (5%) Hospitalisation at 3 weeks CRP: 6 (4%) Usual care: 1 (1%) Antibiotic treatment changes (start, cessation, switch, or prolongation) CRP: 36 (12.2%) Usual care: 26 (16.8%) OR 0.53 (95% CI 0.26 to 1.08) Subgroups COPD Antibiotics prescribed at index consultation CRP: 20/45 (44.4%) Usual care: 23/29 (79.3%)	Number of people with events and proportions reported in Boere 2021 for mortality, hospital admissions, recovery and changes in treatment do not align with the original sample sizes in each group, reasons unclear.

TABLE 11 Included studies of CRP tests (*continued*)

Study details	Participants	Interventions	Outcomes and results	Comments
Cals 2010[40] From Smedemark 2022[16] The Netherlands Open-label RCT, 11 primary care practices Study dates: November 2007–April 2008 Source of funding: Orion Diagnostica Espoo, Finland Follow-up: 28 days	Sample size: 258 patients CRP 129, usual care 129 Inclusion criteria: age ≥ 18 years; suspected acute lower RTI (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign); or rhinosinusitis (< 4 weeks, + 2 symptoms or signs) Exclusion criteria: immediate requirement of hospital admission; antibiotic use or hospitalisation within the previous 14 days; immunocompromised status Key characteristics CRP; usual care Mean age (SD), years: 43.0 (13.4), 45.5 (14.0) COPD, %: 5, 3 Asthma, %: 10, 9 Allergic rhinitis, %: 13, 12 Diabetes, %: 9, 4 Heart disease, %: 6, 8	Interventions: single POC CRP to guide antibiotic decisions: < 20 mg/l, 20–99 mg/l and > 100 mg/l. QuikRead CRP analysers (Orion Diagnostica, Espoo, Finland) Comparator: usual care	*Data from Smedemark 2022* Antibiotics use after index consultation (immediate prescription or delayed prescription and filled) (number of events/number of participants) CRP: 56/129 Usual care: 73/129 RR 0.77 (95% CI 0.60 to 0.98) Antibiotics prescribed within 28 days (number of events/number of participants) CRP: 68/129 Usual care: 84/129 RR 0.81 (95% CI 0.66 to 1.00) Mortality within 28 days (number of events/number of participants) CRP: 0/129 Usual care: 0/129 Hospital admissions within 28 days (number of events/number of participants) CRP: 0/129 Usual care: 0/129 Number of re-consultations within 28 days (number of events/number of participants) CRP: 33/129 Usual care: 23/129 RR 1.43 (95% CI 0.89 to 2.30) Number of participants substantially improved within 7 days (number of events/number of participants) CRP: 27/118 Usual care: 31/125 RR 1.03 (95% CI 0.89 to 1.18) *Data from Cals 2010* Antibiotics prescribed at index consultation (immediate prescription) (number of events/number of participants) CRP: 51/129 Usual care: 52/129 Antibiotics prescribed at index consultation (delayed prescription) (number of events/number of participants) CRP: 22/129 (prescription filled by 5) Usual care: 29/129 (prescription filled by 21) Patient-reported time to full recovery (days), mean (SD) LRTI CRP (n = 51): 17.5 (9.2) Usual care (n = 49): 19.8 (9.5) Rhinitis CRP (n = 67): 17.3 (9.3) Usual care (n = 76): 16.6 (9.9)	The RRs reported in Smedemark 2022 for antibiotics prescribed at index consultation and 28 days differ to those reported in the original study [RR 0.77 (95% CI 0.56 to 0.98) and RR 0.81 (95% CI 0.62 to 0.99), respectively]. These figures are noted in Smedemark 2022, but the reasons for the difference are not described.

continued

TABLE 11 Included studies of CRP tests (*continued*)

Study details	Participants	Interventions	Outcomes and results	Comments
Little 2013[41] Little 2019[42] From Smedemark 2022[16] Belgium, UK, Poland, Spain, The Netherlands Open-label cluster RCT, 246 primary care practices at baseline, 178 at 12 months Study dates: February 2011–May 2012 Source of funding: non-commercial Follow-up: 28 days[41] 12 months[42]	Sample size: 1932 patients with upper or lower RTI CRP 1062 (58 practices), usual care 870 (53 practices) Inclusion criteria: adults (> 18 years) consulting for the first time with upper or lower RTI Exclusion criteria: a non-infective working diagnosis (e.g. pulmonary embolus, heart failure, oesophageal reflux, allergy); antibiotic use in the previous month; pregnant; immunological deficiencies Key characteristics Not reported for the two interventions of relevance	Interventions: single POC CRP to guide antibiotic decisions: < 20 mg/l, 21–50 mg/l, 51–99 mg/l and > 100 mg/l. QuikRead CRP, Orion Diagnostica (Espoo, Finland) Comparator: usual care	*Data from Little 2013* Resolution of moderately bad symptoms, median (IQR), time (days) CRP: 5 (3–8) Usual care: 5 (3–7) Basic HR 0.97 (95% CI 0.82 to 1.15)[e] Adjusted HR 0.87 (95% CI 0.74 to 1.03)[e] Number of re-consultations within 28 days (for new or worsening symptoms) (number of events/number of participants) CRP: 207/760 Usual care: 102/861 RR 1.91 (95% CI 1.26 to 2.77)[f] Adjusted RR 1.75 (1.12 to 2.60)[e] Hospital admissions within 4 weeks (number of events/number of participants) CRP: 10/1062 Usual care: 2/870 Mortality (number of events/number of participants) CRP: 0/1062 Usual care: 0/870	Four practices in the CRP group and 14 in the usual care group did not manage to recruit any patients. Two additional intervention arms were included in Little 2013 and 2019, but data are not reported as they are not relevant to the current review: CRP test + communication training group; usual care group + communication training group. Results reported with the groups combined not extracted.

TABLE 11 Included studies of CRP tests (*continued*)

Study details	Participants	Interventions	Outcomes and results	Comments
				It was unclear where data reported in Smedemark 2022 on antibiotics prescribed at index consultation originated from as these data do not appear to be reported. In Little 2013 data are at 3 months follow-up of the GP practices. There were no new data in Little 2019. Little 2019 is a follow-up study to Little 2013, but it appears that participating clinicians were able to recruit additional participants and no data of relevance to the review were reported.

IPD, individual patient data; NR, not reported; SE, standard error; SR, systematic review.

a Model adjusts for Anthonisen criteria.

b Model adjusts for Anthonisen criteria and corresponding EQ-5D-5L score at baseline as a covariate.

c Calculated and inflated for clustering by using SD inflated by variance inflation factor.

d The adjusted model additionally controlled for diagnosis (upper or lower RTI, pneumonia), sex, age, presence of cough, phlegm, shortness of breath, blocked/runny nose, chest pain, fever, muscle ache, headache, disturbed sleep, feeling generally unwell, interference with social activities, earache, sore throat, facial/sinus pain, crackles, wheeze, pulse > 100 beats per minute, temperature > 37.8 °C, respiratory rate, physician's rating of severity, low blood pressure, duration of cough and duration of illness before consultation.

e The adjusted model additionally controlled for age, smoking, sex, major cardiovascular or respiratory comorbidity, baseline symptoms, crepitations, wheeze, pulse > 100 beats per minute, temperature > 37.8 °C, respiratory rate, blood pressure, physician's rating of severity, and duration of cough.

f The basic model adjusted for baseline prescribing and clustering by physician and practice.

TABLE 12 Included studies of procalcitonin tests

Study details	Participants	Interventions	Outcomes and results	Comments
BRAHMS PCT procalcitonin				
Lhopitallier 2021[43] From Smedemark 2022[16] Switzerland Open-label cluster RCT, 60 primary care practices (36 practices with recruited patients in the relevant trial arms) Study dates: September 2018–March 2020 Source of funding: non-commercial (POCT kits were provided by the manufacturer) Follow-up: 28 days	Sample size: 469 patients with lower RTI/acute cough Procalcitonin 195 (19 practices with recruited patients), usual care 122 (17 practices with recruited patients) Inclusion criteria: adults > 18 years with acute cough < 21 days and at least one of the following signs/symptoms: history of fever for more than 4 days, dyspnoea, tachypnoea (> 22 cycles per minute), abnormal focal findings upon lung auscultation Exclusion criteria: previous antibiotics for the current episode; working diagnosis of acute sinusitis or of a non-infective disorder; previous episode of COPD exacerbation treated with antibiotics during the last 6 months; known pregnancy; severe immunodeficiency Key characteristics Procalcitonin; usual care Mean age (SD), years: 53 (18.0), 50 (18.0) Heart failure, %: 2, 0 Diabetes, %: 7, 3 COPD, %: 9, 7 Asthma, %: 19, 11 Active malignancy, %: 2, 0	Interventions: POC procalcitonin to guide antibiotic decisions: < 25 µg/l and ≥ 25 µg/l. BRAHMS PCT direct POCT Comparator: usual care	*Data from Smedemark 2022* Antibiotics prescribed at index consultation (number of events/number of participants) Procalcitonin: 35/195 Usual care: 69/122 RR 0.32 (95% CI 0.23 to 0.44) Number of re-consultations within 28 days (number of events/number of participants) Procalcitonin: 53/195 Usual care: 33/122 RR 1.00 (95% CI 0.69 to 1.46) Hospital admissions within 7 days (number of events/number of participants, per protocol population) Procalcitonin: 4/163 Usual care: 2/114 RR 1.40 (95% CI 0.26 to 7.51) *Data from Lhopitallier 2021* Antibiotics prescribed within 7 days (number of events/number of participants) Procalcitonin: 58/195 Usual care: 75/122 Antibiotics prescribed within 28 days (number of events/number of participants) Procalcitonin: 78/195 Usual care: 86/122 Mortality within 28 days (number of events/number of participants) Procalcitonin: 0/163 Usual care: 0/114 Censored duration of symptoms by day 28 (days), median Procalcitonin (*n* = 159): 8 Usual care (*n* = 102): 7 Duration difference 1.0 (95% CI -0.39 to 2.43) HR 0.81 (95% CI 0.62 to 1.04)	A third intervention group included UltraPro (*n* = 152) where lung ultrasonography was performed due to procalcitonin concentration ≥ 25 µg/l. Smedemark 2022 reports antibiotics prescribed within 28 days, but the numbers of events differ from those in Lhopitallier 2021 and seem unrealistically low. Smedemark 2022 reports number of participants substantially improved, but the data appear to be the number with 'persisting symptoms at day 7' in Lhopitallier 2021. Unclear why the number of participants for 'duration of symptoms' is lower.

POC, point-of-care.

TABLE 13 Included studies of GAS tests

Study details	Participants	Interventions	Outcomes and results	Comments
RADT OSOM® Strep A				
Llor 2011[44] Spain Open-label cluster RCT, 20 primary healthcare centres Study dates: January–May 2008 Source of funding: non-commercial Follow-up: NR	Sample size: 557 patients RADT 285 (10 centres, 33 GPs), usual care 272 (10 centres, 28 GPs) Inclusion criteria: patients aged 14–60 years with acute pharyngitis and ≥ 1 of: fever, tonsillar exudate, tender enlarged anterior cervical lymph nodes, or absence of cough. Exclusion criteria: patients with > 5 episodes of pharyngitis over the last year; immunosuppressed condition; heart valve disease; rheumatic fever; an episode of pharyngitis treated with antibiotics in the previous 15 days; and tonsillectomy. Key characteristics RADT; usual care Mean age (SD; range), years: 31.8 (11.5), 31.5 (11.4)	Interventions: RADT OSOM® Strep A test (Genzyme) Comparator: usual care	Antibiotics prescribed at index consultation (number of events/number of participants) RADT: 123/281 Usual care: 168/262, $p < 0.001$	Includes patients aged ≥ 14 years, slight difference to current review criteria. The unit of randomisation was the healthcare centre to avoid contamination among physicians working in the same centre. The RADT was undertaken in 280 (99.6%) of participants in the intervention arm. The RADT was also undertaken in 5 (1.9%) of participants in the usual care arm. Patients excluded for incomplete data: RADT: $n = 4$ Usual care: $n = 10$
RADT Clearview® Exact Strep A				
Worrall 2007[45] Canada Open-label cluster RCT, 37 family doctors' offices (19 in relevant trial arms) Study dates: February–April 2005 Source of funding: NR Follow-up: NR	Sample size: total 533 adults, RADT 120 (10 GPs), usual care 141 (9 GPs) Inclusion criteria: patients aged ≥ 19 years with acute sore throat as primary symptom. Exclusion criteria: NR Key characteristics Not reported separately for two relevant treatment groups.	Interventions: RADT Clearview® Exact Strep A dipstick from Wampole Laboratories Comparator: usual care	Antibiotics prescribed at index consultation (number of events/number of participants) RADT: 32/120 Usual care: 82/141, $p < 0.001$	The study included two additional intervention arms not relevant to the current rapid review (simple sore throat decision rules with or without RADT). Authors acknowledged potential clustering of patients by physician.

NR, not reported.

TABLE 14 Included studies of influenza tests

Study details	Participants	Interventions	Outcomes and results	Comments
BD Directigen™ Flu A + B rapid test (not currently available in the UK)				
Berthod 2015[46] NCT00821626[49] Switzerland Open-label RCT, two hospital outpatient clinics Study dates: December 2008–November 2012 Source of funding: NR Follow-up: NR	Sample size: total 93 adults RADT 60, usual care 33 Inclusion criteria: patients aged ≥ 18 years, documented fever ≥ 38 °C or anamnestic fever + cough or sore throat within the last 4 days; illness occurring within 14 days after returning from a trip abroad. Exclusion criteria: definitive alternative diagnosis. Key characteristics RADT; usual care Median age (range), years: 35 (18–79), 35 (18–70)	Interventions: BD Directigen A + B performed on the nasopharyngeal swab (Becton and Dickinson, Maryland, USA) Comparator: usual care	Antibiotics prescribed at index consultation (number of events/number of participants) RADT: 14/60 Usual care: 13/33, $p = 0.15$ No patient received antiviral treatment Mortality (number of events/number of participants) RADT: 0/60 Usual care: 0/33	Six patients had significant comorbidities: asthma ($n = 3$), treated HIV infection ($n = 1$), status post stem cell transplantation 3 years earlier ($n = 1$) and pregnancy ($n = 1$); it was unclear which treatment arms these patients were assigned to. Trial finished early due to low sensitivity of the intervention.

HIV, human immunodeficiency disorder; NR, not reported.

Appendix 3 Explanation of sample size adjustment

An adjustment to the sample size must be made to cluster trials before they can be included in a meta-analysis with individually randomised trials. Instead of extracting this adjusted data from the Smedemark[16] review directly, we decided to also perform the calculations. We carried out this adjustment by dividing the total numbers in each arm and the event numbers in each arm by a quantity called the 'design effect', as advised in the Cochrane Handbook.[17] The design effect for each cluster randomised trial can be calculated using the below formula:

$1 + (M-1) \times ICC$

where *M* is the average cluster size and ICC is the intracluster correlation coefficient. We estimated the average cluster size by dividing the total sample size by the number of clusters in each trial. We believe this is the same approach that the Smedemark authors followed.

After using the above-described adjustment, our numbers differed slightly to those presented in the Smedemark review[16] for some trials.[38,41,42] Since the raw numbers extracted from primary studies are not presented in the said review, it is difficult to fully account for these differences. Here, we present values used in the calculation of the design effect, then we compare our adjusted sample sizes to those presented in Smedemark and discuss potential reasons for the discrepancies.

Table 15 shows the parameters used in the calculation of the design effect for each included study and outcome. *Table 16* shows the adjusted sample size numbers we calculated and those presented in the Smedemark[16] review.

Andreeva[29] did not report the ICC value which means the design effect cannot be calculated. Smedemark[16] contacted the Andreeva[29] authors and obtained additional information. We presume they obtained the ICC value which allowed them to calculate the adjusted sample sizes presented in the review. The review also included two additional outcomes ['Number of re-consultations within 14 days' and 'Hospital admission (time frame unclear)'] that were not presented in the Andreeva paper, which we assume were also obtained when the review authors contacted the Andreeva authors. Therefore, we used the adjusted numbers presented in the Smedemark review for the Andreeva study (see *Table 16*).

The adjusted numbers that we calculated for Boere[38] are almost identical to the Smedemark review[16] (see *Table 16*). There are small differences for outcomes 'Hospital admission within 3 weeks' and 'Mortality rate within 3 weeks', but we believe these are likely due to rounding and will have a negligible impact on the resulting meta-analysis. For this study, we included an additional outcome ('Antibiotic use at index consultation; COPD patients') that was not included in the review.

We noticed an inconsistency in the reported primary outcome numbers in Boere.[38] In the abstract, the paper reports *n* = 84 patients prescribed antibiotics at index consultation in the CRP test group. However, *Table 16* infers that this value should be 89 (73 antibiotic prescriptions avoided; 162–73 = 89). We believe Smedemark[16] used *n* = 84 for the number of antibiotics prescribed at index consultation in the CRP group and we too chose to use this value.

Our calculated adjusted values match the numbers presented in Smedemark exactly for the Cals[33,34] study. Note however that the Cals paper reports an ICC of 0.01 for the outcome of 'Number of re-consultations within 28 days', which is different to the ICCs (0.12) for outcomes 'Antibiotics prescribed at index consultation' and 'Antibiotics prescribed within 28 days'. We believe Smedemark used 0.12 in the adjustment of all outcomes. We obtained data for mortality and hospitalisation from the text in Cals ['no serious adverse events (death or admission to hospital) occurred'], meaning that there were no reported ICCs for these outcomes. Therefore, for consistency across all outcomes and with the Smedemark review, we chose to use an ICC of 0.12 for all outcomes from Cals. For the outcomes extracted from the text, we assumed the denominators were equal to those for the other reported outcomes (*n* = 227 CRP group; *n* = 204 usual care group).

TABLE 15 Numbers and event numbers in each arm for each included outcome and detail of information used to calculate the design effect

Trial	Outcome	*n* CRP	*N* CRP	*n* usual care	*N* usual care	Number of clusters CRP	Number of clusters usual care	*M*	ICC	Design effect
Andreeva[29]	Antibiotic use at index consultation	38	101	46	78	8	9	10.5	–	–
Andreeva[29]	Antibiotics prescribed within 14 days	41	101	56	78	8	9	10.5	–	–
Andreeva[29]	Number of re-consultations within 14 days[a]	–	–	–	–	8	8	–	–	–
Andreeva[29]	Hospital admission (time frame unclear)[a]	–	–	–	–	8	9	–	–	–
Boere[38]	Antibiotic use at index consultation	84[b]	162	65	79	6	5	21.9	0.175	4.66
Boere[38]	Hospital admission 3 weeks	10	139	5	77	6	5	19.6	0.175	4.26
Boere[38]	Mortality rate within 3 weeks	5	143	1	77	6	5	20.0	0.175	4.33
Boere[38]	Antibiotic use at index consultation; COPD patients	20	45	23	29	6	5	4.33	0.175	2.00
Cals[33,34]	Antibiotics prescribed at index consultation	70	227	108	204	10	10	21.6	0.12	3.47
Cals[33,34]	Antibiotics prescribed within 28 days	102	227	119	204	10	10	21.6	0.12	3.47
Cals[33,34]	Number of re-consultations within 28 days	79	227	62	204	10	10	21.6	0.12	3.47
Cals[33,34]	Hospital admission 28 days[c]	0	227	0	204	10	10	21.6	0.12	3.47
Cals[33,34]	Mortality rate within 3 weeks[c]	0	227	0	204	10	10	21.6	0.12	3.47
Little[41]	Antibiotics prescribed within 3 months	368	1062	508	870	58	53	17.4	0.05[d]	1.82
Little[41]	New or worse symptoms within 28 days	207	760	102	861	58	53	14.6	0.05[d]	1.68
Little[41]	Hospital admissions (time frame unclear)[c]	10	1062	2	870	58	53	17.4	0.05[d]	1.82
Little[41]	Mortality (time frame unclear)[c]	0	1062	0	870	58	53	17.4	0.05[d]	1.82

ICC, intracluster correlation; *M*, average cluster size; *n*, number of events; *N*, total number in arm.

a Raw data not presented in paper.

b Number of antibiotics prescribed in CRP group given as *n* = 84 in abstract. Number of antibiotics prescribed (calculated from *Table 12*) is *n* = 89.[38] *N* = 84 used for consistency with Smedemark review.

c Numbers taken from text. Denominators (i.e. total numbers in respective groups) assumed the same as at baseline.

d See appendix of Little.[41]

TABLE 16 Adjusted sample size calculated using the design effect and the adjusted sample size numbers used in Smedemark review[16]

Trial	Outcome	Adjusted *n* CRP	Adjusted *N* CRP	Adjusted *n* usual	Adjusted *N* usual	Adjusted *n* CRP[16]	Adjusted *N* CRP[16]	Adjusted *n* usual[16]	Adjusted *N* usual[16]
Andreeva[29]	Antibiotic use at index consultation	–	–	–	–	18	49	23	38
Andreeva[29]	Antibiotics prescribed within 14 days	–	–	–	–	20	49	27	38
Andreeva[29]	Number of reconsultations within 14 days	–	–	–	–	1	49	1	38
Andreeva[29]	Hospital admission (time frame unclear)[c]	–	–	–	–	0	49	0	38
Boere[38]	Antibiotic use at index consultation	18	35	14	17	18	35	14	17
Boere[38]	Hospital admission within 3 weeks	2	33	1	18	1	32	1	17
Boere[38]	Mortality rate within 3 weeks	1	33	1	18	2	32	1	17
Boere[38]	Antibiotic use at index consultation; COPD patients	10	22	11	14	–	–	–	–
Cals[33,34]	Antibiotics prescribed at index consultation	20	65	31	59	20	65	31	59
Cals[33,34]	Antibiotics prescribed within 28 days	29	65	34	59	29	65	34	59
Cals[33,34]	Number of re-consultations within 28 days	23	65	18	59	23	65	18	59
Cals[33,34]	Hospital admission 28 days[a]	0	65	0	59	0	65	0	59
Cals[33,34]	Mortality rate within 3 weeks[a]	0	65	0	59	0	65	0	59
Little[41]	Antibiotics prescribed within 3 months[b]	202	583	279	478	–	–	–	–
Little[41]	Antibiotics prescribed at index consultation	–	–	–	–	304	920	407	884
Little[42]	Antibiotics prescribed at index consultation	–	–	–	–	476	1068	468	1024
Little[41]	New or worse symptoms within 28 days[b]	123	452	61	512	165	894	149	812
Little[41]	Hospital admissions (time frame unclear)[a,b]	5	583	1	478	4	920	1	844
Little[41]	Mortality (time frame unclear)[a,b]	0	583	0	478	0	920	0	844

ICC, intracluster correlation; *M*, average cluster size; *n*, number of events; *N*, total number in arm.
a Numbers taken from text. Denominators (i.e. total numbers in respective groups) assumed the same as at baseline.
b Different ICC used in calculation compared to Smedemark review.

The Little[41,42] study used a 2 x 2 factorial design and randomised patients to one of four interventions: CRP test, usual care, CRP test with GP communication training and usual care with GP communication training. In the main analysis, the authors combined these four groups and adjusted for the effect of communication training. In other words, the CRP and CRP + communication training groups were combined, and the usual care and usual care + communication training groups were combined, and the model adjusted for the effect of communication training. We believe the Smedemark[16] review used these combined numbers in the calculation of the adjusted sample size. However, since the raw numbers of these groups combined do not adjust for communication training, we decided to use the numbers for CRP test only versus usual care only and used the corresponding number of clusters for these groups. We extracted numbers from the *Report Supplementary Material 1* given in Little 2013[41] for 're-consultations for new or worse symptoms within 28 days'.

Further, we believe the authors of the Smedemark[16] review have incorrectly interpreted the timescale of the primary outcome. The time frame for the primary outcome (antibiotic prescribing) is unclear from the Little (2013)[41] paper. Smedemark believe that the primary outcome refers to 'Antibiotics prescribed at index consultation'. However, we believe that this outcome actually reflects the antibiotics prescribed within 3 months. This is clearer in the Little (2019)[42] publication. The authors state that in the usual care group '58% (508 of 870) were prescribed antibiotics at 3 months' and in the CRP group '(368 of 1062) at 3 months'. These values match those presented in the Little (2013)[41] publication *Report Supplementary Material 1*. We therefore exclude Little (2013)[41] from our meta-analysis of antibiotic use at index consultation.

In addition, we believe Smedemark[16] used an ICC of 0.08 in their calculations. However, we chose to use an ICC of 0.05 since this ICC controls for baseline antibiotic prescribing [see *Report Supplementary Material 1*; Little (2013)[41]]. Finally, we extracted data for outcomes 'Hospital admissions (time frame unclear)' and 'Mortality (time frame unclear)' from the text of Little (2013)[41] ['30 patients were reported as being admitted to hospital (2 in the usual care group, 10 in the CRP group'); 'No patients died']. We assumed the denominators were the same as at the beginning of the study (n = 1062 CRP group; n = 870 usual care group).

These reasons combined explain the marked differences in the adjusted sample sizes for the Little[41,42] study. No additional outcome data were obtained from the Little (2019)[42] publication.

Appendix 4 Quality assessment of included randomised controlled trials

TABLE 17 Risk of bias: CRP tests

Study	Random sequence generation[a]	Allocation concealment[a]	Blinding of participants and personnel[a]	Blinding of outcome assessment		Incomplete outcome data		Selective reporting[a]	Other bias[a]
				Key outcomes[b]	Other outcomes[c]	Key outcomes[b]	Other outcomes[c]		
Althaus 2019[32]	Low risk	Low risk	High risk	1. N/A 2. N/A 3. N/A	Low risk	1. N/A 2. N/A 3. N/A	Unclear risk	Low risk	Unclear risk
Andreeva 2014[29]	Low risk	Unclear risk	High risk	1. N/A 2. N/A 3. N/A	Unclear risk	1. N/A 2. N/A 3. N/A	Low risk	Low risk	High risk
Boere 2021,[38] Boere 2022,[39]	Low risk	Unclear risk	High risk	1. Low risk 2. N/A 3. Low risk	Low risk	1. High risk 2. N/A 3. High risk	Unclear risk	Low risk	High risk
Butler 2019[30]	Low risk	Low risk	High risk	1. Low risk 2. N/A 3. Low risk	Low risk	1. Low risk 2. N/A 3. Low risk	High risk	Low risk	Low risk
Cals 2009[33,34]	Low risk	Unclear risk	High risk	1. Low risk 2. N/A 3. Low risk	Low risk	1. Unclear risk 2. N/A 3. Unclear risk	Low risk	Low risk	High risk
Cals 2010[40]	Low risk	Low risk	High risk	1. Low risk 2. N/A 3. Low risk	Low risk	1. Low risk 2. N/A 3. Low risk	Low risk	Low risk	Low risk
Diederichsen 2000[35]	Low risk	Unclear risk	High risk	1. N/A 2. N/A 3. N/A	Low risk	1. N/A 2. N/A 3. N/A	Low risk	Unclear risk	Unclear risk

TABLE 17 Risk of bias: CRP tests (*continued*)

Study	Random sequence generation[a]	Allocation concealment[a]	Blinding of participants and personnel[a]	Blinding of outcome assessment		Incomplete outcome data		Selective reporting[a]	Other bias[a]
				Key outcomes[b]	Other outcomes[c]	Key outcomes[b]	Other outcomes[c]		
Do 2016[36]	Low risk	Low risk	High risk	1. Unclear risk 2. N/A 3. N/A	Low risk	1. Unclear risk 2. N/A 3. N/A	High risk	Low risk	Low risk
Little 2013,[41] Little 2019[42]	Low risk	Unclear risk	High risk	1. Low risk 2. N/A 3. Low risk	Low risk	1. Low risk 2. N/A 3. Low risk	Unclear risk	Low risk	High risk
Melbye 1995[37] [f]	Unclear risk	Unclear risk	High risk	Low risk[d,e]	High risk[d,f]	Low risk[d,e]	Low risk[d,f]	Unclear risk	Unclear risk

N/A, not applicable.
a Risk-of-bias judgements from Smedemark 2022.[16]
b Reviewer's judgement on key protocol outcomes: (1) 7- or 28-day mortality, (2) escalation of care (including unplanned admission) and (3) hospital admission (immediately after triage or at 28 days).
c Reviewer's judgement on other outcomes: antibiotic/antiviral use, hospital length of stay, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms, HRQoL (using a validated scale).
d Original data from Melbye (1995) have not been assessed for risk of bias by reviewers as the full text was not available and is a non-English-language publication.
e Antibiotic prescribing.
f Recovery, re-consultations, satisfaction.

TABLE 18 Justification for risk-of-bias judgements

Bias	Reviewer's judgement	Justification for reviewer's judgement
Althaus 2019[32]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. N/A	N/A
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use	Low risk	The data on prescribing were recorded independently on site and the outcome was assessed centrally.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. N/A	
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use	Unclear risk	Only antibiotic use reported and not reported separately in adults in the primary publication.
Andreeva 2014[29]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. N/A	Hospital admissions reported in Smedemark 2022 SR but not reported in primary study.
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring	Unclear risk	Details not provided.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. N/A	Hospital admissions reported in Smedemark 2022 SR but not reported in primary study.
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring	Low risk	Data available for all patients for antibiotic use and > 95% patients for clinical recovery.
Boere 2021[38,39]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Low risk 2. N/A 3. Low risk	The study used electronic case report forms that were integrated into the electronic patient record system. Forms were automatically uploaded to the research team's secure database portal.
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, time to clinical cure/resolution of symptoms	Low risk	eCRFs were used and integrated into the nursing home electronic patient record system.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. High risk 2. N/A 3. High risk	The number of people with events and percentages reported do not align with the original sample sizes in each group, the reasons for this is unclear.
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, time to clinical cure/resolution of symptoms	Unclear risk	Baseline eCRFs were missing for three participants, and additionally data were missing for 2 participants for the outcome antibiotic prescribing at baseline and for 25 participants for the outcome full recovery at 3 weeks.

TABLE 18 Justification for risk-of-bias judgements (*continued*)

Bias	Reviewer's judgement	Justification for reviewer's judgement
Butler 2019[30]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Low risk 2. N/A 3. Low risk	Clinicians recorded their management decisions after randomisation on a case report form.
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, HRQoL (using a validated scale)	Low risk	Clinicians recorded their antibiotic prescribing and other management decisions after randomisation on a case report form.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Low risk 2. N/A 3. Low risk	All patients assessed for mortality; 607/649 (93.5%) assessed for hospital admissions.
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, HRQoL (using a validated scale)	High risk	The authors state that 537/649 (82.7%) patients were analysed for antibiotic use at later follow-up. 607/649 (93.5%) patients were included in analysis for follow-up consultations; unclear number of patients assessed for certain HRQoL outcomes.
Cals 2009[33,34]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Low risk 2. N/A 3. Low risk	Data were obtained from the medical records of patients for the 28 days follow-up.
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms	Low risk	Antibiotic prescribing and re-consultation data for the 28 days of follow-up were obtained from the participants' medical records.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Unclear risk 2. N/A 3. Unclear risk	The number of patients assessed was not reported.
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms	Low risk	All patients analysed for antibiotic use and all patients appear to have been analysed for re-consultations.
Cals 2010[40]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Low risk 2. N/A 3. Low risk	After day 28, the electronic medical records were accessed from the physicians' databases to retrieve relevant information on antibiotic prescriptions, additional consultations, relevant comorbidity, and complications.
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms	Low risk	After day 28, the electronic medical records were accessed from the physicians' databases to retrieve relevant information on antibiotic prescriptions, additional consultations, relevant comorbidity, and complications.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Low risk 2. N/A 3. Low risk	Data available for all patients.

continued

TABLE 18 Justification for risk-of-bias judgements (*continued*)

Bias	Reviewer's judgement	Justification for reviewer's judgement
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms	Low risk	All patients analysed for antibiotic use; other outcome data available for 94% patients.
Diederichsen 2000[35]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. N/A	
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use	Low risk	GPs registered relevant data and returned the registration chart to the project leader.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. N/A	
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use	Low risk	Data available for all patients.
Do 2016[36]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Unclear risk 2. N/A 3. N/A	Details not provided
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, time to clinical cure/resolution of symptoms	Low risk	The conductors of the 2-week telephone interview were blinded to the intervention received by the interviewee.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Unclear risk 2. N/A 3. N/A	No deaths occurred in either group, but it was unclear whether data were available for all patients.
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, time to clinical cure/resolution of symptoms	High risk	Data available for all patients for immediate antibiotic prescription, but high number of patient data missing for subsequent antibiotic use (per-protocol analysis). The number of patients assessed for time to resolution of symptoms was not reported.
Lhopitallier 2021[43]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Low risk 2. Low risk 3. Low risk	A standardised phone interview was conducted on days 7 and 28 by a study team member who was blinded to the intervention arm.
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms	Low risk	A standardised phone interview was conducted on days 7 and 28 by a study team member who was blinded to the intervention arm.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. High risk 2. Low risk 3. Low risk	Data available for 87% of patients.

TABLE 18 Justification for risk-of-bias judgements (*continued*)

Bias	Reviewer's judgement	Justification for reviewer's judgement
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms	Unclear risk	Data were missing for the primary outcome but unclear how many missing from each intervention group.
Little 2013[41]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Low risk 2. N/A 3. Low risk	The study used a specially designed case report form and network facilitators uploaded data centrally.
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms	Low risk	The study used a specially designed case report form and network facilitators uploaded data centrally.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Low risk 2. N/A 3. Low risk	Data appear to be available for all patients.
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms	Unclear risk	Antibiotic use available for all patients and 96.7% patients reporting re-consultations. Antibiotic use at 12 months only 74% practices provided data.
Berthod 2015[46]		
Random sequence generation (selection bias)	High risk	Patients were randomly assigned to have an iRDT or not; one of the investigators flipped a coin to decide whether an iRDT had to be done or not.
Allocation concealment (selection bias)	High risk	
Blinding of participants and personnel (performance bias) All outcomes	High risk	The results of the iRDT were available to the attending physician for further medical management.
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Unclear risk 2. N/A 3. N/A	No details provided.
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring	Unclear risk	No details provided.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. Low risk 2. N/A 3. N/A	Data available for 93% patients.
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring	Low risk	Data available for 93% patients.
Selective reporting (reporting bias)	Low risk	Outcomes pre-specified and data reported.

continued

TABLE 18 Justification for risk-of-bias judgements (*continued*)

Bias	Reviewer's judgement	Justification for reviewer's judgement
Other bias	High risk	Interim analysis revealed that the sensitivity of the iRDT was much lower than expected and that the primary objectives of the study could not be reached. The planned number of patients was 400 but only 100 were included (a selected population including only febrile patients for whom no alternative diagnosis had been established after the first medical consultation).
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. Low risk	Data appear to be available for all patients.
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms	Low risk	Data on antibiotic use available for all patients.
Llor 2011[44]		
Random sequence generation (selection bias)	Low risk	Primary healthcare centres were randomised to the intervention or to the control arm of the study, with an allocation ratio of 1 : 1, by a random sequence generated by a computer program.
Allocation concealment (selection bias)	High risk	Physicians allocated to the intervention group were provided with RADT and those assigned to the control group managed streptococcal pharyngitis with only clinical criteria.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not possible to blind participants, patients or doctors.
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. N/A	N/A
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, time to clinical cure/resolution of symptoms	Low risk	Data were analysed blinded to treatment group allocation (taken from study protocol – Madurell 2010).
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. N/A	N/A
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use, time to clinical cure/resolution of symptoms	Low risk	Data available on 97.5% of patients.
Selective reporting (reporting bias)	Unclear risk	Outcomes pre-specified but some secondary outcomes (satisfaction, days without working) not reported.
Other bias	High risk	Risk of selection bias due to cluster-randomised design. The centres and practitioners participating in the study may have been more motivated than others.

TABLE 18 Justification for risk-of-bias judgements (*continued*)

Bias	Reviewer's judgement	Justification for reviewer's judgement
Worrall 2007[45]		
Random sequence generation (selection bias)	High risk	The 40 physicians who agreed to take part in the study were randomly allocated to 1 of 4 trial arms, and they then recruited 20 successive adult patients.
Allocation concealment (selection bias)	High risk	
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided.
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. N/A	N/A
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use	Unclear risk	No details provided.
Incomplete key outcome data (attrition bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	1. N/A 2. N/A 3. N/A	N/A
Incomplete other outcome data (attrition bias) Antibiotic/antiviral use	Low risk	Data available on all patients.
Selective reporting (reporting bias)	Low risk	One outcome assessed and reported.
Other bias	High risk	The authors acknowledged the potential for clustering of patients by physician, and recruitment of patients by physicians may have resulted in selection bias.

eCRF, electronic case report forms; iRDT, influenza rapid diagnostic test; LRTI, lower respiratory tract infection; N/A, not applicable; SR, systematic review.

TABLE 19 Risk of bias: procalcitonin tests

Study	Random sequence generation[a]	Allocation concealment[a]	Blinding of participants and personnel[a]	Blinding of outcome assessment		Incomplete outcome data		Selective reporting[a]	Other bias[a]
				Key outcomes[b]	Other outcomes[c]	Key outcomes[b]	Other outcomes[c]		
Lhopitallier 2021[43]	Low risk	Unclear risk	High risk	1. Low risk 2. Low risk 3. Low risk	Low risk	1. High risk 2. Low risk 3. Low risk	Unclear risk	Low risk	High risk

a Risk-of-bias judgements from Smedemark (2022).[16]
b Reviewer's judgement on key protocol outcomes: (1) 7- or 28-day mortality, (2) escalation of care (including unplanned admission) and (3) hospital admission (immediately after triage or at 28 days).
c Reviewer's judgement on other outcomes: antibiotic/antiviral use, hospital length of stay, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms, HRQoL (using a validated scale).

TABLE 20 Risk of bias: GAS tests

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment		Incomplete outcome data		Selective reporting	Other bias
				Key outcomes[a]	Other outcomes[b]	Key outcomes[a]	Other outcomes[b]		
Llor 2011[44]	Low risk	High risk	High risk	1. N/A 2. N/A 3. N/A	Low risk	1. N/A 2. N/A 3. N/A	Low risk	Unclear risk	High risk
Worrall 2007[45]	High risk	High risk	Unclear risk	1. N/A 2. N/A 3. N/A	Unclear risk	1. N/A 2. N/A 3. N/A	Low risk	Low risk	High risk

N/A, not applicable.
a Reviewer's judgement on key protocol outcomes: (1) 7- or 28-day mortality, (2) escalation of care (including unplanned admission) and (3) hospital admission (immediately after triage or at 28 days).
b Reviewer's judgement on other outcomes: antibiotic/antiviral use, hospital length of stay, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms, HRQoL (using a validated scale).

TABLE 21 Risk of bias: influenza tests

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment		Incomplete outcome data		Selective reporting	Other bias
				Key outcomes[a]	Other outcomes[b]	Key outcomes[a]	Other outcomes[b]		
Berthod 2015[46]	High risk	High risk	High risk	1. Unclear risk 2. N/A 3. N/A	Unclear risk	1. Low risk 2. N/A 3. N/A	Low risk	Low risk	High risk

N/A, not applicable.

a Reviewer's judgement on key protocol outcomes: (1) 7- or 28-day mortality, (2) escalation of care (including unplanned admission) and (3) hospital admission (immediately after triage or at 28 days).

b Reviewer's judgement on other outcomes: antibiotic/antiviral use, hospital length of stay, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms, HRQoL (using a validated scale).

Appendix 5 Grading of Recommendations Assessment, Development and Evaluation tables

Grading of Recommendations Assessment, Development and Evaluation evidence tables are presented below for CRP, procalcitonin and influenza rapid antigen tests. No evidence for the relevant outcomes was identified for GAS rapid antigen tests.

TABLE 22 Clinical evidence profile for comparison of C-reactive POCT vs. usual care in adults with suspected ARI

Quality					Summary of findings				
					Number of patients		Effect		
Number of studies (design)	Limitations	Inconsistency	Indirectness	Imprecision	CRP	Usual care	Result (95%CI)	Quality[a]	Importance
Hospital admission immediately after triage									
NR									
Hospital admission at 3 weeks to 6 months									
1 cluster RCT[b]	Very serious[c]	N/A	No serious indirectness	Not calculable	0/49	0/38	Not reported	Very low	Critical
1 cluster RCT[d]	Very serious[e]	N/A	No serious indirectness	Very serious imprecision[f]	2/33	1/18	RR 1.09 (95% CI 0.11 to 11.22)	Very low	Critical
1 cluster RCT[g]	Very serious[c]	N/A	Serious indirectness[h]	Not calculable	0/65	0/59	Not reported	Very low	Critical
1 cluster RCT[i]	Very serious[c]	N/A	No serious indirectness	Very serious imprecision[f]	5/583	1/478	RR 4.10 (95% CI 0.48 to 34.97)	Very low	Critical
1 RCT[j]	Very serious[c]	N/A	No serious indirectness	Very serious imprecision[f]	35/304	34/301	RR 1.02 (95% CI 0.65 to 1.59)	Very low	Critical
1 RCT[k]	Very serious[c]	N/A	No serious indirectness	Not calculable	0/129	0/129	Not reported	Very low	Critical
Escalation of care: re-consultation/appointment									
3 cluster RCTs/1 RCT[l]	Very serious[c]	Serious inconsistency[m]	Serious indirectness[h]	Serious imprecision[n]	180/695	103/738	RR 1.61 (95% CI 1.07 to 2.41)	Very low	Critical
Escalation of care: virtual ward									
NR									
Escalation of care: ED visit									
NR									
Escalation of care: unplanned hospital admission									
NR									
Mortality at 7 days									
NR									

continued

TABLE 22 Clinical evidence profile for comparison of C-reactive POCT vs. usual care in adults with suspected ARI (*continued*)

Quality					Summary of findings				
					Number of patients		Effect		
Number of studies (design)	Limitations	Inconsistency	Indirectness	Imprecision	CRP	Usual care	Result (95%CI)	Quality[a]	Importance
Mortality at 28 days									
1 cluster RCT[d]	Very serious[e]	N/A	No serious indirectness	Very serious imprecision[f]	1/33	0/19	RR 1.68 (95% CI 0.07 to 39.16)	Very low	Critical
1 cluster RCT[g]	Very serious[c]	N/A	Serious indirectness[h]	Not calculable	0/65	0/59	Not reported	Very low	Critical
1 cluster RCT[i]	Very serious[c]	N/A	No serious indirectness	Not calculable	0/583	0/478	Not reported	Very low	Critical
1 RCT[j]	Very serious[c]	N/A	No serious indirectness	Very serious imprecision[f]	0/325	2/324	RR 0.20 (95% CI 0.01 to 4.14)	Very low	Critical
1 RCT[k]	Very serious[c]	N/A	No serious indirectness	Not calculable	0/129	0/129	Not reported	Very low	Critical
1 RCT[o]	Very serious[e]	N/A	Serious indirectness[h]	Not calculable	0/507	0/501	Not reported	Very low	Critical

N/A, not applicable.
a The overall quality of evidence for each outcome was downgraded to low for any serious factors and to very low for any very serious factors in the quality of evidence.b Andreeva 2014.[29]
c Very serious limitations due to uncertainties around selection bias and high risk of bias due to lack of blinding.
d Boere 2021.[38]
e Very serious limitations due to uncertainties around selection bias and high risk of bias due to lack of blinding and incomplete outcome data reporting.
f Very serious imprecision because the 95% CI for the RR crosses 0.8 and 1.25.
g Cals 2009.[33]
h Serious indirectness as test(s) not currently available in the UK.
i Little 2013.[41]
j Butler 2019.[30]
k Cals 2010.[40]
l Andreeva 2014,[29] Cals 2009,[33] Little 2013[41] and Cals 2010.[40]
m Serious inconsistency due to moderate heterogeneity (I^2 = 56.6%).
n Serious imprecision because the 95% CI for the RR crosses 1.25.
o Do 2016.[36]

TABLE 23 Clinical evidence profile for comparison of procalcitonin POCT vs. usual care in adults with suspected ARI

Quality					Summary of findings				
					Number of patients		Effect		
Number of studies (design)	Limitations	Inconsistency	Indirectness	Imprecision	Procalcitonin	Usual care	Result (95%CI)	Quality[a]	Importance
Hospital admission immediately after triage									
NR									
Hospital admission at 28 days									
NR									
Escalation of care: re-consultation/appointment									
1 cluster RCT[b]	Very serious[c]	N/A	No serious indirectness	Very serious imprecision[d]	53/195	33/122	RR 1.00 (95% CI 0.69 to 1.46)	Very low	Critical
Escalation of care: virtual ward									
NR									
Escalation of care: ED visit									
NR									
Escalation of care: unplanned hospital admission									
NR									
Mortality at 7 days									
1 cluster RCT[b]	Very serious[e]	N/A	No serious indirectness	Not calculable	0/163	0/114	Not reported	Very low	Critical
Mortality at 28 days									
1 cluster RCT[b]	Very serious[e]	N/A	No serious indirectness	Not calculable	0/163	0/114	Not reported	Very low	Critical

N/A, not applicable.
NR, not reported; RR, relative risk.
a The overall quality of evidence for each outcome was downgraded to low for any serious factors and to very low for any very serious factors in the quality of evidence.
b Lhopitallier 2021.[43]
c Very serious limitations due to lack of blinding and unclear allocation concealment.
d Very serious imprecision because the 95% CI for the RR crosses 0.8 and 1.25.
e Very serious limitations due to lack of blinding, unclear allocation concealment and incomplete outcome data.

TABLE 24 Clinical evidence profile for comparison of rapid antigen tests for influenza vs. usual care in adults with suspected ARI

Quality					Summary of findings				
					Number of patients		Effect		
Number of studies (design)	Limitations	Inconsistency	Indirectness	Imprecision	RADT	Usual care	Result (95%CI)	Quality[a]	Importance
Hospital admission immediately after triage									
NR									
Hospital admission at 28 days									
NR									
Escalation of care: re-consultation/appointment									
NR									
Escalation of care: virtual ward									
NR									
Escalation of care: ED visit									
NR									
Escalation of care: unplanned hospital admission									
NR									
Mortality at 7 days									
NR									
Mortality during study (follow-up not reported)									
1 RCT[b]	Very serious[c]	N/A	Serious indirectness[d]	Not calculable	0/60	0/33	Not reported	Very low	Critical

N/A, not applicable.
NR, not reported.
a The overall quality of evidence for each outcome was downgraded to low for any serious factors and to very low for any very serious factors in the quality of evidence.
b Berthod 2015.[46,49]
c Very serious limitations due to high risk of selection bias and lack of blinding.
d Serious indirectness as the test is not currently available in the UK.

Appendix 6 Subgroup and sensitivity analyses for clinical effectiveness outcomes

TABLE 25 Subgroup and sensitivity analyses for clinical effectiveness outcomes

Analysis	Outcome	Number of studies	*n*/*N* CRP	*n*/*N* usual care	Pooled RR (95% CI)	τ^2	I^2
Subgroup analysis of COPD patients (*Butler 2019*[30] *and the COPD subgroup of Boere 2021*[38])	Antibiotics prescribed at index consultation	2	165/347	236/338	0.68 (0.60 to 0.77)	0	0%
Sensitivity analyses							
Excluding Butler 2019[30] *(AECOPD)*	Antibiotics prescribed at index consultation	8	742/1894	822/1529	0.76 (0.67 to 0.86)	0.015	55.7%
	Antibiotic prescribed within 28 days	5	464/805	587/817	0.80 (0.73 to 0.89)	0.003	21.9%
Excluding Boere 2021[38] *(nursing home setting)*	Antibiotics prescribed at index consultation	8	879/2139	1033/1836	0.76 (0.68 to 0.85)	0.013	58.4%
Excluding studies with tests unavailable in the UK (*Althaus 2019*,[32] *Cals 2009*,[33] *Diederichsen 2000*,[35] *Do 2016*,[36] *Melbye 1995*[37])	Antibiotics prescribed at index consultation	4	247/538	335/508	0.69 (0.62 to 0.77)	0	0%
	Antibiotic prescribed within 28 days	3	273/491	363/483	0.74 (0.67 to 0.83)	0.002	13.2%
	Escalation of care: number of re-consultations	3	157/630	85/679	1.87 (1.27 to 2.77)	0.046	37.8%

n, number of events; *N*, total number in arm.

Appendix 7 Critical appraisal of included systematic reviews of cost-effectiveness studies

The critical appraisal tool used in this table was adopted from JBI critical appraisal checklist for systematic reviews and research syntheses, Aromataris *et al.* (2015).[73]

TABLE 26 Critical appraisal of systematic reviews of cost-effectiveness studies

Study reference: van der Pol 2021[20]	**Reviewer: KS. Checked by: BS.**
1. Is the review question clearly and explicitly stated?	Y
2. Were the inclusion criteria appropriate for the review question?	Y
3. Was the search strategy appropriate?	N; broad terms such as 'test' or 'diagnostics' used which are likely to miss key studies
4. Were the sources and resources used to search for studies adequate?	N; no grey literature search
5. Were the criteria for appraising studies appropriate?	N; CHEERS checklist used to create a quality score but should have used a quality appraisal tool, for example Drummond checklist
6. Was critical appraisal conducted by two or more reviewers independently?	N; only 10% of extraction (i.e. critical appraisal since this was based on extraction) duplicated
7. Were there methods to minimize errors in data extraction?	N; see above
8. Were the methods used to combine studies appropriate?	N/A
9. Was the likelihood of publication bias assessed?	N/A
10. Were recommendations for policy and/or practice supported by the reported data?	Y
11. Were the specific directives for new research appropriate?	Y
Study reference: Wubishet 2022[51]	**Reviewer: KS. Checked by: BS**
1. Is the review question clearly and explicitly stated?	Y
2. Were the inclusion criteria appropriate for the review question?	Unclear; inclusion criteria not reported in paper
3. Was the search strategy appropriate?	N; very limited terms included to capture the variety of interventions which may promote antimicrobial stewardship
4. Were the sources and resources used to search for studies adequate?	Y
5. Were the criteria for appraising studies appropriate?	Y
6. Was critical appraisal conducted by two or more reviewers independently?	Unclear; not reported whether critical appraisal was done in duplicate
7. Were there methods to minimize errors in data extraction?	Y
8. Were the methods used to combine studies appropriate?	N/A
9. Was the likelihood of publication bias assessed?	N/A
10. Were recommendations for policy and/or practice supported by the reported data?	N; doesn't explicitly give recommendations for future policy
11. Were the specific directives for new research appropriate?	Y

CHEERS, Consolidated Health Economic Evaluation Reporting Standards.

Appendix 8 Applicability of included cost–utility studies to our review question

TABLE 27 Applicability of cost–utility studies

Study identification: Bilir 2021[52]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Age distribution reflects US not UK; any age; suspected GAS; test used to guide antibiotic prescribing
1.2 Are the interventions appropriate for the review question?	Partly	US standard of care is the comparator
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US-based study but presume setting is primary care
1.4 Is the perspective for costs appropriate for the review question?	No	US payer perspective for cost-effectiveness analysis
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALDs
1.6 Are all future costs and outcomes discounted appropriately?	Partly	No discounting required for cost-effectiveness analysis since time horizon is 1 year; no discounting of costs for budget impact analysis which has a time horizon of 5 years
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	QALDs used; estimated using previous models but methods unclear
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	NA	US payer perspective means cost-effectiveness results unlikely to be useful; includes children
Study identification: Chew 2022[53]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Subgroups focus on children < 5 years, 5–14 years and adults; ARI in primary care
1.2 Are the interventions appropriate for the review question?	No	Pulse oximetry not specified as a test of interest; Thai standard of care is the comparator
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	No	Setting is rural area of Northern Thailand
1.4 Is the perspective for costs appropriate for the review question?	Yes	Health system perspective

TABLE 27 Applicability of cost–utility studies (*continued*)

1.5 Is the perspective for outcomes appropriate for the review question?	Partly	DALYs but does not include impact on morbidity or disability
1.6 Are all future costs and outcomes discounted appropriately?	N/A	Time horizon is 1 year
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	DALYs used but no EQ-5D-5L
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	NA	The test and setting are not applicable to this review
Study identification: Francis 2020[31]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Patients with COPD in primary care; test used to guide antibiotic prescribing
1.2 Are the interventions appropriate for the review question?	Yes	CRP; comparator is UK standard-of-care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK-based study
1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	N/A	Time perspective is 6 months
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	EQ-5D-5L score collected in trial; mapped back to UK valuation set
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	Directly applicable	
Study identification: Fraser 2020[54]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Adult population in primary care; test used to guide antibiotic prescribing for GAS
1.2 Are the interventions appropriate for the review question?	Yes	Relevant tests identified from a systematic review; comparator is standard of care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK-based study

continued

TABLE 27 Applicability of cost–utility studies (*continued*)

1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	N/A	Time horizon is 1 year
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D-5L not used but used UK population norm data and previous economic evaluation; doesn't explicitly state but presume UK EQ-5D valuation set used
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	Directly applicable	Methods of QALY derivation likely to be acceptable since this is an NIHR HTA report; unlikely to affect cost-effectiveness results
Study identification: Holmes 2018[55]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Adult population in primary care; test used to guide antibiotic prescribing for ARI
1.2 Are the interventions appropriate for the review question?	Yes	CRP; comparator is UK standard of care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK-based study
1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	N/A	Time horizon is 28 days
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EuroQoL EQ-5D-5L from observational study; does not explicitly state but presume UK EQ-5D valuation set used
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	Directly applicable	Methods of deriving QALYs unlikely to make cost-effectiveness results not applicable
Study identification: Hunter 2015[56]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Adult population in primary care; test used to guide antibiotic prescribing for RTI
1.2 Are the interventions appropriate for the review question?	Yes	CRP; comparator is UK standard of care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK-based study

TABLE 27 Applicability of cost–utility studies (*continued*)

1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	Yes	Costs and QALYs discounted at 3.5%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D-5L not used but used UK population data, a previous model and NICE RTI guidelines; does not explicitly state but presume UK EQ-5D valuation set used
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	Directly applicable	Methods of deriving QALYs unlikely to make cost-effectiveness results not applicable
Study identification: Little 2014[57]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Patients aged ≥ 3 years; primary care; A/C/G streptococci
1.2 Are the interventions appropriate for the review question?	Partly	Clinical scoring algorithm (FeverPAIN) + RADT if score high on algorithm; comparator is FeverPAIN alone and a separate control group; FeverPAIN not relevant for inclusion criteria
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK-based study
1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	N/A	Time horizon is 28 days
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Yes	EQ-5D data collected within trial; standard UK tariff used for valuation
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	Partially applicable	Intervention includes FeverPAIN which is not relevant to review inclusion criteria; includes children; results may still be useful given UK-based study and NHS perspective
Study identification: Mac 2020[58]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Patients aged 65 with suspected influenza-like illness; ED

continued

TABLE 27 Applicability of cost–utility studies (*continued*)

1.2 Are the interventions appropriate for the review question?	Partly	Comparator is not UK standard of care; only one of the three tests is relevant
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Canada-based study; setting is ED
1.4 Is the perspective for costs appropriate for the review question?	No	Single healthcare payer perspective; applicable to each province in Canada
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	No	Costs and QALYs discounted at 1.5%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D-5L not used; used previous US economic evaluation, Cochrane review and previous literature; methods of valuation unclear
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	N/A	Canadian payer perspective means cost-effectiveness results unlikely to be useful; disease of interest is influenza
Study identification: Michaelidis 2014[59]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Adult population in outpatient clinic; test used to guide antibiotic prescribing for ARTI; ARTI includes influenza and COPD exacerbations but subgroup results not presented
1.2 Are the interventions appropriate for the review question?	Partly	POC procalcitonin; comparator is US usual care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	US-based study
1.4 Is the perspective for costs appropriate for the review question?	Yes	Healthcare system perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	Unclear	Time horizon is ARTI treatment episode; unlikely to require discounting but unclear
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D not used; used previous literature and assumptions; method of valuation unclear
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	Partially applicable	US-based but took a healthcare system perspective; results may be relevant
Study identification: Nicholson 2014[61]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**

TABLE 27 Applicability of cost–utility studies (*continued*)

1.1 Is the study population appropriate for the review question?	Partly	Patients ages > 65 or > 18 years with chronic heart or lung disease; hospital setting; influenza included; no results by subgroups
1.2 Are the interventions appropriate for the review question?	Partly	BinaxNOW (influenza) is a urinary antigen test which is included in review; Quidel (pneumococcal) is a rapid antigen test; comparator is not standard of care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	UK-based
1.4 Is the perspective for costs appropriate for the review question?	Yes	NHS perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	N/A	Time horizon is 28 days
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D data from trial used; valuation set not explicitly stated
1.8 Overall judgement: Directly applicable/partially applicable/not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	Directly applicable	Valuation for QALYs likely to be appropriate given this is a HTA report; includes pneumococcal infection; although no subgroups presented the population still meets review inclusion criteria
Study identification: Oppong 2013[62]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Yes	Adult population in GP setting; test used to guide antibiotic prescribing for LRTI
1.2 Are the interventions appropriate for the review question?	Partly	CRP test; comparator is not UK standard of care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Sweden and Norway
1.4 Is the perspective for costs appropriate for the review question?	Yes	Health service perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	N/A	Time horizon is 28 days
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D data from observational trial; European harmonised value set used to value EQ-5D data
1.8 Overall judgement: Directly applicable/partially applicable/not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	Partially applicable	Conducted in Sweden and Norway but used a health service perspective; population is applicable; index test is applicable; unlikely to vastly affect cost-effectiveness result so that they are not applicable

continued

TABLE 27 Applicability of cost–utility studies (*continued*)

Study identification: Rothberg 2003 [63]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Adults aged > 65 years with influenza-like illness; primary care
1.2 Are the interventions appropriate for the review question?	Partly	Rapid antigen test; comparator not UK standard of care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	No	US-based and from 2003
1.4 Is the perspective for costs appropriate for the review question?	Partly	Societal perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	Unclear	Time horizon unclear; no mention of discounting
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D not used; used estimates from another study; estimated utilities for side effects and hospitalisation; methods of valuation unclear
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	N/A	US-based study and from 2003; unlikely to reflect current UK NHS context; influenza only; cost-effectiveness results unlikely to be applicable
Study identification: Rothberg 2003[64]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Adults with influenza-like illness; setting unclear
1.2 Are the interventions appropriate for the review question?	Partly	Rapid antigen tests; comparator not UK standard of care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	No	US-based and from 2003
1.4 Is the perspective for costs appropriate for the review question?	Partly	Societal perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	Unclear	Time horizon unclear; no mention of discounting
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D not used; Health Utilitieslindex (HUI-3) from 15 patients used; methods of valuation unclear
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	N/A	US-based study and from 2003; unlikely to reflect current UK NHS context; influenza only; cost-effectiveness results unlikely to be applicable

TABLE 27 Applicability of cost–utility studies (*continued*)

Study identification: Smith 2002[65]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Adults aged 32 years with influenza-like illness; setting unclear
1.2 Are the interventions appropriate for the review question?	Partly	Rapid antigen test; comparator not UK standard of care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	No	US-based and from 2002
1.4 Is the perspective for costs appropriate for the review question?	Partly	Societal perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	Quality-adjusted days gained
1.6 Are all future costs and outcomes discounted appropriately?	Unclear	Time horizon unclear; no mention of discounting
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D not used; used National Health Interview Survey or estimated utilities; method of valuation unclear
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	N/A	US-based study and from 2002; unlikely to reflect current UK NHS context; influenza only; cost-effectiveness results unlikely to be applicable
Study identification: You 2017[66]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/N/A**	**Comments**
1.1 Is the study population appropriate for the review question?	Partly	Elderly patients (65–90) with influenza-like illness; ambulatory setting (outpatient)
1.2 Are the interventions appropriate for the review question?	Partly	Rapid molecular PCR; comparator is no test and clinical judgement which is likely same as UK standard of care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Partly	Hong Kong
1.4 Is the perspective for costs appropriate for the review question?	Yes	Health service perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALYs
1.6 Are all future costs and outcomes discounted appropriately?	No	QALY loss as a result of death was discounted at 3%
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D not used; use previous literature on HrQoL and projected age-specific life expectancies; method of valuation unclear

continued

TABLE 27 Applicability of cost–utility studies (*continued*)

1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	N/A	Hong Kong based; influenza only; cost-effectiveness results unlikely to be applicable
Study identification: Neuner 2003[60]		
Guidance topic: cost-effectiveness of rapid and POC testing for ARIs		**Question no**: RQ1.3
Checklist completed by: KS		
Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5). This checklist should be used first to filter out irrelevant studies.	**Yes/partly/no/ unclear/NA**	**Comments**
1.1 Is the study population appropriate for the review question?	Unclear	Population and setting unclear
1.2 Are the interventions appropriate for the review question?	Unclear	Not clear whether optical immunoassay is eligible for inclusion in review; comparator is not UK standard of care
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	No	US-based study and from 2003
1.4 Is the perspective for costs appropriate for the review question?	Partly	Societal perspective
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	QALDs
1.6 Are all future costs and outcomes discounted appropriately?	N/A	Time horizon is 1 year
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	EQ-5D not used; previous literature used to derive utilities; method of valuation unclear
1.8 Overall judgement: Directly applicable/partially applicable/ not applicable. There is no need to use *Methods* of the checklist if the study is considered 'not applicable'.	N/A	US-based study and from 2003; unlikely to reflect current UK NHS context; question eligibility of index test; population and setting unclear

LRTI, lower respiratory tract infection; N/A, not applicable; QALD, quality-adjusted life day.
Note
The checklist used in the table was adapted from NICE appraisal checklist for economic evaluations.[23]

EME
HSDR
HTA
PGfAR
PHR

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