Evidence review [B]

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

Keywords: humans, biomarkers, anti-bacterial agents, triage, respiratory, infection, economic evaluation, cost utility, clinical effectiveness, evidence synthesis

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List of abbreviations

AMR	Antimicrobial resistance
ARI	Acute respiratory infection
CEAC	Cost-effectiveness acceptability curve
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CUA	Cost-utility analysis
DIA	Digital immunoassay
GAS	Group A streptococcus
GP	General practice / general practitioner
HRQoL	Health-related quality of life
ICD	International Classification of Diseases
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
LRTI	Lower respiratory tract infection
NAAT	Nucleic acid amplification tests
NAI	Neuraminidase inhibitors
NMB	Net monetary benefit
NR	Not reported
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OIA	Optical immunoassay
PCR	Polymerase chain reaction
POC	Point of care
POCT	Point of care test
QALD	Quality-adjusted life day
QALE	Quality-adjusted life expectancy
QALY	Quality-adjusted life year
RADT	Rapid antigen detection test
RIDT	Rapid influenza diagnostic test
RCT	Randomised controlled trial
RR	Risk ratio
RSV	Respiratory syncytial virus
RTI	Respiratory tract infection
SD	Standard deviation
SE	Standard error
US	United States
WTP	Willingness to pay

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Abstract

Background

This review assessed the clinical- and cost-effectiveness of point of care tests (POCTs) to guide the triage and treatment of people (≥16 years old) presenting with suspected acute respiratory infection (ARI).

Methods

Searches for systematic reviews, RCTs and cost utility studies were conducted in May 2023. Sources included MEDLINE, Epistemonikos Embase, Cochrane CENTRAL, the CEA Registry and reference checking.

Eligible studies included people aged 16 and over making initial contact with the health system with symptoms suggestive of ARI.

Risk of bias of RCTs was assessed using the Cochrane RoB tool. The Drummond checklist was used for cost utility studies.

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

The study characteristics and main results of included cost utility studies were summarised narratively and tabulated.

Results

Clinical effectiveness

Fourteen studies were included; all were at a high risk of bias. Ten studies analysed POC C-reactive protein (CRP) tests. The effects of CRP tests compared with usual care on hospital admissions and mortality were highly uncertain due to sparse data. Three studies had heterogeneous findings on resolution of symptoms/time to full recovery. The risk of re-consultations increased in patients receiving CRP POCT (risk ratio 1.61, 95% CI 1.07 to 2.41; 4 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; 9 studies).

The effects of procalcitonin POCT compared with usual care on hospital admission, escalation of care, and duration of symptoms were very uncertain as evidence was available from only one study. The study found a large reduction in initial antibiotic prescriptions within 7 days.

Two studies found a large reduction in initial antibiotic prescriptions for Group A Streptococcus (GAS) POCTs versus usual care. Only one study compared an influenza POCT with usual care. The effect on antibiotics prescribed was very uncertain. No deaths occurred in either treatment group.

Cost-effectiveness

Six of the included cost utility studies were judged to be directly applicable to our review question, four of which evaluated the cost-effectiveness of 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 cost utility study evaluated 14 different POCTs for GAS and found that none of the POCTs evaluated 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.

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Registration

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Plain Language Summary

Acute respiratory infection is a group of common diseases caused by viruses or bacteria. Examples of acute respiratory infection 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 used to take 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 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 more in our blood when we have an infection caused by bacteria) may reduce the 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. Previous studies suggested that the test may represent good value for money but most studies only considered costs and outcomes in the short-term. Evidence is either very limited to draw conclusions or did not indicate good value for money for other rapid tests that we evaluated.

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 treatments 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 self-present to a hospital emergency department (ED) department. 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 gap.

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 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 (TNF)-related apoptosis-inducing ligand (TRAIL),[5] and Interferon-γ-induced protein-10 (IP-10, also known as C-X-C motif chemokine ligand 10 [CXCL 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-hemolytic 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/electrolytes analysis, including lactate, sodium and urea. These could alternatively 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).

2 Objectives

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.

3 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 documented in a protocol (Appendix 1), which was registered on Prospero (reference: 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).

3.1 Clinical Effectiveness Review

3.1.1 Search Strategy

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

3.1.1.1 Systematic reviews

The following databases were searched from inception to May 2023 (see Appendix 2 for exact dates) for systematic reviews:

- MEDLINE via Ovid
- Epistemonikos

Search concepts combined acute respiratory infection 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, with some terms removed (see excluded conditions listed in section 3.1.2.1 below). Appendix 2 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.

3.1.1.2 RCTs

Additional searches to find RCTs were conducted in the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL), from inception
- Embase (Ovid), limited by date
- MEDLINE (Ovid), limited by date

The same subject search terms to 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 2 for our full record of searches. As the identified systematic reviews were all limited to specific populations, interventions and outcomes (that is, 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 to 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. A sensitive RCT filter was used in MEDLINE and Embase (based on the latest versions of Cochrane's sensitivity- and precision-maximizing 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.

3.1.2 Inclusion and Exclusion Criteria

3.1.2.1 Population

Inclusion criteria

People aged 16 years or over with suspected acute respiratory infection.

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 acute respiratory infections that rarely require or lead to escalation of care to hospital admission such as otitis media and sinusitis.

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

3.1.2.2 Intervention

Inclusion criteria

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

- Rapid antigen test
- Rapid PCR tests
- Urinary antigen tests
- C-reactive protein
- Procalcitonin
- Serum sodium
- Urea nitrogen
- Partial pressure O_2
- Blood gases
- Full blood count
- White blood cell count
- Myxovirus resistance protein A
- TNF-related apoptosis-induced ligand (TRAIL)
- Interferon-γ-induced protein-10 (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

3.1.2.3 Comparator

Current practice

3.1.2.4 Outcomes

- Hospital admission (immediately after triage or at 28 days)
- Escalation of care (some time after initial consultation):
  - Re-consultation/appointment
  - Virtual Ward
  - Emergency department visit
  - Unplanned hospital admission
- Hospital length of stay
- Follow-up consultation/ongoing monitoring
- Antibiotic/antiviral use
- Time to clinical cure/resolution of symptoms
- Mortality
- HRQoL (using a validated scale)

3.1.2.5 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

3.1.3 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 text 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.

3.1.4 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 section 3.1.6). Systematic reviews of good quality that closely match the review protocol were extracted rather than extracting from the primary studies. Where a good quality review was found, earlier reviews with largely overlapping scope 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 (for example 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 de-duplicated.

3.1.5 Data extraction

A pre-piloted and standardised form was used to extract data from studies. All extractions were checked by a second reviewer.

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

3.1.6 Risk of bias assessment

The quality of included systematic reviews and RCTs were assessed by one reviewer, with the initial 20% assessed by a second reviewer to ensure that consistency was achieved. For systematic reviews we used the tool produced by the Joanna Briggs Institute (https://jbi.global/critical-appraisal-tools); for RCTs we used the Cochrane RoB 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 by the Cochrane review authors for study level bias and conducted new assessments for outcomes relevant to the present review.

We assessed the certainty of the evidence using the 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.

3.1.7 Evidence Synthesis

All included RCTs were tabulated and summarised narratively.

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. 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 a lack of time.

3.1.8 Analysis of sub-groups

We pre-specified that stratified data for the following subgroups were to be considered for subgroup analyses irrespective of statistical heterogeneity:

- Age of patient (65 years and under, 66 – 80 years, over 80 years)
- Presence of chronic co-morbidity (for example, COPD)
- Pregnancy & post-partum (up to 28 days)

Only data stratified by the presence or absence of COPD were available among included studies.

3.1.9 Sensitivity analyses

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

3.2 Cost Effectiveness Review

3.2.1 Search Strategy

Searches combined the concepts of: a) acute respiratory infections, 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
- CEA registry, from inception

A precise, yet highly sensitive cost utility study filter was used in Embase and Medline.[19] See Appendix 2 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.

3.2.2 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 section

3.1.2). 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.

3.2.2.1 Outcomes

Inclusion criteria

- Incremental cost (NHS and personal social services perspective)
- Life-years gained
- Incremental QALYs
- Incremental DALYS
- ICER/ cost per QALY
- Incremental net health/monetary benefit

3.2.2.2 Study Designs

Inclusion criteria

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

3.2.3 Screening

Initial screening of titles and abstracts, followed by full text screening was carried out using Rayyan https://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.

3.2.4 Data extraction

3.2.5 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 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).

3.2.6 Evidence Synthesis

All included systematic reviews and cost utility studies were tabulated and summarised narratively.

4 Results

4.1 Clinical effectiveness review results

4.1.1 Results of the search

4.1.1.1 Systematic reviews

A systematic search carried out to identify potentially relevant systematic reviews found 1355 references (see Appendix 2 for the literature search strategy).

These 1355 references were screened at title and abstract level against the review protocol, with 1292 excluded at this level. Twenty percent of references were screened separately by two reviewers with 96.6% agreement. Discrepancies were resolved by discussion. An additional seven references were identified through examining reference lists.

The full texts of 70 systematic reviews were ordered for closer inspection. Five of these systematic reviews 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. One systematic review was included as a source of data only (Sections 4.1.2 and 4.1.3).

The systematic review evidence selection is presented as a PRISMA diagram in Appendix 3.

Details of reviews excluded at full text, along with reasons for exclusion are given in Appendix 4.

4.1.1.2 RCTs

A systematic search carried out to identify potentially relevant studies found 2341 references (see Appendix 2 for the literature search strategy).

These 2341 references were screened at title and abstract level against the review protocol, with 2265 excluded at this level. 20% of references were screened separately by two reviewers with 98.8% agreement. Discrepancies were resolved by discussion. An additional 42 references were identified through examining reference lists of relevant systematic reviews.

The full texts of 118 records were ordered for closer inspection. Fourteen of these studies met the criteria specified in the review protocol.

The clinical evidence study selection is presented as a PRISMA diagram in Appendix 5.

See Table 1, Table 4, Table 5, and Table 7 for the full references of the included studies and Appendix 6 for the data extraction of the 14 included studies.

Details of studies excluded at full text, along with reasons for exclusion are given in Appendix 7

No eligible evidence was identified for the following tests specified in the review protocol:

- Rapid PCR tests
- Urinary antigen tests
- Serum sodium
- Urea nitrogen
- Partial pressure O2
- Blood gases
- Full blood count
- White blood cell count
- Myxovirus resistance protein A
- TNF-related apoptosis-induced ligand (TRAIL)

4.1.2 C-reactive protein

A recent systematic review[16] assessed 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 use in adults. On closer inspection, we could not replicate the computation of the effective sample size for some of the cluster RCTs (Appendix 8), 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 (Table 1 and Appendix 6). All ten 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,[24] and another study was conducted in Europe, including the UK.[25] Three studies were conducted in The Netherlands,[26-28] and the remaining studies were conducted in each of Russia,[29] Thailand and Myanmar,[30] Denmark,[31] Norway[32] and North Vietnam.[33] Study sample sizes ranged from 179[29] to 1932 adults.[25]

Five of the studies assessed a test not currently available in the UK (Nycocard II CRP point-of-care testing),[26, 30-33] however a pragmatic decision was taken to include these studies. Two tests that are currently available in the UK were assessed: Afinion CRP point-of-care testing (two studies[24, 29]) and QuikRead CRP (three studies[25, 27, 28]).

Eight studies were conducted in a primary care setting,[24-26, 28, 29, 31-33] one in primary care and outpatients,[30] and one study was conducted in nursing homes.[27] There were some differences in the populations eligible for inclusion in the studies. Most included people with acute LRTI or upper or lower RTI, using slightly differing definitions, however Butler 2019[24] limited inclusion to people with acute exacerbation of COPD (AECOPD) (Table 1). Three studies included children in their population; Do 2016[33] presented subgroup data for adults in their study of non-severe ARI, while Althaus 2019[30] and Diederichsen 2000 [31]) provided raw data for adults with ARI to Smedemark 2022.[16]

Three studies received funding or test kits from the manufacturer.[28, 29, 32]

4.1.2.1 Risk of bias in included CRP studies

The overall risk of bias was considered high for all ten studies assessing CRP POC tests because of the lack of blinding of participants and personnel (Appendix 9).[24-33] In addition, six studies were considered to have an unclear risk of selection bias due to unclear allocation concealment,[25-27, 29, 31, 32] and four studies were considered to be at high risk of bias because of 'other bias.'[25-27, 29] One study was at high risk of bias due to lack of blinding in the assessment of 'other outcomes'.[32] Based on reviewer's judgments, 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).[27] 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).[24, 33] Risk of bias for other domains (e.g. random sequence generation and selective reporting) were considered to be low or unclear (Appendix 9).

Table 1: Characteristics of included studies for C-reactive protein point of care tests

Study Details	Participants	Interventions	Outcomes	Comments[a]
Afinion CRP point-of-care testing				
Andreeva 2014 [29] Russia Open-label cluster RCT January to 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 [24] **Francis 2020** [34] UK (England & Wales) Open-label RCT January 2015 to September 2017 **Follow-up:** 4 weeks and 6 months	649 patients: CRP 325, usual care 324 Acute exacerbation of COPD 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 point-of-care testing *(Not currently available in the UK)*				
Althaus 2019 [30] Thailand and Myanmar Open-label RCT	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

Study Details	Participants	Interventions	Outcomes	Comments[a]
June 2016 to June 2017 **Follow-up:** Day 5 + 14				
Cals 2009 [26] **Cals 2013**[35] The Netherlands Open-label cluster-RCT Winter periods 2005-06 and 2006-07 **Follow-up:** 28 days	431 patients CRP 227, usual care 204 Suspected lower respiratory tract infection	**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 [31] Denmark Open-label RCT January to 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
Do 2016 [33] Northern Vietnam Open-label RCT March 2014 to July 2015 **Follow-up:** 14 days	1008 patients CRP 507, usual care 501 Non-severe acute respiratory tract infection	**Interventions**: Single POC CRP **Comparator**: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 14 days (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

Study Details	Participants	Interventions	Outcomes	Comments[a]
Melbye 1995 [32] Norway Open-label RCT 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 [27] **Boere 2022** [36] The Netherlands Open-label cluster RCT September 2018 to March 2020 **Follow-up:** 3 weeks	241 patients CRP 162, usual care 79 Nursing home residents with suspected LRTI	**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 [28] The Netherlands Open-label RCT	258 patients CRP 129, usual care 129 Suspected acute LRTI 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	Funding: Orion Diagnostica Espoo, Finland Overall risk of bias: High

Study Details	Participants	Interventions	Outcomes	Comments[a]
November 2007 to April 2008 **Follow-up:** 28 days			• Number of participants substantially improved within 7 days • Patient reported time to full recovery	
Little 2013 [25] **Little 2019** [37] Belgium, UK, Poland, Spain, The Netherlands Open-label cluster-RCT February 2011 to May 2012 **Follow-up:** 12 months	1932 patients CRP 1062, usual care 870 Upper or lower respiratory tract infection	**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

[a] Overall risk of bias: see Appendix 9 for details. Abbreviations: AECOPD – acute exacerbation of chronic obstructive pulmonary disease; ARI – acute respiratory infection; COPD – chronic obstructive pulmonary disease; CRP – C-reactive protein; CRQ-SAS - Chronic Respiratory Disease Questionnaire; EQ-5D-5L - European Quality of Life–5 Dimensions 5-Level questionnaire; GP – general practice; POC – point-of-care; RCT – randomised controlled trial; RTI – respiratory tract infection.

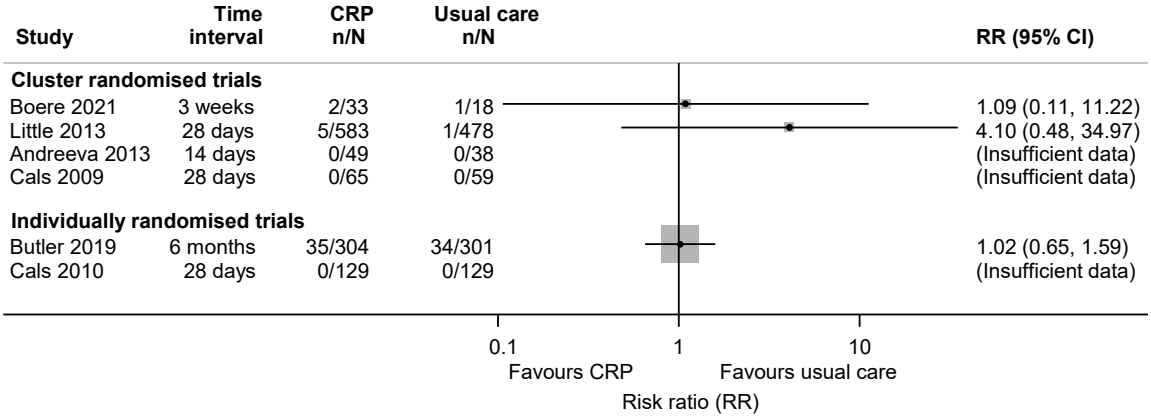
4.1.2.2 *Hospital admission (immediately after triage or at 28 days)*

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

Four cluster RCTs[25-27, 29] and two individual RCTs[24, 28] reported data on hospital admissions at varying timepoints (where reported), ranging from two weeks[29] to six months.[24] It was not possible to calculate risk ratios for two cluster-RCTs[26, 29] and one individual RCT[28] due to zero events in both intervention arms. Three RCTs provided data allowing calculation of risk ratios: two cluster-RCTs with follow-up between 3-4 week reported very few events;[25, 27] one RCT with follow-up at 6 months showed no difference between CRP and usual care groups, RR 1.02 (95% CI 0.65 to 1.59; 1 RCT, n=605; very low certainty evidence).[24]

Meta-analysis was not conducted for the studies reporting hospital admissions due to the very different duration of follow-up. However, data are presented as a forest plot in Figure 1.

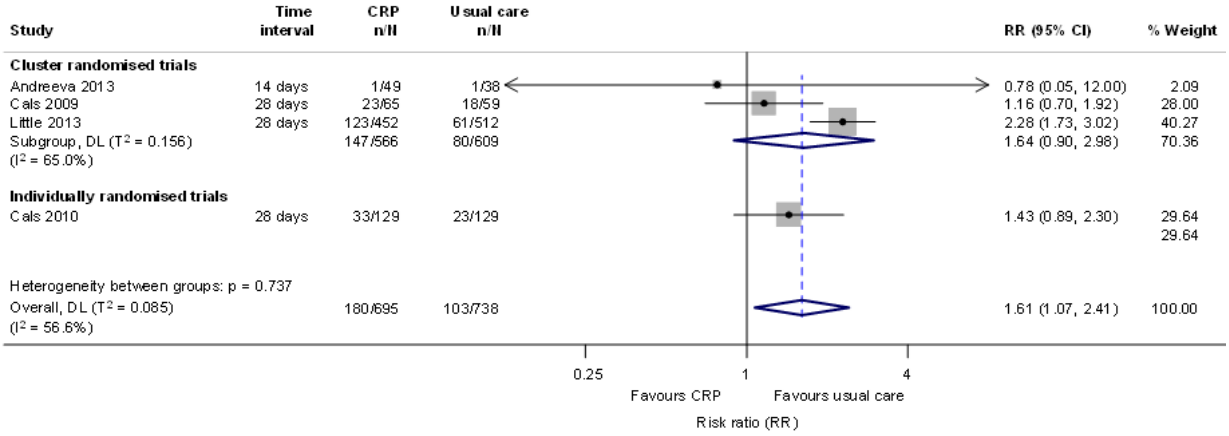
Figure 1: CRP POCT vs usual care - Hospital Admission



4.1.2.3 *Escalation of care (some time after initial consultation): Re-consultation/appointment*

Three cluster RCTs[25, 26, 29] and one individual RCT[28] reported data on the number of re-consultations at 14 days,[29] or at 28 days,[26, 28] or re-consultations due to 'new or worsening symptoms' within 28 days.[25] 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 2): RR 1.61 (95% CI 1.07 to 2.41, I^2=56.6%; 4 RCTs/cluster-RCTs, n=1,433; very low certainty evidence).

Figure 2: CRP POCT vs usual care - Escalation of care: number of re-consultations



4.1.2.4 Escalation of care (some time after initial consultation): Virtual Ward

No eligible evidence was identified for this outcome.

4.1.2.5 Escalation of care (some time after initial consultation): Emergency department visit

No eligible evidence was identified for this outcome.

4.1.2.6 Escalation of care (some time after initial consultation): Unplanned hospital admission

No eligible evidence was identified for this outcome.

4.1.2.7 Hospital length of stay

No eligible evidence was identified for this outcome.

4.1.2.8 Follow-up consultation/ongoing monitoring

No eligible evidence was identified for this outcome.

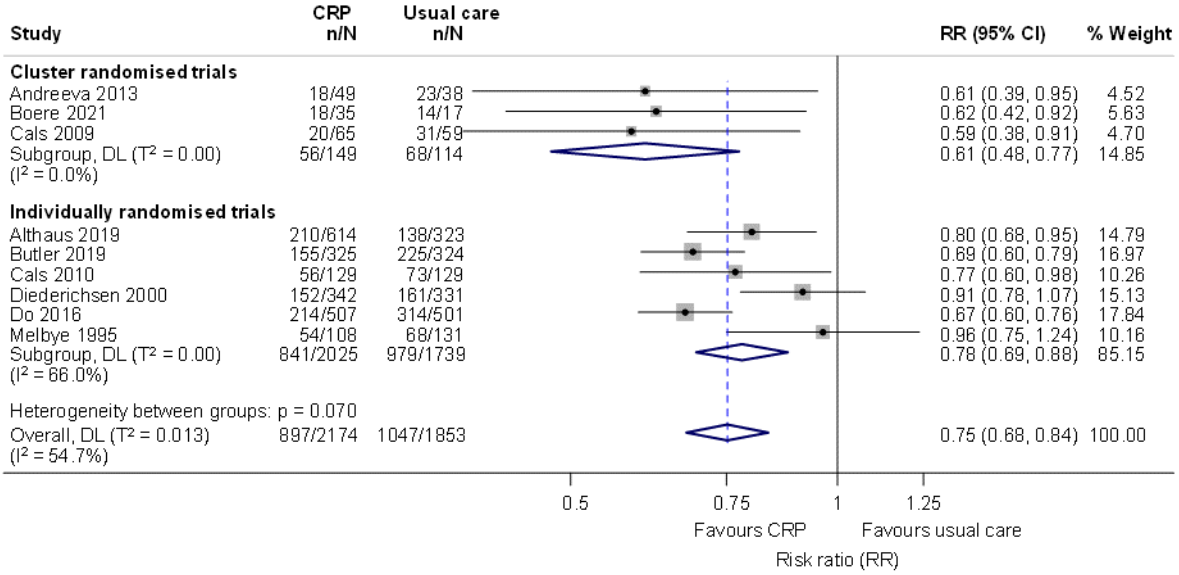
4.1.2.9 Antibiotic/antiviral use

Three cluster RCTs[26, 27, 29] and six individual RCTs[24, 28, 30-33] 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 to usual care (Figure

3): RR 0.75 (95% CI 0.68 to 0.84, I^2=54.7%; 9 RCTs/cluster-RCTs, n=4,027). Heterogeneity among estimated effects between individually randomised trials.

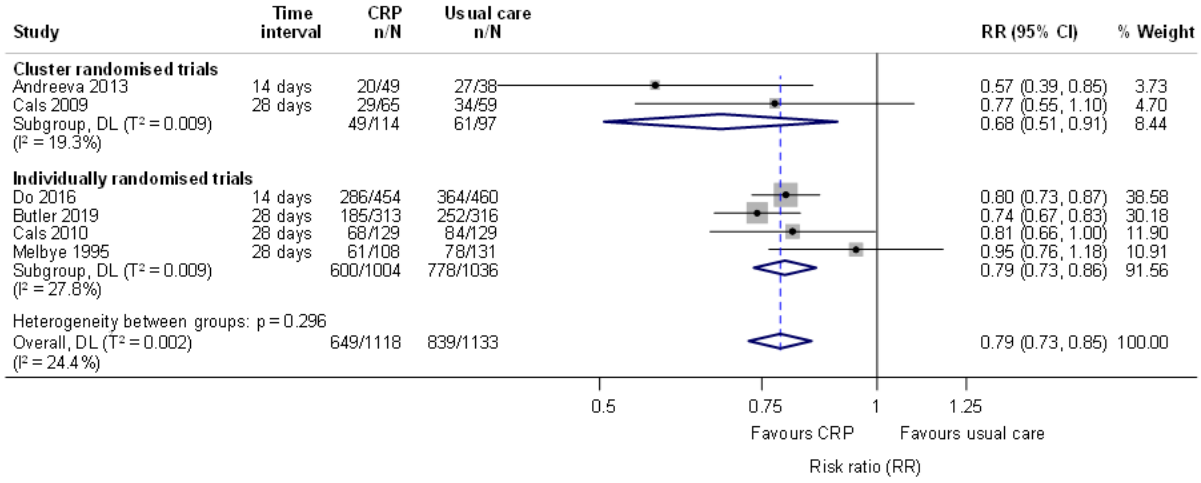
In contrast to the Smedemark 2022 review,[16] data on antibiotics prescribed at index consultation for Little 2013[25] and Little 2019 [37] were excluded from meta-analysis in the current review because it was clear from Little 2019[37] that the data related to antibiotics prescribed at 3 months. The data reported at three months also appeared to be based on GP practices, suggesting the data reported was not necessarily follow-up of the same patients initially included in the study (see Appendix 8).

Figure 3: CRP POCT vs usual care - Antibiotics prescribed at index consultation



Two cluster RCTs[26, 29] and four individual RCTs[24, 28, 32, 33] 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 4): RR 0.79 (95% CI 0.73 to 0.85, I^2=24.4%; 6 RCTs/cluster-RCTs, n=2,251).

Figure 4: CRP POCT vs usual care - Antibiotics prescribed within 28 days



Three studies reported additional data relating to antibiotic use or changes to antibiotic treatment that could not be meta-analysed.[24, 27, 33, 34] Butler 2019[24, 34] assessed patient-reported antibiotic use for an AECOPD within four weeks after randomisation and found a reduction in antibiotic consumption in the CRP group (57.0%) compared to the usual care group (77.4%): adjusted OR 0.31 (95% CI 0.20 to 0.47; 1 RCT, n=537).

Boere 2021[27] found that antibiotic treatment changes (start, cessation, switch, or prolongation) occurred less frequently in the CRP group during follow-up (12.2%) compared with usual care group (16.8%), OR 0.53 (95% CI 0.26 to 1.08; 1 cluster-RCT); Do 2016[33] 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% respectively, OR 0.73 (95% CI 0.45 to 1.17; 1 RCT, n=386), and a small 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; 1 RCT, n=430). All the above evidence was highly uncertain.

4.1.2.10 Time to clinical cure/resolution of symptoms

Three studies provided evidence on time to resolution of symptoms/time to full recovery (Table 2).[16, 25, 28, 33]

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; 1 RCT)[33] and adjusted HR 0.87 (95% CI 0.74 to 1.03; 1 cluster-RCT)[16, 25]

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); 1 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); 1 cluster-RCT, n=143).[28]

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; 1 RCT, n=230)[16, 32] and RR 1.03 (95% CI 0.89 to 1.18; 1 RCT, n=243)[16, 28]

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 usual care group (92.3%; n=78, original sample size).[29] [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 usual care group (90.8%), OR 0.49 (0.21 to 1.12).[27] 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 on 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; 1 cluster-RCT [modified sample size due to cluster level data, n=124)[16, 26] and RR 0.85 (95% CI 0.57 to 1.29; 1 RCT, n=219).[16, 32]

Table 2: CRP POCT vs usual care - Time to resolution of symptoms/time to full recovery

Study	Outcome	CRP test	Usual care	Effect size
Cals 2010 [28]	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 [33]	Time to resolution of symptoms, days	Median 6 (IQR 4–10)	Median 5 (IQR 4–8)	HR 0·89 (95% CI 0·77, 1·03)
Little 2013 [25]	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, 1.03)

Abbreviations: CRP – C-reactive protein; HR – hazard ratio; IQR – interquartile range; LRTI – lower respiratory tract infection; SD – standard deviation.

[a] The adjusted model additionally controlled for age, smoking, sex, major cardiovascular or respiratory comorbidity, baseline symptoms, crepitations, wheeze, pulse > 100 beats per min, temperature > 37·8°C, respiratory rate, blood pressure, physician's rating of severity, and duration of cough.

Table 3: CRP POCT vs usual care - Number of patients substantially improved

Study	Outcome	CRP test n/N	Usual care n/N	Effect size
Cals 2010 [28]	Substantially improved within 7 days	27/118	31/125	RR 1.03 (95% CI 0.89, 1.18)
Melbye 1995 [32]	Substantially improved within 7 days	46/102	53/128	RR 0.94 (95% CI 0.75, 1.18)
Melbye 1995 [32]	Substantially improved within 28 days	71/98	82/121	RR 0.85 (95% CI 0.57, 1.29)
Andreeva 2014 [29]	Fully or almost recovered within 14 days	92/101	72/78	Not reported
Boere 2021 [27]	Substantially improved within 3 weeks	86.4% [a]	90.8% [a]	OR 0.49 (0.21, 1.12)
Cals 2009 [26]	Substantially improved within 28 days	49/65 [b]	44/59 [b]	RR 0.97 (95% CI 0.53, 1.78)

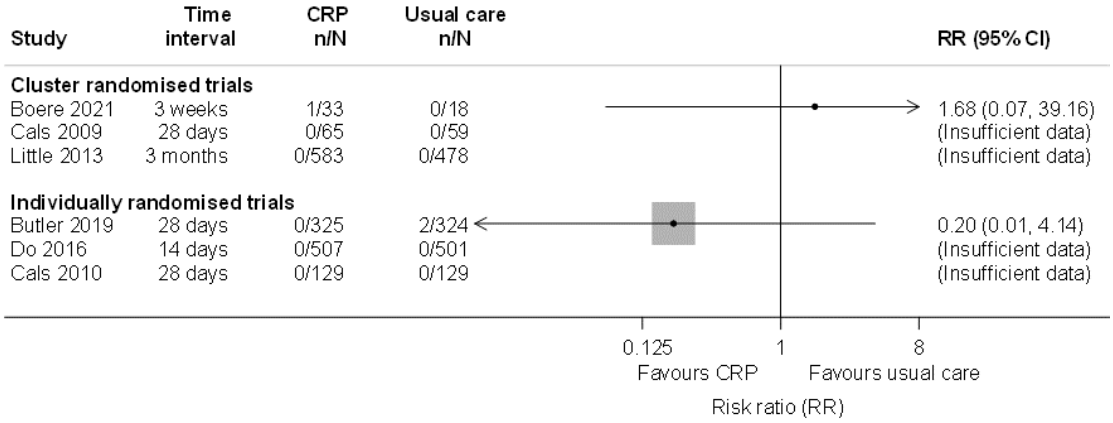
[a] Sample size unclear. [b] Modified sample size. Abbreviations: CRP – C-reactive protein; RR – relative risk.

4.1.2.11 Mortality

Three cluster RCTs[25-27] and three individual RCTs[24, 28, 33] provided evidence on mortality rates at varying timepoints. It was not possible to calculate risk ratios for two cluster-RCTs[25, 26] and two individual RCTs[28, 33] due to zero events in both intervention and usual care arms. Two RCTs provided data to calculate risk ratios but the event rates were very low.[24, 27]

Meta-analysis was not conducted, however, data are presented as a forest plot in Figure 5.

Figure 5: CRP POCT vs usual care - Mortality



4.1.2.12 HRQoL

One UK study reported HRQoL (Appendix 6, Table 11), measured using the EQ-5D-5L index value, EQ-5D visual analogue scale (VAS; with scores ranging from 0 to 100 and higher scores indicating better health), and the CRQ-SAS which measures disease-specific health-related quality of life, 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).[24]

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 timepoints (i.e. at weeks 1, 2 and 4, and at 6 months): adjusted mean difference 0.03 (95% CI -0.04 to 0.09; 1 RCT). By contrast, EQ-5D VAS scores were 3 points higher in the CRP group compared to usual care group measured across different timepoints (i.e. at weeks 1, 2 and 4, and at 6 months): adjusted mean difference 3.12 (95% CI 0.50 to 5.74; 1 RCT).[24]

No 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; 1 RCT, n=399); adjusted mean difference for fatigue domain 0.13 (95% CI -0.12 to 0.38; 1 RCT, n=436); adjusted mean difference for emotional function domain 0.15 (95% CI -0.04 to 0.34; 1 RCT, n=441); adjusted mean difference for mastery domain -0.09 (95% CI -0.18 to 0.01; 1 RCT, n=435).[24]

4.1.2.13 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.[24, 27] Sensitivity analyses were conducted to assess the impact of excluding one study each in patients with AECOPD[24] or in a nursing home setting,[27] 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.[26, 30-33] I Findings for subgroup and sensitivity analyses did not change the conclusions inferred from the main analyses (Appendix 11).

4.1.3 Procalcitonin

The recent systematic review[16] assessed 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 data for one included cluster RCT on the effects of procalcitonin testing.[38] 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 point-of-care test) to guide antibiotic decisions in adults with acute cough in a primary care setting in Switzerland (Table 4 and Appendix 6).[38]

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

4.1.3.1 Risk of bias in included procalcitonin study

Based on the Cochrane Review assessment,[16] the single study assessing procalcitonin[38] 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 reviewer's judgements, the study was also at high risk of bias due to incomplete outcome reporting for 7- or 28-day mortality (Appendix 9).

Table 4: Characteristics of included studies for procalcitonin tests

Study Details	Participants	Interventions	Outcomes and Results	Comments[a]
BRAHMS PCT Procalcitonin				
Lhopitallier 2021 [38] Switzerland Open-label cluster-RCT September 2018 to March 2020 **Follow-up:** 28 days	469 patients Procalcitonin 195, usual care 122 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. POC test kits were provided by the manufacturer Overall risk of bias: High
[a] Overall risk of bias: see Appendix 9 for details. Abbreviations: POC – point-of-care; RCT – randomised controlled trial; RTI – respiratory tract infection.				

4.1.3.2 Hospital admission (immediately after triage or at 28 days)

No 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; 1 cluster-RCT, n=277, very low certainty evidence). [16, 38]

4.1.3.3 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; 1 cluster-RCT, n=317; very low certainty evidence).[16, 38]

4.1.3.4 Escalation of care (some time after initial consultation): Virtual Ward

No eligible evidence was identified for this outcome.

4.1.3.5 Escalation of care (some time after initial consultation): Emergency department visit

No eligible evidence was identified for this outcome.

4.1.3.6 Escalation of care (some time after initial consultation): Unplanned hospital admission

No eligible evidence was identified for this outcome.

4.1.3.7 Hospital length of stay

No eligible evidence was identified for this outcome.

4.1.3.8 Follow-up consultation/ongoing monitoring

No eligible evidence was identified for this outcome.

4.1.3.9 Antibiotic/antiviral use

At the index consultation, antibiotic prescriptions were substantially lower in the procalcitonin group compared to usual care group (RR 0.32, 95% CI 0.23 to 0.44; 1 cluster-RCT, n=317).[16, 38]

Similarly, the number of antibiotic prescriptions was substantially lower in the procalcitonin group compared to the usual care group within 7 days (29.7% versus 61.5%, respectively; 1 cluster-RCT, n=317) and within 28 days follow-up (40.0% versus 70.5%, respectively; 1 cluster-RCT, n=277).[38]

4.1.3.10 Time to clinical cure/resolution of symptoms

No difference in 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; 1 cluster-RCT, n=261).[38]

4.1.3.11 Mortality

No deaths occurred in the procalcitonin group (0/163) or usual care group (0/114); 1 cluster-RCT, n=317; very low certainty evidence).[38]

4.1.3.12 HRQoL

No eligible evidence was identified for this outcome.

4.1.4 Rapid antigen test - Group A Streptococcus tests

Two cluster RCTs assessed the effects of RADT Group A Streptococcus tests in adults with acute sore throat (RADT OSOM® Strep A[39] and RADT Clearview® Exact Strep A (Table 5 and Appendix 6).[40] The studies were conducted in 2011 and 2007, in Spain and Canada, respectively. Sample sizes in the relevant intervention groups were 557[39] and 261.[40] One of the studies included people aged 14 years or over, [39] 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[39] and not reported in the other study. [40]

4.1.4.1 Risk of bias in included of Group A Streptococcus tests studies

The two studies that assessed Group A Streptococcus 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'

(Appendix 9).[39, 40] In addition, one study was at high risk of bias due to lack of blinding of participants and personnel.[39]

Table 5: Characteristics of included studies for Group A Streptococcus tests

Study Details	Participants	Interventions	Outcomes and Results	Comments[a]
RADT OSOM® Strep A				
Llor 2011 [39] Spain Open-label cluster-RCT 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 [40] Canada Open-label cluster-RCT 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

[a] Overall risk of bias: see Appendix 9 for details. Abbreviations: NR – not reported; POC – point of care; RADT – rapid antigen detection test; RCT – randomised controlled trial.

4.1.4.2 Hospital admission (immediately after triage or at 28 days)

No eligible evidence was identified for this outcome.

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

No eligible evidence was identified for this outcome.

4.1.4.4 Escalation of care (some time after initial consultation): Virtual Ward

No eligible evidence was identified for this outcome.

4.1.4.5 Escalation of care (some time after initial consultation): Emergency department visit

No eligible evidence was identified for this outcome.

4.1.4.6 Escalation of care (some time after initial consultation): Unplanned hospital admission

No eligible evidence was identified for this outcome.

4.1.4.7 Hospital length of stay

No eligible evidence was identified for this outcome.

4.1.4.8 Follow-up consultation/ongoing monitoring

No eligible evidence was identified for this outcome.

4.1.4.9 Antibiotic/antiviral use

Two cluster-RCTs found that antibiotic prescriptions were substantially lower in the RADT group compared to usual care group at the index consultation: 43.8% in the RADT group versus 64.1% in the usual care group; p<0.001 (1 cluster-RCT, n=543)[39] and 26.7% in the RADT group versus 58.2% in the usual care group; p<0.001 (1 cluster-RCT, n=261) (Table 6).[40] Neither trial reported data allowing for adjustment of sample sizes for clustering effect.

Table 6: Rapid antigen detection test versus usual care - Antibiotic prescriptions at index consultation

Study	RADT test n/N	Usual care n/N	P-value

Llor 2011 [39]	123/281	168/262	<0.001
Worrall 2007 [40]	32/120	82/141	<0.001
Abbreviations: RADT – rapid antigen detection test			

4.1.4.10 Time to clinical cure/resolution of symptoms

No eligible evidence was identified for this outcome.

4.1.4.11 Mortality

No eligible evidence was identified for this outcome.

4.1.4.12 HRQoL

No eligible evidence was identified for this outcome.

4.1.5 Rapid antigen test – Influenza tests

One RCT (n= 93) conducted 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 Appendix 6). The test used, BD Directigen™ Flu A + B rapid test, is not currently available in the UK.[41]

The source of funding was not reported. The trial was terminated early due to low sensitivity of the intervention.

4.1.5.1 Risk of bias in included study of influenza tests

The single study assessing an influenza test[41] was judged by reviewers 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' (Appendix 9).

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 [41] **NCT00821626** [42] Switzerland Open-label RCT December 2008 to 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 • Mortality	Funding: Not reported Trial finished early due to low sensitivity of the intervention. Overall risk of bias: High
[a] Overall risk of bias: see Appendix 9 for details. Abbreviations: NR – not reported; RADT – rapid antigen detection test; RCT – randomised controlled trial.				

4.1.5.2 Hospital admission (immediately after triage or at 28 days)

No eligible evidence was identified for this outcome.

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

No eligible evidence was identified for this outcome.

4.1.5.4 Escalation of care (some time after initial consultation): Virtual Ward

No eligible evidence was identified for this outcome.

4.1.5.5 Escalation of care (some time after initial consultation): Emergency department visit

No eligible evidence was identified for this outcome.

4.1.5.6 Escalation of care (some time after initial consultation): Unplanned hospital admission

No eligible evidence was identified for this outcome.

4.1.5.7 Hospital length of stay

No eligible evidence was identified for this outcome.

4.1.5.8 Follow-up consultation/ongoing monitoring

No eligible evidence was identified for this outcome.

4.1.5.9 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 (1 RCT, n=93).[41] No patient received antiviral treatment.

4.1.5.10 Time to clinical cure/resolution of symptoms

No eligible evidence was identified for this outcome.

4.1.5.11 Mortality

No deaths occurred in the RADT group (0/60) or usual care group (0/33) (1 RCT, n=93; very low certainty evidence).[41].

4.1.5.12 HRQoL

No eligible evidence was identified for this outcome.

4.1.6 GRADE

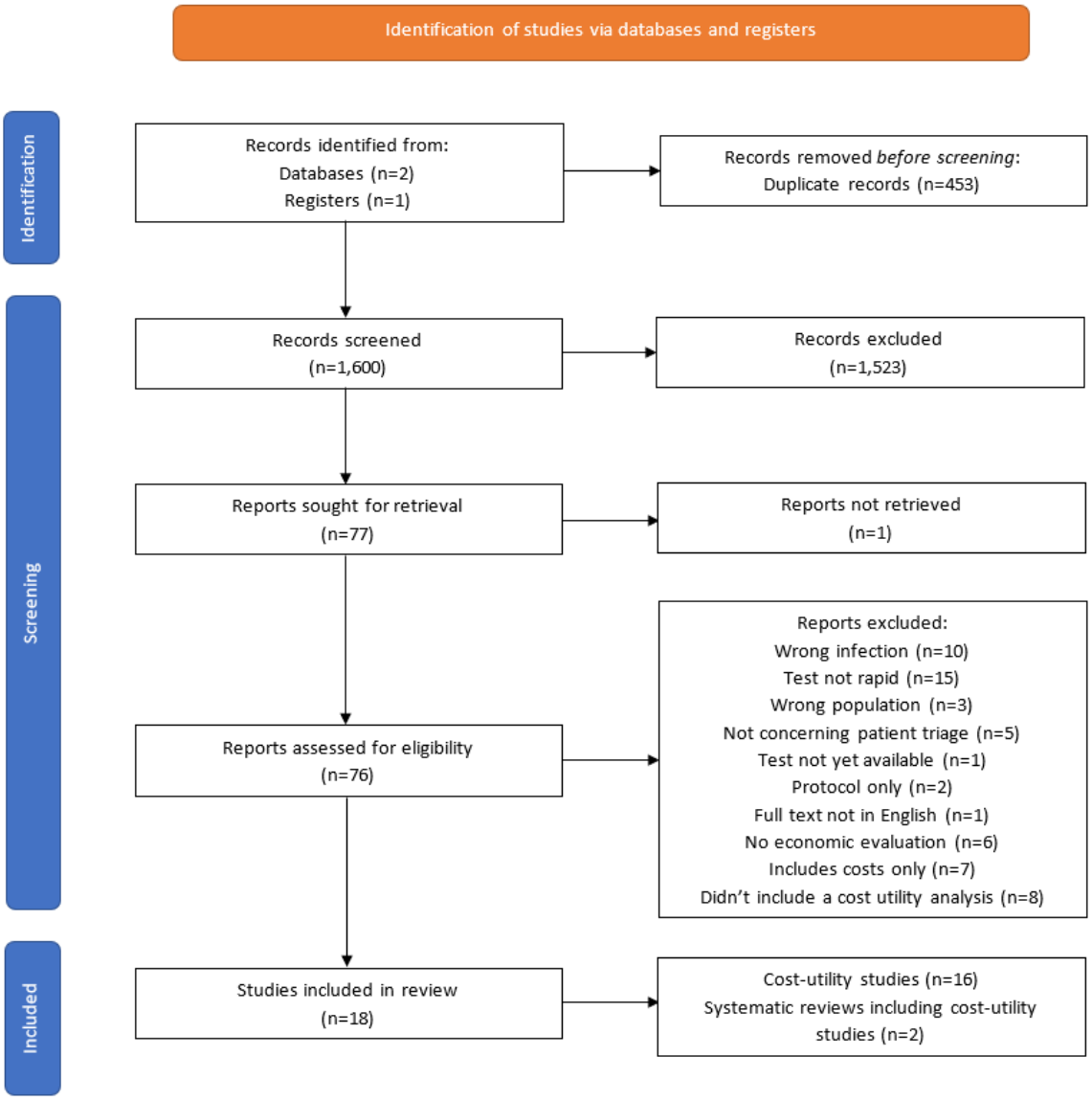
Appendix 10 provides the GRADE summary of the overall evidence for the included tests.

4.2 Cost effectiveness review results

4.2.1 Search Results

The titles and abstracts of 1,600 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 [43] 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 6, with the full references and reasons available in Appendix 13.

Figure 6: PRISMA flowchart for the selection of systematic reviews and cost utility studies



No eligible additional references were identified through examining reference lists.

Two systematic reviews [20, 44] and 16 individual cost-utility studies [34, 45-59] met the pre-defined the eligibility criteria (Figure 6).

4.2.2 Narrative summary, appraisal and applicability – Systematic Reviews

Two potentially relevant systematic reviews were identified.[20, 44] 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, as long as 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, C-reactive protein 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 12). The key issues identified were that 1) the search strategy used terms which are likely to be inconsistently used in the literature e.g. "diagnostic" and was limited in breadth, 2) the grey literature was not searched, 3) the CHEERS checklist [60] 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 objective, 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 heavily in the discussion of this report.[20]

Wubishet 2022

The main objective of the Wubishet 2022 review [44] 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 intervention 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 respiratory tract infection. Six of the included studies focused on adults specifically, with a further 4 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 12). The key issues identified were 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, 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 objective, 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.

4.2.3 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.[44]

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
Billir, 2021 [45]	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 nucleic acid amplification tests (POC NAAT)	RADTs + culture confirmation of negative results (current standard of care)	GAS	Model-based
Chew, 2022 [46]	Patients (any age): systemic antibiotic prescription; ICD 10 code for infection; fever as the chief complaint; documented temperature >37.5C. 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
Francis, 2020 [34]	Patients aged ≥40y; has exacerbation that has lasted at least 34 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
Fraser, 2020 [47]	Adults and children who present with an acute sore throat. Primary and secondary care (urgent care/walk-in centres and emergency departments, modelled separately).	UK NHS and Personal Social Services. 1 year. UK.	POCT (14 tests evaluated) in conjunction with clinical scoring tools e.g. Centor and FeverPAIN score for strep A.	Current standard of care: clinical assessment incorporating clinical scoring tools (no POCT).	GAS	Model-based
Holmes, 2018 [48]	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

Author, Year	Patient Characteristics, Setting	Perspective, Time Horizon, Country	Index Testing Strategy	Comparator Testing Strategy(s)	Target Condition	Analytic Approach
Hunter, 2015 [49]	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
Little, 2014 [50]	Patients aged ≥3y; 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
Mac, 2020 [51]	Patients aged 65; signs of symptoms suggestive of influenza. Emergency Department.	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 5) batch PCR test, do not treat until results available	Influenza-like illness	Model-based
Michael-idis, 2014 [52]	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
Nicholson, 2014 [54]	Patients aged >65y or >18y 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.	POC tests (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, respiratory syncytial virus and pneumococcal infection	RCT

Author, Year	Patient Characteristics, Setting	Study Perspective, Time Horizon, Country	Index Testing Strategy	Comparator Testing Strategy(s)	Target Condition	Analytic Approach
Oppong, 2013 [55]	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.
Rothberg, 2003a [57]	Unvaccinated, healthy, working adults between 20 and 50 years of age presenting with influenza-like illness during the influenza season. 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
Rothberg, 2003b [56]	Non-institutionalised patients aged >65y; 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
Smith, 2002 [58]	Patients aged 32y; influenza-like symptoms and a fever ≥37.8c; different ages included in sensitivity analyses. Not explicitly 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
You, 2017 [59]	Elderly patients (65-90); 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
Neuner, 2003 [53]	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.	Societal. 1 year. US.	Optical immunoassay (OIA)	1) Observation only 2) Antibiotics for all 3) Throat culture +antibiotics for positives 4) OIA followed by culture to confirm negative results, antibiotic treatment for positive cases	GAS	Model-based

	Not explicitly stated; assume primary care.					

CRP: C-reactive protein; GAS: Group A streptococcus; GP: general practice; LRTI: lower respiratory tract infection; OIA: optical immunoassay; POC: point of care; POCT: point of care test US: United States

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 randomised controlled trials.[34, 50, 54]. The majority of the remaining studies were model-based evaluations, 11 of which were decision trees, [45-48, 51-53, 56-59] and one 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.[49] One study was an economic evaluation based on an observational study.[55] 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,[48, 50, 54, 55] 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,[35] with 3 years follow-up.[49]

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 at a range of settings, with many studies (n=7/16) focusing solely or partially on primary care.[34, 46-50, 55] 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.[45, 53, 56-58] Five studies focused their evaluation either solely or partially on a secondary care setting, including ambulatory care, outpatient, or emergency departments.[47, 51, 52, 54, 59]

A wide range of different rapid tests were evaluated, the most common of which being POCT for CRP (n=4/17),[34, 48, 49, 55] and rapid tests for influenza (n=5/17).[54, 56-59] 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.[51, 54, 56-59] 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)[56-58]. Nicholson 2014 evaluated multiple tests (rapid molecular and near-patient diagnostic tests for influenza, respiratory syncytial virus (RSV) and Streptococcus pneumoniae infections) in a UK RCT to evaluate the impact on prescribing and clinical outcomes and cost-effectiveness.[54]

Four of the included studies focused on the use of rapid tests to manage individuals presenting with symptoms suggestive of Group A streptococcus pharyngitis (GAS).[45, 47, 50, 53]. 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 point of care tests for detecting group A Streptococcus bacteria (14 of

these tests featured in the economic evaluation).[47] Another of these studies was an economic evaluation alongside an RCT conducted in the UK.[50]

One of the included studies focused specifically on a sub-group of patients, those who are diagnosed COPD and experiencing an exacerbation.[34] This study was an economic evaluation conducted alongside a RCT [34].

4.2.4 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 14 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 POC CRP.[34, 47-49, 54, 55] Fraser 2020 undertook an extensive systematic review of the evidence of 21 different point of care tests for Group A streptococcus.[47] Nicholson 2014 evaluated rapid near-patient tests for Influenza A and B and pneumococcal infection.[54]

Two studies were judged to be partially applicable to our review question.[50, 52] Little 2014 is an RCT-based economic evaluation focused on a rapid test for A/C/G streptococci in conjunction with the FeverPAIN clinical scoring algorithm. [50] 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.[52] 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.[45, 46, 51, 53, 56-59] These studies were all focused on non-UK settings.

4.3 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 POC CRP in patients presenting to primary care with symptoms suggestive of ARI. All studies found POC CRP to be cost-effective. [48, 49, 55]

Despite being cost-effective, Oppoing 2013 warned about the potential resource implications of widespread use. Holmes 2018 addresses this issue in their evaluation by comparing POC CRP testing and treatment in line with NICE CG191 clinical recommendations i.e. test only when clinical assessment is not conclusive and do not routinely offer antibiotics if CRP is <20mg/L, and offer a delayed prescription if CRP is between 20-100mg/L, compared to pragmatic use of POC CRP.[61] They found that allowing POC 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 incremental cost-effectiveness ratio. A further study evaluated POC CRP specifically in patients experiencing a COPD exacerbation and found that POC CRP was cost-effective at a willingness to pay threshold £20,000 per QALY.[34]

Michaelidis 2014 conducted a model-based economic evaluation of POC PCT, concluding that POC PCT could be cost-effective if the cost of antimicrobial resistance is 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.[52]

Fraser 2020 evaluated 14 different point of care (POC) tests for Group A streptococcus (GAS) and found that none of the POC tests evaluated were cost-effective compared with usual care in both a primary care and secondary setting.[47] Little 2014 conducted an 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 an 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.

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
C-Reactive Protein tests (ARI) *Note, see Francis et al. (2020) below who also focused on POC CRP but specifically for COPD exacerbation							
Holmes, 2018 [48]	Alere Afinion AS100 CRP POCT	ARI	Costs per patient Pragmatic use of testing: Test £52.35 No test £40.41 Adhering to guidelines: Test £48.79 No test £39.48	QALYs per patient Pragmatic use of testing: Test 0.0615 No test 0.0609 Adhering to guidelines: Test 0.0577 No test 0.0556	Pragmatic use of testing: £19,705 Adhering to guidelines: £4,390	*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 the NICE CRP recommendation (by restricting 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 antimicrobial resistance improves the cost-effectiveness of the test.
Hunter, 2015 [49]	Afinion Analyzer CRP POCT by GP; CRP POCT by nurse; CRP POCT by GP+ communication training for GP	RTI	Cost per 100 patients GP+CRP: £18,039 Nurse+CRP: £17,401 GP+CRP+training: £18,431 No test: £18,081	QALYs per 100 patients 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.

Author, Year	Index Testing Strategy	Target Condition	Key Costs Results	Key Effectiveness Results	ICER Results	Headline Results of Uncertainty Analyses	Key Conclusions
Oppong, 2013 [55]	CRP POCT	Community-acquired LRTI	Test increases healthcare costs by €11.27 per patient	QALY gain of 0.0012 with test per patient	€ 9,391	At a WTP threshold of €30,000, the probability of POC CRP being cost-effective is approximately 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 widespread use of the test.
Tests for COPD exacerbation							
Francis, 2020 [34]	Alere Afinion CRP POCT	Bacterial exacerbation of COPD	Costs per patient: Test: £759.35 No test: £629.72	QALYs per patient: 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 £1,054 if COPD-related costs only were included. Most results found CRP POCT to be more costly but more effective. The CUA (using imputation and an ITT 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.
Group A Streptococcus tests (including Group C/G)							
Billir, 2021 [45]	POC NAAT	Group A streptococcus (GAS) pharyngitis	Costs per patient: POC NAAT: $44 RADT+culture: $78	QALDs lost per patient: 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 results robust.	Use of POC NAAT is slightly more effective than RADT+culture without incurring additional costs. POC NAAT also reduces unnecessary antibiotic use.

Author, Year	Index Testing Strategy	Target Condition	Key Costs Results	Key Effectiveness Results	ICER Results	Headline Results of Uncertainty Analyses	Key Conclusions
Little, 2014 [50]	Clinical scoring algorithm (FeverPAIN) +RADT if score high on algorithm	Lancefield group A/C/G streptococci	Costs per patient: RADT £48.50 Clinical algorithm: £45.90 Control: £49.70	QALYs per patient: 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.
Fraser, 2020 [47]	POCT (14 tests evaluated) in conjunction with clinical scoring tools e.g. Centor and FeverPAIN score for strep A	Group A streptococcus (GAS)	Costs per 1000 patients in primary care: 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: 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: 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: 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).

Author, Year	Index Testing Strategy	Target Condition	Key Costs Results	Key Effectiveness Results	ICER Results	Headline Results of Uncertainty Analyses	Key Conclusions
Neuner, 2003 [53]	Optical immunoassay (OIA)	Group A streptococcus (GAS) pharyngitis	Costs per patient: OIA test: $11.73 Observation: $9.84 Culture: $6.66 Empirical therapy: $12.74 OIA+culture: $15.15	QALDs lost per patient: 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.

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 [51]	Rapid influenza diagnostic tests (RIDTs); Digital immunoassays (DIA); rapid nucleic acid amplification tests (NAAT); followed by antiviral therapy	Influenza-like illness	Costs per patient: RIDT: $622.52 DIA: $618.99 NAAT: $636.75 No test (no treatment): $608.19 No test (treat everyone): $630.01; Batch PCR (treat): $661.19; Batch PCR (wait): $661.30 Clinical judgement: $611.02	QALYs per patient: RIDT 15.0175 DIA 15.0338 NAAT 15.0404 No test (no treatment): 14.9961 No test (treat everyone): 15.0470 Batch PCR (treat): 15.0450 Batch PCR (wait): 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)[a] 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, 2003a [56]	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.

Author, Year	Index Testing Strategy	Target Condition	Key Costs Results	Key Effectiveness Results	ICER Results	Headline Results of Uncertainty Analyses	Key Conclusions
Rothberg, 2003b [57]	Rapid antigen test QuickVue; followed by different antiviral therapies	Influenza A and B	Costs for unvaccinated patient aged 75y 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 75y 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.
Smith, 2002 [58]	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 less than 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.

Author, Year	Index Testing Strategy	Target Condition	Key Costs Results	Key Effectiveness Results	ICER Results	Headline Results of Uncertainty Analyses	Key Conclusions
You, 2017 [59]	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; odds ratio 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.

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 [46]	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 over-use. The WHO guideline could be extended to cover all ages.
Michaelidis, 2014 [52]	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.

Author, Year	Index Testing Strategy	Target Condition	Key Costs Results	Key Effectiveness Results	ICER Results	Headline Results of Uncertainty Analyses	Key Conclusions
Nicholson, 2014 [54]	Rapid near-patient diagnostic tests (Quidel for influenza, and BinaxNOW for the pneumococcal antigen)	Influenza A and B, respiratory syncytial virus and pneumococcal infection	Cost per patient: PCR: £1,978 Traditional: £2,327 POCT: £2,159	QALYs per patient PCR: 0.007779 Traditional: 0.007588 POCT: 0.008035	Traditional laboratory culture 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.

CRP – C-reactive protein; NAAT – nucleic acid amplification tests; PCR – polymerase chain reaction; OIA – optical immunoassay; DIA – digital immunoassays; RIDT – rapid influenza diagnostic tests; POCT – point-of-care test; ARI – acute respiratory infection; NAI – neuraminidase inhibitors; RTI – respiratory tract infection; LRTI – lower respiratory tract infection; COPD – chronic obstructive pulmonary disorder; QALYs – quality-adjusted life years; QALDs – quality-adjusted life days; QALEs – quality-adjusted life expectancy; ICER – incremental cost-effectiveness ratio; WTP – willingness to pay; NMB – net monetary benefit; CEAC – cost-effectiveness acceptability curve; HRQoL – health related quality of life; GP – general practitioner; NICE – National Institute for Health and Care Excellence. [a]Batch PCR and treat everyone until results become available, [b]Batch PCR and wait until results are available before making treatment decisions, [c]ARTI judged by their doctor to require antibiotics, [d]ARTI prior to any decision about antibiotics

4.4 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 antimicrobial resistance-related costs separately. We felt this was important additional detail for these studies given that the majority had a short-term time horizon.

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 POC CRP is cost-effective, three of the four economic evaluations focused on this test were limited to capturing short-term costs and consequences. [34, 48, 55] Hunter 2015 however did base their analysis of POC CRP on longer-term (3 year) data from an RCT and also found it to be cost-effective.[49]

A key motivation for rapid testing is to reduce future antimicrobial resistance (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 attempt to incorporate an estimated cost associated with AMR into their sensitivity analyses, but the validity of their calculations was unclear.[46, 48].

Another key potential benefit or harm of rapid, point of care 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 POC 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 attending 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.[35] Although the mean number of episodes of respiratory tract infections during follow-up was lower for the POC CRP arm compared to no CRP, the difference was not statistically significant. Hunter et al. (2015) was the only study to incorporate this data into their evaluation, and rightly noted that any harms associated with reduced attendance will not have been captured in their analysis.[49]

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.

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?
Billir, 2021	✓	X	?	Short ? Long X AMR X	✓	?	NA	✓	✓	✓
Chew, 2022	✓	✓	X	Short X Long X AMR ✓	✓	?	NA	✓	X	✓
Francis, 2020	✓	✓	✓	Short ✓ Long X AMR X	✓	✓	NA	✓	✓	✓
Fraser, 2020	✓	✓	✓	Short ✓ Long X AMR X	✓	✓	NA	✓	✓	✓
Holmes, 2018	✓	✓	✓	Short ✓ Long X AMR ✓	✓	✓	NA	✓	✓	✓
Hunter, 2015	✓	✓	✓	Short ✓ Long ✓ AMR X	✓	✓	✓	✓	✓	✓
Little, 2014	✓	✓	X	Short ✓ Long X AMR X	✓	✓	NA	✓	X	✓
Mac, 2020	✓	✓	?	Short ? Long ? AMR X	X	?	✓	✓	✓	✓

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?
Michaelidis, 2013	✓	✓	X	Short X Long X AMR X	?	?	NA	✓	X	✓
Neuner, 2003	✓	✓	✓	Short ✓ Long X AMR X	✓	✓	NA	✓	✓	✓
Nicholson, 2014	✓	✓	?	Short ✓ Long X AMR X	?	?	NA	✓	X	✓
Oppong, 2013	?	?	X	Short Long X AMR X	X	?	NA	X	✓	X
Rothberg, 2003a	?	?	X	Short Long X AMR X	X	?	?	✓	✓	X
Rothberg, 2003b	?	?	X	Short Long X AMR X	✓	✓	NA	✓	✓	✓
Smith, 2002	?	?	?	Short Long X AMR	X	X	NA	✓	✓	✓
You, 2017	✓	?	X	Short ? Long ? AMR X	✓	?	✓	✓	✓	✓

5 References

1. NHS England. *Combined adult and paediatric Acute Respiratory Infection (ARI) hubs (previously RCAS hubs)*. 2022. URL: https://www.england.nhs.uk/wp-content/uploads/2022/10/BW2064-combined-adult-paediatric-ari-hubs-october-22.pdf (Accessed 10 June 2023).
2. NHS England and NHS Improvement. *Point of care testing in community pharmacies: Guidance for commissioners and community pharmacies delivering NHS services*. 2022. URL: https://www.england.nhs.uk/wp-content/uploads/2022/01/B0722-Point-of-Care-Testing-in-Community-Pharmacies-Guide_January-2022.pdf (Accessed 10 June 2023).
3. Saleh MAA, van de Garde EMW, van Hasselt JGC. Host-response biomarkers for the diagnosis of bacterial respiratory tract infections. *Clin Chem Lab Med* 2019;**57**(4):442-51. http://dx.doi.org/10.1515/cclm-2018-0682
4. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld AB. The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. *Clin Microbiol Infect* 2015;**21**(5):474-81. http://dx.doi.org/10.1016/j.cmi.2014.12.026
5. Tsao YT, Tsai YH, Liao WT, Shen CJ, Shen CF, Cheng CM. Differential Markers of Bacterial and Viral Infections in Children for Point-of-Care Testing. *Trends Mol Med* 2020;**26**(12):1118-32. http://dx.doi.org/10.1016/j.molmed.2020.09.004
6. Hayney MS, Henriquez KM, Barnet JH, Ewers T, Champion HM, Flannery S*, et al.* Serum IFN-γ-induced protein 10 (IP-10) as a biomarker for severity of acute respiratory infection in healthy adults. *J Clin Virol* 2017;**90**:32-7. http://dx.doi.org/10.1016/j.jcv.2017.03.003
7. Shapiro NI, Filbin MR, Hou PC, Kurz MC, Han JH, Aufderheide TP*, et al.* Diagnostic Accuracy of a Bacterial and Viral Biomarker Point-of-Care Test in the Outpatient Setting. *JAMA Network Open* 2022;**5**(10):e2234588-e. http://dx.doi.org/10.1001/jamanetworkopen.2022.34588
8. Vos LM, Bruning AHL, Reitsma JB, Schuurman R, Riezebos-Brilman A, Hoepelman AIM*, et al.* Rapid Molecular Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review of Diagnostic Accuracy and Clinical Impact Studies. *Clin Infect Dis* 2019;**69**(7):1243-53. http://dx.doi.org/10.1093/cid/ciz056
9. Lean WL, Arnup S, Danchin M, Steer AC. Rapid diagnostic tests for group A streptococcal pharyngitis: a meta-analysis. *Pediatrics* 2014;**134**(4):771-81. http://dx.doi.org/10.1542/peds.2014-1094
10. Kim P, Deshpande A, Rothberg MB. Urinary Antigen Testing for Respiratory Infections: Current Perspectives on Utility and Limitations. *Infect Drug Resist* 2022;**15**:2219-28. http://dx.doi.org/10.2147/idr.S321168
11. *SR / MA / HTA / ITC - MEDLINE, Embase, PsycInfo. In. CADTH Search Filters Database*. Ottawa: CADTH; 2021. URL: https://searchfilters.cadth.ca/link/33 (Accessed 23 June 2023).
12. Cochrane. *How CENTRAL is created*. Cochrane Library; 2023. URL: https://www.cochranelibrary.com/central/central-creation (Accessed 23 June 2023).
13. Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Marshall C*, et al. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*. Cochrane; 2022. URL: https://training.cochrane.org/handbook/current/chapter-04 (Accessed 26 May 2023).
14. *MEDLINE Sensitivity- and precision-maximizing version (2023 revision) for Ovid. In: Randomized Controlled Trials and Other Trials: Filters*. The ISSG Search Filter Resource; 2023. URL: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/rcts (Accessed 26 May 2023).

15. Glanville J. *Embase RCT filter for Ovid: 30 April 2023 revision*. The ISSG Search Filter Resource; 2023. URL: https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/rcts/embase-rct-filter#h.ge0knbymsrdx (Accessed 28 May 2023).
16. Smedemark SA, Aabenhus R, Llor C, Fournaise A, Olsen O, Jørgensen KJ. Biomarkers as point-of-care tests to guide prescription of antibiotics in people with acute respiratory infections in primary care. *Cochrane Database Syst Rev* 2022(10):CD010130. http://dx.doi.org/10.1002/14651858.CD010130.pub3
17. Higgins J, Eldridge S, Li Te. Chapter 23: Including variants on randomized trials. In: *Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)* 2022. http://www.training.cochrane.org/handbook
18. Langan D, Higgins JPT, Jackson D, Bowden J, Veroniki AA, Kontopantelis E*, et al.* A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Res Synth Methods* 2019;**10**(1):83-98. http://dx.doi.org/10.1002/jrsm.1316
19. Hubbard W, Walsh N, Hudson T, Heath A, Dietz J, Rogers G. Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Med Res Methodol* 2022;**22**(1):310. http://dx.doi.org/10.1186/s12874-022-01796-2
20. van der Pol S, Garcia PR, Postma MJ, Villar FA, van Asselt ADI. Economic Analyses of Respiratory Tract Infection Diagnostics: A Systematic Review. *Pharmacoeconomics* 2021;**39**(12):1411-27. http://dx.doi.org/10.1007/s40273-021-01054-1
21. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016;**5**(1):210. http://dx.doi.org/10.1186/s13643-016-0384-4
22. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. 4 edn. Oxford, UK: Oxford University Press; 2015.
23. National Institute for Health and Care Excellence. *Appendix H: Appraisal checklists, evidence tables, GRADE and economic profiles. In: Developing NICE guidelines: the manual Process and methods [PMG20]*. 2022. URL: https://www.nice.org.uk/process/pmg20/resources/appendix-h-appraisal-checklists-evidence-tables-grade-and-economic-profiles-pdf-8779777885 (Accessed 31 May 2023).
24. Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E*, et al.* C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations. *N Engl J Med* 2019;**381**(2):111-20. http://dx.doi.org/10.1056/NEJMoa1803185
25. Little P, Stuart B, Francis N, Douglas E, Tonkin-Crine S, Anthierens S*, et al.* Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet (london, england)* 2013;**382**(9899):1175-82. http://dx.doi.org/10.1016/S0140-6736(13)60994-0
26. Cals JW, Butler CC, Hopstaken RM, Hood K, Dinant GJ. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ (Clinical research ed)* 2009;**338**:b1374. http://dx.doi.org/10.1136/bmj.b1374
27. Boere TM, van Buul LW, Hopstaken RM, van Tulder MW, Twisk J, Verheij TJM*, et al.* Effect of C reactive protein point-of-care testing on antibiotic prescribing for lower respiratory tract infections in nursing home residents: cluster randomised controlled trial. *BMJ* 2021;**374**:n2198. http://dx.doi.org/10.1136/bmj.n2198
28. Cals JW, Schot MJ, de Jong SA, Dinant GJ, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. *Ann Fam Med* 2010;**8**(2):124-33. http://dx.doi.org/10.1370/afm.1090

29. Andreeva E, Melbye H. Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomized clinical trial with C-reactive protein testing in the intervention group. *BMC Fam Pract* 2014;**15**:80. http://dx.doi.org/10.1186/1471-2296-15-80
30. Althaus T, Greer RC, Swe MMM, Cohen J, Tun NN, Heaton J*, et al.* Effect of point-of-care C-reactive protein testing on antibiotic prescription in febrile patients attending primary care in Thailand and Myanmar: an open-label, randomised, controlled trial. *Lancet Glob Health* 2019;**7**(1):e119-e31. http://dx.doi.org/10.1016/S2214-109X(18)30444-3
31. Diederichsen HZ, Skamling M, Diederichsen A, Grinsted P, Antonsen S, Petersen PH*, et al.* Randomised controlled trial of CRP rapid test as a guide to treatment of respiratory infections in general practice. *Scand J Prim Health Care* 2000;**18**(1):39-43. http://dx.doi.org/10.1080/02813430050202541
32. Melbye H, Aaraas I, Fleten N, Kolstrup N, Mikalsen JI. The value of C-reactive protein testing in suspected lower respiratory tract infections. A study from general practice on the effect of a rapid test on antibiotic research and course of the disease in adults. *Tidsskr Nor Laegeforen* 1995;**115**(13):1610-5.
33. Do NT, Ta NT, Tran NT, Than HM, Vu BT, Hoang LB*, et al.* Point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in Vietnamese primary health care: a randomised controlled trial. *Lancet Glob Health* 2016;**4**(9):e633-41. http://dx.doi.org/10.1016/S2214-109X(16)30142-5
34. Francis NA, Gillespie D, White P, Bates J, Lowe R, Sewell B*, et al.* C-reactive protein point-of-care testing for safely reducing antibiotics for acute exacerbations of chronic obstructive pulmonary disease: the PACE RCT. *Health Technol Assess* 2020;**24**(15):1-108. http://dx.doi.org/10.3310/hta24150
35. Cals JW, de Bock L, Beckers PJ, Francis NA, Hopstaken RM, Hood K*, et al.* Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year follow-up of a cluster randomized trial. *Ann Fam Med* 2013;**11**(2):157-64. http://dx.doi.org/10.1370/afm.1477
36. Boere TM, El Alili M, van Buul LW, Hopstaken RM, Verheij TJM, Hertogh C*, et al.* Cost-effectiveness and return-on-investment of C-reactive protein point-of-care testing in comparison with usual care to reduce antibiotic prescribing for lower respiratory tract infections in nursing homes: a cluster randomised trial. *BMJ open* 2022;**12**(9):e055234. http://dx.doi.org/10.1136/bmjopen-2021-055234
37. Little P, Stuart B, Francis N, Douglas E, Tonkin-Crine S, Anthierens S*, et al.* Antibiotic Prescribing for Acute Respiratory Tract Infections 12 Months After Communication and CRP Training: a Randomized Trial. *Ann Fam Med* 2019;**17**(2):125-32. http://dx.doi.org/10.1370/afm.2356
38. Lhopitallier L, Kronenberg A, Meuwly JY, Locatelli I, Mueller Y, Senn N*, et al.* Procalcitonin and lung ultrasonography point-of-care testing to determine antibiotic prescription in patients with lower respiratory tract infection in primary care: pragmatic cluster randomised trial. *BMJ* 2021;**374**:n2132. http://dx.doi.org/10.1136/bmj.n2132
39. Llor C, Madurell J, Balagué-Corbella M, Gómez M, Cots JM. Impact on antibiotic prescription of rapid antigen detection testing in acute pharyngitis in adults: a randomised clinical trial. *Br J Gen Pract* 2011;**61**(586):e244-51. http://dx.doi.org/10.3399/bjgp11X572436
40. Worrall G, Hutchinson J, Sherman G, Griffiths J. Diagnosing streptococcal sore throat in adults: randomized controlled trial of in-office aids. *Can Fam Physician* 2007;**53**(4):666-71.
41. Berthod D, Genton B, Hatz C, Blum J, de Vallière S. Ability of physicians to diagnose influenza and usefulness of a rapid influenza antigen test in febrile returning travelers: a randomized controlled trial. *Travel Med Infect Dis* 2015;**13**(5):394-9. http://dx.doi.org/10.1016/j.tmaid.2015.08.001

42. *Rapid Flu Tests in Travelers With Fever*. ClinicalTrials.gov; 2009. URL: https://www.clinicaltrials.gov/study/NCT00821626 (Accessed 20 June 2023).
43. Benson MSG, R.; Kubilis, P. S.; Pierson, D. J. Erratum: Non-bronchoscopic diagnosis of Pneumocystis carinii pneumonia: Is it cost-effective? (Respiratory Care 1990; 35:1100). *Respir Care* 1991;**36**:22.
44. Wubishet BL, Merlo G, Ghahreman-Falconer N, Hall L, Comans T. Economic evaluation of antimicrobial stewardship in primary care: a systematic review and quality assessment. *J Antimicrob Chemother* 2022;**77**(9):2373-88. http://dx.doi.org/10.1093/jac/dkac185
45. Bilir SP, Kruger E, Faller M, Munakata J, Karichu JK, Sickler J*, et al.* US cost-effectiveness and budget impact of point-of-care NAAT for streptococcus. *Am J Manag Care* 2021;**27**(5):e157-e63. http://dx.doi.org/10.37765/ajmc.2021.88638
46. Chew R, Greer RC, Tasak N, Day NPJ, Lubell Y. Modelling the cost-effectiveness of pulse oximetry in primary care management of acute respiratory infection in rural northern Thailand. *Trop Med Int Health* 2022;**27**(10):881-90. http://dx.doi.org/10.1111/tmi.13812
47. Fraser H, Gallacher D, Achana F, Court R, Taylor-Phillips S, Nduka C*, et al.* Rapid antigen detection and molecular tests for group A streptococcal infections for acute sore throat: systematic reviews and economic evaluation. *Health Technol Assess* 2020;**24**(31):1-232. http://dx.doi.org/10.3310/hta24310
48. Holmes EAF, Harris SD, Hughes A, Craine N, Hughes DA. Cost-Effectiveness Analysis of the Use of Point-of-Care C-Reactive Protein Testing to Reduce Antibiotic Prescribing in Primary Care. *Antibiotics* 2018;**7**(4):07. http://dx.doi.org/10.3390/antibiotics7040106
49. Hunter R. Cost-effectiveness of point-of-care C-reactive protein tests for respiratory tract infection in primary care in England. *Adv Ther* 2015;**32**(1):69-85. http://dx.doi.org/10.1007/s12325-015-0180-x
50. Little P, Hobbs FD, Moore M, Mant D, Williamson I, McNulty C*, et al.* PRImary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive randomised controlled trial with nested qualitative study and cost-effectiveness study. *Health Technol Assess* 2014;**18**(6):vii-xxv, 1-101. http://dx.doi.org/10.3310/hta18060
51. Mac S, O'Reilly R, Adhikari NKJ, Fowler R, Sander B. Point-of-care diagnostic tests for influenza in the emergency department: A cost-effectiveness analysis in a high-risk population from a Canadian perspective. *PLoS One* 2020;**15**(11):e0242255. http://dx.doi.org/10.1371/journal.pone.0242255
52. Michaelidis CI, Zimmerman RK, Nowalk MP, Fine MJ, Smith KJ. Cost-effectiveness of procalcitonin-guided antibiotic therapy for outpatient management of acute respiratory tract infections in adults. *J Gen Intern Med* 2014;**29**(4):579-86. http://dx.doi.org/10.1007/s11606-013-2679-7
53. Neuner JM, Hamel MB, Phillips RS, Bona K, Aronson MD. Diagnosis and management of adults with pharyngitis. A cost-effectiveness analysis. *Ann Intern Med* 2003;**139**(2):113-22. http://dx.doi.org/10.7326/0003-4819-139-2-200307150-00011
54. Nicholson KG, Abrams KR, Batham S, Medina MJ, Warren FC, Barer M*, et al.* Randomised controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and Streptococcus pneumoniae infection on the management of acute admissions in the elderly and high-risk 18- to 64-year-olds. *Health Technol Assess* 2014;**18**(36):1-274, vii-viii. http://dx.doi.org/10.3310/hta18360
55. Oppong R, Jit M, Smith RD, Butler CC, Melbye H, Molstad S*, et al.* Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions. *Br J Gen Pract* 2013;**63**(612):e465-71. http://dx.doi.org/10.3399/bjgp13X669185

56. Rothberg MB, Bellantonio S, Rose DN. Management of influenza in adults older than 65 years of age: cost-effectiveness of rapid testing and antiviral therapy. *Ann Intern Med* 2003;**139**(5):321-9. http://dx.doi.org/10.7326/0003-4819-139-5_part_1-200309020-00007
57. Rothberg MB, He S, Rose DN. Management of influenza symptoms in healthy adults. *J Gen Intern Med* 2003;**18**(10):808-15. http://dx.doi.org/10.1046/j.1525-1497.2003.20822.x.
58. Smith KJ, Roberts MS. Cost-effectiveness of newer treatment strategies for influenza. *Am J Med* 2002;**113**(4):300-7. http://dx.doi.org/doi:
59. You JHS, Tam LP, Lee NLS. Cost-effectiveness of molecular point-of-care testing for influenza viruses in elderly patients at ambulatory care setting. *PLoS ONE [Electronic Resource]* 2017;**12**(7):e0182091. http://dx.doi.org/10.1371/journal.pone.0182091
60. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D*, et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Pharmacoeconomics* 2013;**31**(5):361-7. http://dx.doi.org/10.1007/s40273-013-0032-y
61. National Institute for Health and Care Excellence. *Pneumonia in adults: diagnosis and management: Clinical guideline [CG191]*. 2014. URL: https://www.nice.org.uk/guidance/cg191 (Accessed 14 June 2023).

6 Appendices

Appendix 1: Review protocol

Version/Date: Version 1, 18 May 2023

ID	Field	Content
0	PROSPERO registration number	PROSPERO CRD42023429515
1	Review Title	Clinical effectiveness and cost-effectiveness of rapid, near-patient tests for guiding initial management for adult patients with suspected acute respiratory infection: a rapid evidence synthesis
2	Review question	RQ1.3: In people aged 16 and over with suspected acute respiratory infection, what is the clinical effectiveness and cost-effectiveness of near-patient, rapid microbiological or biomarker tests or combination of tests for guiding patient management?
3	Objective	To conduct a rapid review to assess the clinical effectiveness and cost effectiveness of different near-patient, rapid tests alone or in combination to guide management in people aged 16 and over with suspected acute respiratory infection.
4	Searches	Clinical effectiveness Searches will combine the concepts of acute respiratory infections with near patient, rapid tests and study type filters. 1. Searches to find systematic reviews. The following databases will be searched for systematic reviews: • MEDLINE via Ovid • Epistemonikos Search concepts will combine acute respiratory infection and rapid tests (broad concept). These elements are based on the draft search strategy developed by Bristol ESG for RQ1.4, with some terms removed (see section 6 below). See Appendix 1 for our draft search for MEDLINE. Search filters: A sensitive systematic review filter (based on CRD and CADTH) will be applied to Medline. Date: no date limit References identified by the project team via highly targeted searches during the scoping phase will also be reviewed. 2. Additional searches to find recent RCTs will be conducted in the following databases.

		• Embase (Ovid) • MEDLINE (Ovid) • Cochrane Central Register of Controlled Trials (CENTRAL) A sensitive RCT filter will be used in Embase and Medline (based on Cochrane HSSS balanced 'sensitivity- and precision-maximizing' version). Date limit: the dates of searches in relevant systematic reviews. If there are evidence gaps (e.g. in terms of missing interventions) in the systematic reviews, we will run focussed RCT searches to address those gaps with no date limit. <u>Cost-effectiveness</u> Searches will combine the concepts of acute respiratory infections with near patient, rapid tests / diagnostics / testing and cost-utility. 3. Additional searches for cost-utility studies will be conducted in the following databases: • Embase (Ovid) • MEDLINE (Ovid) • CEA registry A precise, yet highly sensitive cost-utility study filter will be used in Embase and Medline (Hubbard W, Walsh N, Hudson T, Heath A, Dietz J, Rogers G. Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. BMC Med Res Methodol. 2022;22:310.) See Appendix 1 for our draft search for MEDLINE, which finds a known systematic review (van der Pol S, et al. Economic analyses of respiratory tract infection diagnostics: a systematic review. Pharmacoeconomics. 2021 Jul 15:1-7.) and the 13 studies from this review that are likely to be relevant to our research question. Date limit: no date limit References identified by the project team via highly targeted searches during the scoping phase will also be reviewed. Searches will be restricted to: English language Humans

		Searches will exclude: Dissertations and theses Conference abstracts Editorials, letters, news items and commentaries Pre-print sources will not be searched References of included studies and relevant reviews will be checked.
5	Condition or domain being studied	Acute respiratory infection
6	Population	Inclusion: People aged 16 years or over with suspected acute respiratory infection. Exclusion: 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 acute respiratory infections that rarely require or lead to escalation of care to hospital admission such as otitis media and sinusitis. Children and young people under 16 years. Acute respiratory infection mostly found in children and infants such as croup, bronchiolitis and whooping cough are therefore excluded.
7	Intervention	Near patient, rapid tests (turnaround time ≤ 45mins, also known as point of care tests) which are currently licensed and available for use in the UK as follows: • Rapid antigen test • Rapid PCR tests • Urinary antigen tests • C-reactive protein • Procalcitonin • Serum sodium • Urea nitrogen • Partial pressure O2 • Blood gases • Full blood count • White blood cell count • Myxovirus resistance protein A

		• TNF-related apoptosis-induced ligand (TRAIL) • Interferon-γ-induced protein-10 (IP-10) Exclusion: Tests for Covid-19
8	Comparator	Current practice
9	Types of study to be included	For the clinical effectiveness review: • Systematic reviews of RCTs • RCTs For the cost-effectiveness review: • Systematic reviews of economic evaluations • Cost-utility studies
10	Other exclusion criteria	• Non systematic reviews • Non RCTs • Studies not published in English • Pre-prints • Dissertations & theses • Registry entries for ongoing clinical trials • Editorials, letters, news items and commentaries • Animal studies • Conference abstracts and posters • Derivation studies
11	Context	At the initial face-to-face contact with the health system (e.g. at GP surgeries, walk-in centres, acute respiratory hubs or emergency departments), people over 16 years with suspected acute respiratory infections can be sent home for self-monitoring (with or without being prescribed antibiotics or antivirals), be referred to acute respiratory infection virtual wards for further monitoring, or be referred to or admitted to a hospital. This review aims to assess whether rapid tests used in these settings are clinically and cost effective. Acute respiratory infections cover a wide range of different conditions. The primary concerns here are conditions for which rapid or point of care tests may be used to identify serious cases or predict potential to deteriorate (which would require a different level of monitoring and healthcare).

12	Outcomes	Clinical effectiveness review:
		• Hospital admission (immediately after triage or at 28 days)
		• Escalation of care (some time after initial consultation):
		  ○ Re-consultation/appointment
		  ○ Virtual Ward
		  ○ A&E visit
		  ○ Unplanned hospital admission
		• Hospital length of stay
		• Follow-up consultation/ongoing monitoring

		• Antibiotic/antiviral use • Time to clinical cure/resolution of symptoms • Mortality • HRQoL (using a validated scale) Cost-effectiveness review: • Incremental cost (NHS and personal social services perspective) • Life-years gained • Incremental QALYs • Incremental DALYS • ICER/ cost per QALY • Incremental net health/monetary benefit
13	Data extraction (selection and coding)	Identified systematic reviews will be considered for the rapid review both as the primary source of evidence and as a source of RCTs and cost-utility studies. Starting with the most recent published reviews, identified systematic reviews will be assessed for their applicability, and those eligible will be quality assessed using published tools (see Risk of bias assessment below). Systematic reviews of good quality that closely match the review protocol will be extracted rather than extracting from the primary studies. Where a good quality review is found, earlier reviews with largely overlapping scope and RCTs covered by the review will not be assessed or extracted. If no good quality, applicable systematic reviews are identified, or where there are evidence gaps (for example missing interventions or outcomes) in the systematic reviews, we will conduct searches for RCTs and cost-utility studies following the methods described above. All references identified by the searches and from other sources will be uploaded into Endnote and de-duplicated. Titles and abstracts will be reviewed by one reviewer with 20% of the titles and abstracts being reviewed by two reviewers. We aim to achieve at least 90% agreement before proceeding to single reviewer screening. Any disagreements will be resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above by one reviewer. 20% of potentially eligible studies will be assessed by two reviewers.

		A pre-piloted and standardised form will be used to extract data from studies. The initial 20% of extractions will be checked by a second reviewer. Disagreements between reviewers will be resolved by discussion, with involvement of a third review author where necessary.
14	Risk of bias (quality) assessment	Quality of included systematic reviews, RCTs and cost-utility studies will be assessed by one reviewer, with the initial 20% assessed by a second reviewer to ensure that consistency is achieved. For systematic reviews we will use the tool produced by the Joanna Briggs Institute (https://jbi.global/critical-appraisal-tools); for RCTs we will use Cochrane RoB tool(s) consistent with published reviews and for cost utilities we will use the Drummond checklist. For cost-utility studies that are based on decision analytic models, we will supplement the quality assessment with the Philips checklist if time permits. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;313(7052):275-83. doi: 10.1136/bmj.313.7052.275 Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004;8(36):1-158. doi: 10.3310/hta8360 We will assess the certainty of the evidence using the 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)
15	Strategy for data synthesis	All included systematic reviews, RCTs and cost-utility studies will be tabulated and summarised narratively. Meta-analysis of clinical effectiveness outcomes will be considered if time allows and sufficient data reasonably homogeneous studies are available. This will be guided by study design, population, outcomes, and risk of bias assessment. Homogeneity will be measured using I^2 statistic and chi square test and by assessing study characteristics. Funnel plots will be constructed for assessing small study effects if sufficient number (≥10) of studies are available in individual meta-analyses.

		Missing data will be excluded from analyses. Methods of imputation will not be performed, nor will we attempt to contact authors to get pertinent missing data due to a lack of time.	
16	Analysis of sub-groups	Where stratified data for the following subgroups are reported, they will be considered for subgroup analyses irrespective of statistical heterogeneity: • Age of patient (65 years and under, 66 – 80 years, over 80 years) • Presence of chronic co-morbidity (for example, COPD) • Pregnancy & post-partum (up to 28 days)	
17	Type and method of review	x	Intervention
			Diagnostic
			Prognostic
			Qualitative
			Epidemiologic
			Service Delivery
			Other (specify)
18	Language	English	
19	Country	England	
20	Named contact	Jill Colquitt Yen-Fu Chen	
21	Review team members	Jill Colquitt, Clinical Effectiveness Lead Bethany Shinkins, Cost-effectiveness Lead Rachel Court, Information Specialist Emma Loveman, Senior Reviewer Fiona Whiter, Evidence Reviewer Katie Scandrett, Evidence Reviewer & Statistician Janette Parr, Evidence Reviewer Lena Alkhudairy, Senior Reviewer Yemisi Takwoingi, Senior Reviewer Amy Grove, Senior Reviewer Daniel Lasserson, Clinical Advisor Paramjit Gill, Clinical Advisor Sarah Abrahamson, Project Manager Yen-Fu Chen, Project Lead	
22	Funding sources	NIHR Evidence Synthesis Programme, NIHR153453.	
23	Conflicts of interest	None declared.	

Appendix 2: Literature Search Strategies

Searches for systematic reviews

MEDLINE (Ovid)

Searched: 04 May 2023

Ovid MEDLINE(R) ALL <1946 to May 03, 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 meta-pneumovir* 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

1 31 (rapid molecular or multiplex*).mp. 72823

2 32 lab-on-a-chip.tw,kf. 3494

3 33 ((lateral flow adj (assay* or immunoassay* or test*)) or LFA or LFIA).tw,kf. 9954

4 34 (immunochromatograph* or immuno-chromatograph* or immuno-chromato-graph* or
5 direct immunofluorescence or direct immuno-fluorescence or enzym* immunoassay* or enzym*
6 immuno-assay* or fluorescence immunoassay* or fluorescence immuno-assay* or optical
7 immunoassay* or optical immuno-assay*).mp. or (ICA or EIA or FIA or OIA).tw,kf. 60364

8 35 ((chemiluminescen* or chemi-luminescen*) adj (immunoassay* or immuno-assay* or
9 assay*)).mp. 4693

10 36 (((mobile or portable or handheld or hand-held) adj3 (analy#er? or device? or meters or
11 metres)) and (blood? or plasma or saliva or sputum or spit or mucus or urine or urea or urinalys* or
12 fluids or gas or gases)).mp. 2602

13 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
14 [Rapid Tests] 452888

15 38 20 and 37 [RTIs / RTI Viral Infection / RTI Bacterial Infection AND Rapid Tests] 33006

16 39 (systematic review or meta-analysis).pt. 309240

17 40 meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as
18 topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment,
19 biomedical/ or network meta-analysis/ 347218

20 41 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or
21 overview*))).ti,ab,kf. 313541

22 42 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or
23 overview*))).ti,ab,kf. 15381

24 43 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or
25 (pool* adj3 analy*)).ti,ab,kf. 38276

26 44 (data synthes* or data extraction* or data abstraction*).ti,ab,kf. 39706

27 45 (handsearch* or hand search*).ti,ab,kf. 11062

28 46 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin
29 square*).ti,ab,kf. 35169

30 47 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology
31 overview* or technology appraisal*).ti,ab,kf. 11998

32 48 (meta regression* or metaregression*).ti,ab,kf. 14264

33 49 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or
34 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 69	856

Total after 7 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: 26/05/2023 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,kw	51341
#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,kw 1072

#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 #19 74475

#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 #37 20117

#39 #20 AND #38 2081

CDSR: 37

Protocols: 3

CENTRAL: 2035

Editorials: 1

Clinical Answers: 5

MEDLINE (Ovid)

Searched: 26 May 2023

Ovid MEDLINE(R) ALL <1946 to May 25, 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 meta-pneumovir* 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 46 1525057

48 exp animals/ not humans/ 5123796

49 47 not 48 1403647

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 language 1959

57 limit 56 to yr="2022 -Current" 418

58 limit 57 to (comment or editorial or letter or news) 2

59 57 not 58 416

Embase (Ovid)

Searched: 28 May 2023

Embase Classic+Embase <1947 to 2023 May 25>

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 meta-pneumovir* 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 19 1474981

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 37 682176

39 37 and 20 1955

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/40-58 10289233

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/60-72 4378964

74 59 not 73 8989986

75 39 and 74 681

76 limit 75 to english language 672

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 78 69

Searches for cost-effectiveness

MEDLINE (Ovid)

Searched: 16 May 2023

Ovid MEDLINE(R) ALL <1946 to May 15, 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 meta-pneumovir* 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

1 33 ((lateral flow adj (assay* or immunoassay* or test*)) or LFA or LFIA).tw,kf. 9974

2 34 (immunochromatograph* or immuno-chromatograph* or immuno-chromato-graph* or
3 direct immunofluorescence or direct immuno-fluorescence or enzym* immunoassay* or enzym*
4 immuno-assay* or fluorescence immunoassay* or fluorescence immuno-assay* or optical
5 immunoassay* or optical immuno-assay*).mp. or (ICA or EIA or FIA or OIA).tw,kf. 60440

6 35 ((chemiluminescen* or chemi-luminescen*) adj (immunoassay* or immuno-assay* or
7 assay*)).mp. 4700

8 36 (((mobile or portable or handheld or hand-held) adj3 (analy#er? or device? or meters or
9 metres)) and (blood? or plasma or saliva or sputum or spit or mucus or urine or urea or urinalys* or
10 fluids or gas or gases)).mp. 2611

11 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
12 [Rapid Tests] 453799

13 38 20 and 37 [RTIs / RTI Viral Infection / RTI Bacterial Infection AND Rapid Tests] 33110

14 39 exp Diagnosis/ 9337079

15 40 di.fs. 2925815

16 41 diagnos*.ti,ab,kf. 3041447

17 42 (test or tests or testing).ti,ab,kf. 2837989

18 43 39 or 40 or 41 or 42 [Diagnosis / Testing (broad)]12968950

19 44 20 and 43 [RTIs / RTI Viral Infection / RTI Bacterial Infection AND Diagnosis / Testing (broad)]
20 420239

21 45 Cost-Benefit Analysis/ 92348

22 46 (cost* and (((qualit* adj2 adjust*) and life*) or qaly*)).tw,kf. 17443

23 47 ((incremental* adj2 cost*) or ICER).tw,kf. 17647

24 48 (cost adj2 utilit*).tw,kf. 7139

25 49 (cost* and ((net adj benefit*) or ((net adj monetary) and benefit*) or ((net adj health) and
26 benefit*))).tw,kf. 2345

27 50 ((cost adj2 effect*) and ((quality adj of) and life)).tw,kf. 12651

28 51 (cost and (effect* or utilit*)).ti. 38213

29 52 45 or 46 or 47 or 48 or 49 or 50 or 51 113868 [cost-utility filter – precise version - based
30 on Hubbard et al 2022]

31 53 38 and 52 203

32 54 44 and 52 1292

33 55 53 or 54 1301

56 limit 55 to english language 1238

57 limit 56 to (comment or editorial or letter or news or newspaper article) 56

58 56 not 57 1182

Embase (Ovid)

Searched: 18 May 2023

Embase Classic+Embase <1947 to 2023 May 17>

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 meta-pneumovir* 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 52 1108

55 53 or 54 1121

56 limit 55 to english language 1087

57 limit 56 to (conference abstract or conference paper or "conference review" or editorial or letter) 261

58 56 not 57 826

CEA 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

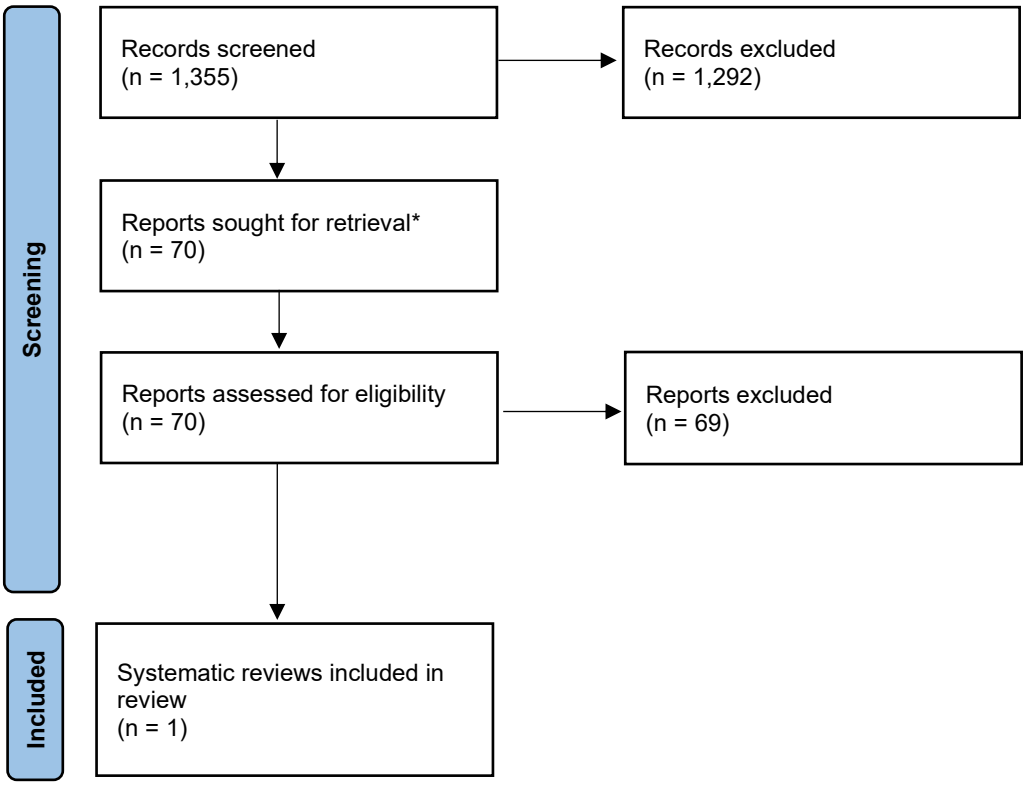
#8 Keyword is: extra laboratory and Disease (ICD-10) is: 10 [Diseases of the respiratory system (J00-J99)] = 0 articles

Total: 45

Total after duplicates removed: 35

Total after duplicates found in MEDLINE or Embase removed: 17

Appendix 3: Study flow diagram: Systematic reviews of clinical effectiveness



*Includes 7 records identified through examining reference lists.

Modified from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 4: Excluded systematic reviews

Full reference	Reason for exclusion
Aabenhus R, Jensen JU, Jorgensen KJ, Hrobjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database Syst Rev. 2014(11):CD010130.	Updated by Smedemark 2022 Cochrane Review.
Abraham MK, Perkins J, Vilke GM, Coyne CJ. Influenza in the Emergency Department: Vaccination, Diagnosis, and Treatment: Clinical Practice Paper Approved by American Academy of Emergency Medicine Clinical Guidelines Committee. J Emerg Med. 2016;**50**(3):536-42.	Outcomes – no relevant outcomes reported (limited outcome data – diagnostic accuracy data).
Alter DN. Point-of-Care Testing for the Emergency Department Patient: Quantity and Quality of the Available Evidence. Arch Pathol Lab Med. 2021;**145**(3):308-19.	Outcomes – no relevant outcomes reported (inpatient LOS, change in testing practice, change in treatment plan, disposition, or use of additional diagnostic services).
Bernstein DI, Mejias A, Rath B, Woods CW, Deeter JP. Summarizing Study Characteristics and Diagnostic Performance of Commercially Available Tests for Respiratory Syncytial Virus: A Scoping Literature Review in the COVID-19 Era. The Journal of Applied Laboratory Medicine 2023;**8**(2):353-371.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Bouzid D, Zanella MC, Kerneis S, Visseaux B, May L, Schrenzel J, et al. Rapid diagnostic tests for infectious diseases in the emergency department. Clin Microbiol Infect. 2021;**27**(2):182-91.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Bruning AHL, Leeflang MMG, Vos J, Spijker R, de Jong MD, Wolthers KC, et al. Rapid Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review and Meta-analysis. Clin Infect Dis. 2017;**65**(6):1026-32.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Carlton HC, Savovic J, Dawson S, Mitchelmore PJ, Elwenspoek MMC. Novel point-of-care biomarker combination tests to differentiate acute bacterial from viral respiratory tract infections to guide antibiotic prescribing: a systematic review. Clin Microbiol Infect. 2021;**27**(8):1096-108.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Chartrand C, Leeflang MM, Minion J, Brewer T, Pai M. Accuracy of rapid influenza diagnostic tests: a meta-analysis. Ann Intern Med. 2012;**156**(7):500-11.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Chartrand C, Tremblay N, Renaud C, Papenburg J. Diagnostic Accuracy of Rapid Antigen Detection Tests for Respiratory Syncytial Virus Infection: Systematic Review and Meta-analysis. J Clin Microbiol. 2015;**53**(12):3738-49.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Clark TW, Lindsley K, Wigmosta TB, Bhagat A, Hemmert RB, Uye J, et al. Rapid multiplex PCR for respiratory viruses reduces time to result and improves clinical care: Results of a	Intervention – not all POC tests; subgroup analysis was planned

Full reference	Reason for exclusion
systematic review and meta-analysis. Journal of Infection 2023;**86**(5):462-475.	but not performed due to lack of evidence.
Cohen JF, Pauchard JY, Hjelm N, Cohen R, Chalumeau M. Efficacy and safety of rapid tests to guide antibiotic prescriptions for sore throat. Cochrane Database Syst Rev. 2020;**6**:CD012431.	Outcomes – subgroup analyses in adults only not conducted for relevant outcomes.
Cooke J, Butler C, Hopstaken R, Dryden MS, McNulty C, Hurding S, et al. Narrative review of primary care point-of-care testing (POCT) and antibacterial use in respiratory tract infection (RTI). BMJ Open Respir Res. 2015;**2**(1):e000086.	Outcomes - relevant studies not synthesised quantitatively; includes diagnostic accuracy outcome data.
Cooke J, Llor C, Hopstaken R, Dryden M, Butler C. Respiratory tract infections (RTIs) in primary care: narrative review of C reactive protein (CRP) point-of-care testing (POCT) and antibacterial use in patients who present with symptoms of RTI. BMJ Open Respir Res. 2020;**7**(1):09.	Outcomes - relevant studies not synthesised quantitatively.
Delaney BC, Hyde CJ, McManus RJ, Wilson S, Fitzmaurice DA, Jowett S, et al. Systematic review of near patient test evaluations in primary care. BMJ 1999;**319**(7213):824-7.	Outcomes - relevant impact studies not synthesised quantitatively.
Dubois C, Smeesters PR, Refes Y, Levy C, Bidet P, Cohen R, et al. Diagnostic accuracy of rapid nucleic acid tests for group A streptococcal pharyngitis: systematic review and meta-analysis. Clin Microbiol Infect. 2021;**27**(12):1736-45.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Egilmezer E, Walker GJ, Bakthavathsalam P, Peterson JR, Gooding JJ, Rawlinson W, et al. Systematic review of the impact of point-of-care testing for influenza on the outcomes of patients with acute respiratory tract infection. Rev Med Virol. 2018;**28**(5):e1995.	Population – mixed age population with influenza-like illness in mixed settings.
Engel MF, Paling FP, Hoepelman AI, van der Meer V, Oosterheert JJ. Evaluating the evidence for the implementation of C-reactive protein measurement in adult patients with suspected lower respiratory tract infection in primary care: a systematic review. Fam Pract. 2012;**29**(4):383-93.	Outcomes - relevant studies not synthesised quantitatively.
Fraser H, Gallacher D, Achana F, Court R, Taylor-Phillips S, Nduka C, et al. Rapid antigen detection and molecular tests for group A streptococcal infections for acute sore throat: systematic reviews and economic evaluation. Health Technol Assess. 2020;**24**(31):1-232.	Outcomes – most studies reporting diagnostic accuracy data; clinical outcome studies include mixed age population.
Gentilotti E, De Nardo P, Cremonini E, Gorska A, Mazzaferri F, Canziani LM, et al. Diagnostic accuracy of point-of-care tests in acute community-acquired lower respiratory tract infections. A systematic review and meta-analysis. Clinical Microbiology & Infection 2022;**28**(1): 13-22.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Goyder C, Tan PS, Verbakel J, Ananthakumar T, Lee JJ, Hayward G, et al. Impact of point-of-care panel tests in ambulatory care:	Population – not patients with ARI (includes all patients presenting to the ED).

Full reference	Reason for exclusion
a systematic review and meta-analysis. BMJ Open 2020;**10**:e032132.	
Gubbins PO, Klepser ME, Adams AJ, Jacobs DM, Percival KM, Tallman GB. Potential for Pharmacy-Public Health Collaborations Using Pharmacy-Based Point-of-Care Testing Services for Infectious Diseases. J Public Health Manag Pract. 2017;**23**(6):593-600.	Study design – not a systematic review.
Han MY, Xie TA, Li JX, Chen HJ, Yang XH, Guo XG. Evaluation of Lateral-Flow Assay for Rapid Detection of Influenza Virus. Biomed Res Int. 2020;**2020**:3969868.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Hankey B, Riley B. BET 1: use of a procalcitonin algorithm to guide antimicrobial therapy in COPD exacerbations can reduce antibiotic consumption with no increase in rates of treatment failure or mortality. Emergency medicine journal : EMJ. 2015;**32**(6):493-5.	Publication type – Editorial/commentary.
Hey J, Thompson-Leduc P, Kirson NY, Zimmer L, Wilkins D, Rice B, et al. Procalcitonin guidance in patients with lower respiratory tract infections: a systematic review and meta-analysis. Clinical chemistry and laboratory medicine. 2018;**56**(8):1200-9.	Population – includes inpatients; no subgroup analysis in relevant population.
Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. The British journal of general practice : the journal of the Royal College of General Practitioners 2013;**63**(616):e787–e794.	Population – includes mixed age population; no subgroup analysis in adults only.
Huang HS, Tsai CL, Chang J, Hsu TC, Lin S, Lee CC. Multiplex PCR system for the rapid diagnosis of respiratory virus infection: systematic review and meta-analysis. Clin Microbiol Infect. 2018;**24**(10):1055-63.	Outcomes – compares diagnostic accuracy of three rapid multiplex PCR tests.
Joseph P, Godofsky E. Outpatient Antibiotic Stewardship: A Growing Frontier-Combining Myxovirus Resistance Protein A With Other Biomarkers to Improve Antibiotic Use. Open forum infect. 2018;**5**(2):ofy024.	Study design – not a systematic review.
Joshi A, Perin DP, Gehle A, Nsiah-Kumi PA. Feasibility of using C-reactive protein for point-of-care testing. Technol Health Care. 2013;**21**(3):233-40.	Outcomes – limited outcome data reported (frequency data).
Kawasaki T, Nakagawa N, Murata M, Yasuo S, Yoshida T, Ando K, et al. Diagnostic accuracy of urinary antigen tests for legionellosis: A systematic review and meta-analysis. Respiratory Investigation 2022;**60**(2): 205-214.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Ko F, Drews SJ. The impact of commercial rapid respiratory virus diagnostic tests on patient outcomes and health system utilization. Expert Rev Mol Diagn. 2017;**17**(10):917-31.	Study design – not a systematic review.
Kochling A, Loffler C, Reinsch S, Hornung A, Bohmer F, Altiner A, et al. Reduction of antibiotic prescriptions for acute	Intervention – includes POC tests and non-POC tests; relevant

Full reference	Reason for exclusion
respiratory tract infections in primary care: a systematic review. Implement Sci. 2018;**13**(1):47.	studies not synthesised quantitatively.
Koski RR, Klepser ME. A systematic review of rapid diagnostic tests for influenza: considerations for the community pharmacist. J Am Pharm Assoc (2003). 2017;**57**(1):13-9.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Lean WL, Arnup S, Danchin M, Steer AC. Rapid diagnostic tests for group A streptococcal pharyngitis: a meta-analysis. Pediatrics. 2014;**134**(4):771-81.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Lee JJ, Verbakel JY, Goyder CR, Ananthakumar T, Tan PS, Turner PJ, et al. The Clinical Utility of Point-of-Care Tests for Influenza in Ambulatory Care: A Systematic Review and Meta-analysis. Clin Infect Dis. 2019;**69**(1):24-33.	Outcomes – reports outcomes for non-RCTs and RCTs in children.
Lee J, Song JU, Kim YH. Diagnostic Accuracy of the Quidel Sofia Rapid Influenza Fluorescent Immunoassay in Patients with Influenza-like Illness: A Systematic Review and Meta-analysis. Tuberculosis & Respiratory Diseases 2021;**84**(3): 226-236.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Lingervelder D, Koffijberg H, Kusters R, MJ IJ. Point-of-care testing in primary care: A systematic review on implementation aspects addressed in test evaluations. Int J Clin Pract. 2019;**73**(10):e13392.	Population – not limited to patients with ARI; no subgroup analysis conducted in relevant population.
Little P, Hobbs FD, Moore M, Mant D, Williamson I, McNulty C, et al. PRImary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive randomised controlled trial with nested qualitative study and cost-effectiveness study. Health Technol Assess. 2014;**18**(6):vii-xxv, 1-101.	Study design – not a systematic review.
Marchello CS, Ebell MH, Dale AP, Harvill ET, Shen Y, Whalen CC. Signs and Symptoms That Rule out Community-Acquired Pneumonia in Outpatient Adults: A Systematic Review and Meta-Analysis. J Am Board Fam Med. 2019;**32**(2):234-47.	Intervention - Clinical decision rule (including POC test) to diagnose, predict or rule out community-acquired pneumonia.
Martínez-González NA, Coenen S, Plate A, Colliers A, Rosemann T, Senn O, Neuner-Jehle S. The impact of interventions to improve the quality of prescribing and use of antibiotics in primary care patients with respiratory tract infections: a systematic review protocol. BMJ open 2017;**7**(6), e016253.	Publication type – protocol only.
Martinez-Gonzalez NA, Keizer E, Plate A, Coenen S, Valeri F, Verbakel JYJ, et al. Point-of-Care C-Reactive Protein Testing to Reduce Antibiotic Prescribing for Respiratory Tract Infections in Primary Care: Systematic Review and Meta-Analysis of Randomised Controlled Trials. Antibiotics (Basel). 2020;**9**(9):16.	Outcomes - relevant studies not synthesised quantitatively.
McDonagh M, Peterson K, Winthrop K, Cantor A, Holzhammer B, Buckley DI. Agency for Healthcare Research and Quality (US). 2016;**15**(16):01.	Outcomes - relevant studies not synthesised quantitatively.

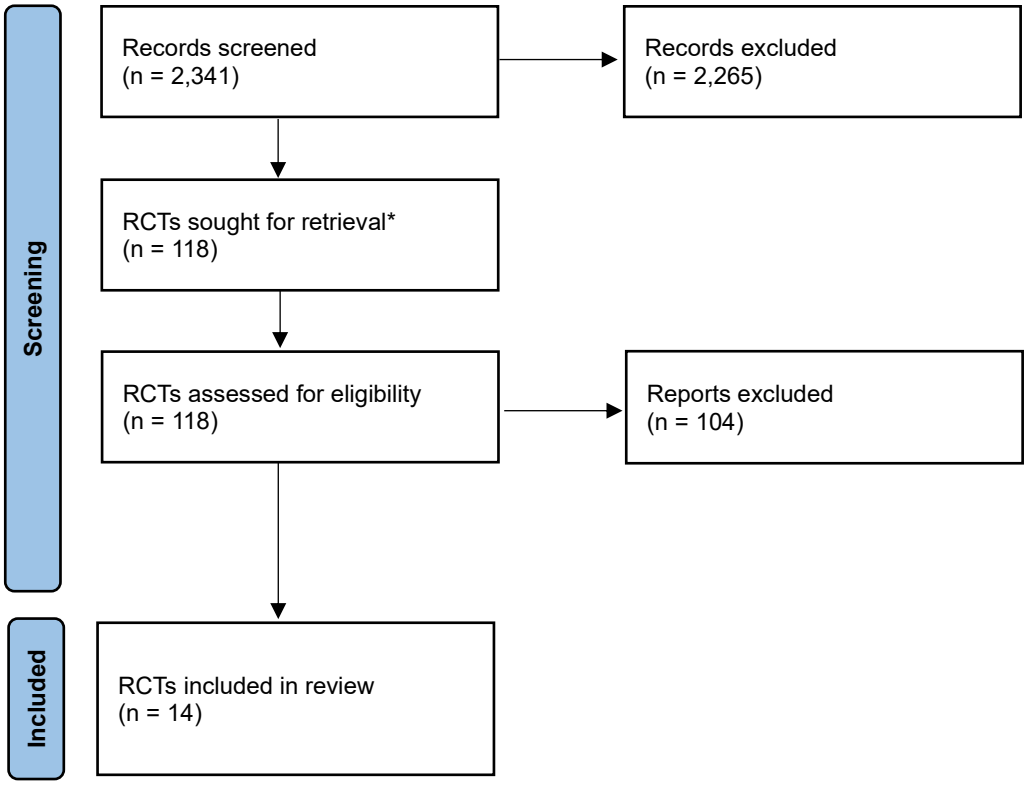
Full reference	Reason for exclusion
Moore C. Point-of-care tests for infection control: should rapid testing be in the laboratory or at the front line? J Hosp Infect. 2013;**85**(1):1-7.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Morehouse ZP, Chance N, Ryan GL, Proctor CM, Nash RJ. A narrative review of nine commercial point of care influenza tests: an overview of methods, benefits, and drawbacks to rapid influenza diagnostic testing. Journal of Osteopathic Medicine 2023;**123**(1): 39-47.	Study design – not a systematic review.
Neuner JM, Hamel MB, Phillips RS, Bona K, Aronson MD. Diagnosis and management of adults with pharyngitis. A cost-effectiveness analysis. Ann Intern Med. 2003;**139**(2):113-22.	Outcomes – cost-effectiveness analysis.
Nicholson KG, Abrams KR, Batham S, Medina MJ, Warren FC, Barer M, et al. Randomised controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and Streptococcus pneumoniae infection on the management of acute admissions in the elderly and high-risk 18- to 64-year-olds. Health Technol Assess. 2014;**18**(36):1-274, vii-viii.	Intervention – not near patient/rapid POC tests (turnaround time approximately 29 hours).
Odermatt J, Friedli N, Kutz A, Briel M, Bucher HC, Christ-Crain M, et al. Effects of procalcitonin testing on antibiotic use and clinical outcomes in patients with upper respiratory tract infections. An individual patient data meta-analysis. Clinical chemistry and laboratory medicine. 2017;**56**(1):170-7.	Intervention – not POC tests (laboratory testing).
Onwuchekwa C, Moreo LM, Menon S, Machado B, Curcio D, Kalina W, et al. Under-ascertainment of Respiratory Syncytial Virus infection in adults due to diagnostic testing limitations: A systematic literature review and meta-analysis. Journal of Infectious Diseases 2023;**20**:20.	Outcomes – diagnostic accuracy of tests (not all relevant POC tests).
Petel D, Winters N, Gore GC, et al. Use of C-reactive protein to tailor antibiotic use: a systematic review and meta-analysis. BMJ Open 2018;**8**:e022133	Outcomes - relevant studies not synthesised quantitatively.
Petrozzino JJ, Smith C, Atkinson MJ. Rapid diagnostic testing for seasonal influenza: an evidence-based review and comparison with unaided clinical diagnosis. J Emerg Med. 2010;**39**(4):476-90.e1.	Outcomes – outcomes not reported separately in adults or relevant setting.
Said MA, Johnson HL, Nonyane BA, Deloria-Knoll M, O'Brien KL, Andreo F, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS ONE. 2013;**8**(4):e60273.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Schuetz P, Müller B, Christ-Crain M, Stolz D, Tamm M, Bouadma L, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database of Systematic Reviews 2012, Issue 9.	Updated by Schuetz 2017 Cochrane Review.
Schuetz P, Muller B, Christ-Crain M, Stolz D, Tamm M, Bouadma L, et al. Procalcitonin to initiate or discontinue	Intervention – outcomes not reported separately in relevant

Full reference	Reason for exclusion
antibiotics in acute respiratory tract infections. Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No: CD007498.	populations or for relevant POC test (includes inpatients and patients with conditions other than ARIs; tests not all POC tests).
Shaolei M, Yujie W, Quan C, Xiangrong Z. A meta-analysis of the diagnostic accuracy of streptocuccus pneumoniae urinary antigen test for adult community acquired streptocuccus pneumoniae pneumoniae. Chinese Critical Care Medicine. 2016;**28**(6):528-33.	Non-English language (Chinese).
Solvik UO, Boija EE, Ekvall S, Jabbour A, Breivik AC, Nordin G, et al. Performance and user-friendliness of the rapid antigen detection tests QuickVue Dipstick Strep A test and DIAQUICK Strep A Blue Dipstick for pharyngotonsillitis caused by Streptococcus pyogenes in primary health care. Eur J Clin Microbiol Infect Dis. 2021;**40**(3):549-58.	Study design – not a systematic review.
Stewart EH, Davis B, Clemans-Taylor BL, Littenberg B, Estrada CA, Centor RM. Rapid antigen group A streptococcus test to diagnose pharyngitis: a systematic review and meta-analysis. PLoS ONE. 2014;**9**(11):e111727.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Thornton HV, Turner KME, Harrison S, Hammond A, Hawcroft C, Hay AD. Assessing the potential of upper respiratory tract point-of-care testing: a systematic review of the prognostic significance of upper respiratory tract microbes. Clin Microbiol Infect. 2019;**25**(11):1339-46.	Comparator – no relevant comparator.
Timbrook TT, Wigmosta TB, Hemmert RB, Dimas JB, Krause A, Spinali S. Measuring clinical outcomes of highly multiplex molecular diagnostics for respiratory infections: A systematic review and conceptual framework. Antimicrobial Stewardship & Healthcare Epidemiology : ASHE 2023;**3**(1):e9.	Study design – review of reviews.
Tonkin-Crine SK, Tan PS, van Hecke O, Wang K, Roberts NW, McCullough A, et al. Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. Cochrane Database Syst Rev. 2017;**9**:CD012252.	Population – includes mixed age population; adult subgroup analysis was planned but data were not available.
van der Meer V, Neven AK, van den Broek PJ, Assendelft WJ. Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review. BMJ. 2005;**331**(7507):26.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
van der Velden AW, Pijpers EJ, Kuyvenhoven MM, Tonkin-Crine SK, Little P, Verheij TJ. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. The British journal of general practice : the journal of the Royal College of General Practitioners. 2012;**62**(605):e801-7.	Intervention – not POC tests (interventions aimed at physicians).
Verbakel JY, Lee JJ, Goyder C, Tan PS, Ananthakumar T, Turner PJ, et al. Impact of point-of-care C reactive protein in	Outcomes - relevant studies not synthesised quantitatively.

Full reference	Reason for exclusion
ambulatory care: a systematic review and meta-analysis. BMJ Open 2019;**9**:e025036.	
Vos LM, Bruning AHL, Reitsma JB, Schuurman R, Riezebos-Brilman A, Hoepelman AIM, et al. Rapid Molecular Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review of Diagnostic Accuracy and Clinical Impact Studies. Clin Infect Dis. 2019;**69**(7):1243-53.	Outcomes – outcomes not reported separately in relevant impact studies (includes mixed study designs, mixed age population and settings).
Weber NC, Klepser ME, Akers JM, Klepser DG, Adams AJ. Use of CLIA-waived point-of-care tests for infectious diseases in community pharmacies in the United States. Expert Rev Mol Diagn. 2016;**16**(2):253-64.	Study design – not a systematic review.
Xie X, Sinclair A, Dendukuri N. Evaluating the accuracy and economic value of a new test in the absence of a perfect reference test. Res. 2017;**8**(3):321-32.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Xie LM, Yin X, Xie TA, Su JW, Huang Q, Zhang JH, et al. Meta-Analysis of the Diagnostic Efficacy of the Luminex xTAG Respiratory Viral Panel FAST v2 Assay for Respiratory Viral Infections. Yonsei Medical Journal 2022;**63**(1): 95-103.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Yasuo S, Murata M, Nakagawa N, Kawasaki T, Yoshida T, Ando K, et al. Diagnostic accuracy of urinary antigen tests for pneumococcal pneumonia among patients with acute respiratory failure suspected pneumonia: a systematic review and meta-analysis. BMJ Open 2022;**12**(8): e057216.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Yoon SH, Min IK, Ahn JG. Immunochromatography for the diagnosis of Mycoplasma pneumoniae infection: A systematic review and meta-analysis. PLoS ONE. 2020;**15**(3):e0230338.	Outcomes – no relevant outcomes reported (diagnostic accuracy data only).
Zhang K, Xie K, Zhang C, Liang Y, Chen Z, Wang H. C-reactive protein testing to reduce antibiotic prescribing for acute respiratory infections in adults: a systematic review and meta-analysis. Journal of Thoracic Disease 2022;**14**(1): p. 123-134.	Outcomes - relevant studies not synthesised quantitatively.

1

Appendix 5: Study flow diagram: RCTs



*Includes 42 records identified through examining reference lists of relevant systematic reviews.

Modified from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n7

Appendix 6: Studies included in the clinical effectiveness review

Table 11: Included studies of C-reactive protein tests

Study Details	Participants	Interventions	Outcomes and Results	Comments
Afinion CRP point-of-care testing				
Andreeva 2014 [29] From Smedemark 2022[16] Russia Open-label cluster RCT, 17 general practice offices **Study dates**: January 2010 to 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	**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, 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	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.

Study Details	Participants	Interventions	Outcomes and Results	Comments
	Pulmonary diseases, %: 15; 18 Heart diseases, %: 17; 4 Diabetes, %: 5; 4		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	
Butler 2019 [24] From Smedemark 2022[16] **Francis 2020** [34] UK (England & Wales) Open-label RCT, 86 general medical practices **Study dates**: January 2015 to 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 acute exacerbation of COPD with at least 1 of AECOPD criteria (with at least 1 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	**Interventions**: Single POC CRP to guide antibiotic decisions: ≤ 20 mg/L, 20 to 40 mg/L, ≥40 mg/L. Afinion desktop devices for CRP point-of-care 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, 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, 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, 4.14) Hospital admissions within 6 months (number of events/number of participants) CRP: 35/304 Usual care: 34/301	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

Study Details	Participants	Interventions	Outcomes and Results	Comments
	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 **Key characteristics** CRP; usual care Mean age (SD; range), years: 67.8 (9.53; 41 to 90); 68.3 (9.31; 40 to 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		RR 1.02 (95% CI 0.65, 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, 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)	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

Study Details	Participants	Interventions	Outcomes and Results	Comments
			Adjusted mean difference (averaged across timepoints): 0.03 (95% CI -0.04, 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) 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 timepoints): 3.12 (95% CI 0.50, 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)	

Study Details	Participants	Interventions	Outcomes and Results	Comments
			Adjusted mean difference (averaged across timepoints): 0.06 (95% CI -0.20, 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 timepoints): 0.13 (95% CI -0.12, 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 timepoints): 0.15 (95% CI -0.04, 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 timepoints): -0.09 (95% CI -0.18, 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	

Study Details	Participants	Interventions	Outcomes and Results	Comments
			Adjusted OR 0.31 (95% CI 0.20, 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, 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, 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 risk ratio: 1.02 (95% CI 0.91, 1.15)[a]	
Nycocard II CRP point-of-care testing *(Not currently available in the UK)*				
Althaus 2019 [30] From Smedemark 2022[16] Thailand and Myanmar	**Sample size**: 937 (adults with ARI subgroup) CRP 614, usual care 323 **Inclusion criteria**: Age > 1 year; documented fever or chief complaint of	**Interventions**: Single POC CRP to guide antibiotic decisions at thresholds: a) Low 20mg/L b) High 40 mg/L	*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, 0.95)	Smedemark 2022 reports published and unpublished data for Althaus 2019. Study population is patients with fever

Study Details	Participants	Interventions	Outcomes and Results	Comments
Open-label RCT, 9 centres in public primary care, and 1 outpatient setting **Study dates**: June 2016 to June 2017 Funding: non-commercial **Follow-up** Day 5 and 14	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	NycoCard II Reader, Axis Shield, Oslo, Norway **Comparator**: usual care		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.
Cals 2009 [26] From Smedemark 2022[16] **Cals 2013**[35] The Netherlands Open-label cluster-RCT, 20 primary care practices	**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 respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	**Interventions**: Single POC CRP to guide antibiotic decisions: < 20 mg/L, 20 to 99 mg/L, >100 mg/L. Nycocard II Reader (Axis-Shield, Norway) **Comparator**: usua0l 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, 1.78) *Data from Cals 2009* Antibiotics prescribed at index consultation	Cluster RCT therefore modified sample size used in Smedemark 2022 analysis. Source of data for 'substantial improvement' reported in Smedemark 2022 unclear.

Study Details	Participants	Interventions	Outcomes and Results	Comments
Study dates: Winter periods 2005-06 and 2006-07 Source of funding: non-commercial **Follow-up:** 28 days	**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		(number of events/number of participants) CRP: 70/227; 30.8% (crude 95% CI 21.8, 39.8[c]) Usual care: 108/204; 52.9% (crude 95% CI 43.0, 62.8[c]) Antibiotics prescribed within 28 days (number of events/number of participants) CRP: 102/227; 44.9% (crude 95% CI 35.2, 54.6[c]) Usual care: 119/204; 58.3% (crude 95% CI 48.5, 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, 41.3[c]) Usual care: 62/204; 30.4% (crude 95% CI 23.9, 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	Originally 2x2 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.

Study Details	Participants	Interventions	Outcomes and Results	Comments
			(number of events/number of participants) CRP: 39/110; 43.0% (crude 95% CI 25.6, 52.6[c]) Usual care: 67/120; 80% (crude 95% CI 53.9, 79.5[c])	
Diederichsen 2000 [31] From Smedemark 2022[16] Denmark Open-label RCT, 35 primary care practices **Study dates**: January 1997 to 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 general practitioner 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, <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, 1.07)	Specific details and raw data to differentiate adult participants provided to Smedemark 2022. Baseline characteristics of adults not reported.
Do 2016 [33] From Smedemark 2022[16] Northern Vietnam	**Sample size**: 1008 (adults with non-severe ARI) CRP 507, usual care 501 **Inclusion criteria**: Patients aged 1 to 65 years presenting with non-severe	**Interventions**: Single POC CRP to guide antibiotic decisions: < 20 mg/L, >100 mg/L. Nycocard analyser (Nycocard II Reader,	*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, 0.76)	Baseline characteristics of adults not reported. Subsequent antibiotic use and antibiotic

Study Details	Participants	Interventions	Outcomes and Results	Comments
Open-label RCT, 10 primary healthcare centres **Study dates**: March 2014 to July 2015 Source of funding: non-commercial **Follow-up:** 14 days	acute respiratory tract infection (At least 1 focal and 1 systemic sign or symptom by the treating physician) **Exclusion criteria:** Sign of severe ARI **Key characteristics** NR for adults	Alere Technologies, Norway) **Comparator**: usual care	*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, 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, 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, 4.64) Time to resolution of symptoms, days (median, IQR) CRP: 6 (4–10) Usual care: 5 (4–8) HR 0·89 (95% CI0·77, 1·03)[f]	management change are in patients without immediate antibiotic prescription, i.e. they refer to non-randomised comparisons because the denominator population depends on the treatment group

Study Details	Participants	Interventions	Outcomes and Results	Comments
			Mortality within 14 days CRP: 0/507 Usual care: 0/501	
Melbye 1995 [32] 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) 1 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 to 83); 44 (18 to 82)	**Interventions**: Single POC CRP to guide antibiotic decisions: < 11 mg/L, 11 to 49 mg/L, >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, 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, 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, 1.18) Number of participants substantially improved within 28 days (number of events/number of participants) CRP: 71/98 Usual care: 82/121	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.

Study Details	Participants	Interventions	Outcomes and Results	Comments
			RR 0.85 (95% CI 0.57, 1.29)	
QuikRead CRP				
Boere 2021 [27] From Smedemark 2022[16] **Boere 2022** [36] The Netherlands Open-label cluster RCT, 11 nursing homes **Study dates**: September 2018 to 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 to 60 mg/L, and > 60 mg/L. QuikRead Go C-reactive protein, 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	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.

Study Details	Participants	Interventions	Outcomes and Results	Comments
			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, 1.08) Subgroups COPD Antibiotics prescribed at index consultation CRP: 20/45 (44.4%) Usual care: 23/29 (79.3%)	
Cals 2010 [28] From Smedemark 2022[16] The Netherlands Open-label RCT, 11 primary care practices	**Sample size**: 258 patients CRP 129, usual care 129 **Inclusion criteria**: Age ≥ 18 years; suspected acute lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1	**Interventions**: Single POC CRP to guide antibiotic decisions: < 20 mg/L, 20 to 99 mg/L, >100 mg/L. QuikRead CRP analyzers (Orion Diagnostica, Espoo, Finland)	*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	The RRs reported in Smedemark 2022 for antibiotics prescribed at index consultation and 28 days differ to those reported in the original study (RR

Study Details	Participants	Interventions	Outcomes and Results	Comments
Study dates: November 2007 to April 2008 Source of funding: Orion Diagnostica Espoo, Finland **Follow-up:** 28 days	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	**Comparator**: usual care	RR 0.77 (95% CI 0.60, 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, 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, 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, 1.18)	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.

Study Details	Participants	Interventions	Outcomes and Results	Comments
			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)	
Little 2013 [25] **Little 2019** [37] From Smedemark 2022[16]	**Sample size**: 1932 patients with upper or lower RTI CRP 1062 (58 practices), usual care 870 (53 practices)	**Interventions**: Single POC CRP to guide antibiotic decisions: < 20 mg/L, 21 to 50 mg/L, 51 to 99 mg/L, >100 mg/L.	*Data from Little 2013* Resolution of moderately bad symptoms, median (IQR), time (days) CRP: 5 (3 to 8) Usual care: 5 (3 to 7) Basic HR 0.97 (95% CI 0.82, 1.15)[e]	4 practices in the CRP group and 14 in the usual care group did not manage to recruit any patients.

Study Details	Participants	Interventions	Outcomes and Results	Comments
Belgium, UK, Poland, Spain, The Netherlands Open-label cluster-RCT, 246 primary care practices at baseline, 178 at 12 months **Study dates**: February 2011 to May 2012 Source of funding: non-commercial **Follow-up:** 28 days[25] 12 months[37]	**Inclusion criteria**: Adults (> 18 years) consulting for the first time with upper or lower respiratory tract infection **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	QuikRead C-reactive protein, Orion Diagnostica (Espoo, Finland) **Comparator**: usual care	Adjusted HR 0.87 (95% CI 0.74, 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, 2.77)[d] Adjusted RR 1.75 (1.12, 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	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. 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

Study Details	Participants	Interventions	Outcomes and Results	Comments
				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.

Abbreviations: AECOPD – acute exacerbation of chronic obstructive pulmonary disease; ARI – acute respiratory infection; COPD – chronic obstructive pulmonary disease; CI – confidence interval; CRP – C-reactive protein; CRQ-SAS - Chronic Respiratory Disease Questionnaire; EQ-5D-5L - European Quality of Life–5 Dimensions 5-Level questionnaire; GP – general practice; IPD – individual patient data; NR – not reported; POC – point-of-care; RCT – randomised controlled trial; RTI – respiratory tract infection; RR –risk ratio; SD – standard deviation; 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 standard deviation inflated by variance inflation factor
[d]The basic model adjusted for baseline prescribing and clustering by physician and practice.
[e] The adjusted model additionally controlled for age, smoking, sex, major cardiovascular or respiratory comorbidity, baseline symptoms, crepitations, wheeze, pulse > 100 beats per min, temperature > 37·8°C, respiratory rate, blood pressure, physician's rating of severity, and duration of cough.
[f]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.

Table 12: Included studies of Procalcitonin tests

Study Details	Participants	Interventions	Outcomes and Results	Comments
BRAHMS PCT Procalcitonin				
Lhopitallier 2021 [38] 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 to March 2020 Source of funding: non-commercial (POC test 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 1 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	**Interventions**: POC procalcitonin to guide antibiotic decisions: < 25 µg/L, ≥25 µg/L. BRAHMS PCT direct point-of-care test **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, 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, 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, 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)	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

Study Details	Participants	Interventions	Outcomes and Results	Comments
	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		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, 2.43) HR 0.81 (95% CI 0.62, 1.04)	at day 7' in Lhopitallier 2021. Unclear why the number of participants for 'duration of symptoms' is lower.

Abbreviations: COPD – chronic obstructive pulmonary disease; CI – confidence interval; HR – hazard ratio; NR – not reported; POC – point-of-care; RCT – randomised controlled trial; RTI – respiratory tract infection; RR –risk ratio; SD – standard deviation.

Table 13: Included studies of Group A Streptococcus tests

Study Details	Participants	Interventions	Outcomes and Results	Comments
RADT OSOM® Strep A				
Llor 2011 [39] Spain Open-label cluster-RCT, 20 primary healthcare centres **Study dates**: January to 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 ≥ one 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	**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:

Study Details	Participants	Interventions	Outcomes and Results	Comments
	Mean age (SD; range), years: 31.8 (11.5); 31.5 (11.4)			RADT: n=4 Usual care: n=10
RADT Clearview® Exact Strep A				
Worrall 2007 [40] Canada Open-label cluster-RCT, 37 family doctors' offices (19 in relevant trial arms) **Study dates**: February to 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.

Abbreviations: GP – general practice; NR – not reported; RADT – rapid antigen detection test; RCT – randomised controlled trial; SD – standard deviation.

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 [41] **NCT00821626** [42] Switzerland Open-label RCT, two hospital outpatient clinics **Study dates**: December 2008 to 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 to 79); 35 (18 to 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 Mortality (number of events/number of participants) RADT: 0/60 Usual care: 0/33	6 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.

Abbreviations: HIV – human immunodeficiency disorder; NR – not reported; RADT – rapid antigen detection test; RCT – randomised controlled trial.

Appendix 7: Studies excluded from the clinical effectiveness review

Full reference	Reason for exclusion
Ameyaw E, Nguah SB, Ansong D, Page I, Guillerm M, Bates I. The outcome of a test-treat package versus routine outpatient care for Ghanaian children with fever: a pragmatic randomized control trial. Malaria Journal 2014;**13**:461. [DOI:10.1186/1475-2875-13-461]	Population - children under 16 years.
Andrade A, Bang H, Reddick K, Villaseñor B, Tran NK, May L. Evaluation of pharmacist guided intervention using procalcitonin and respiratory virus testing. The American journal of emergency medicine 2023;**66**:146–151. https://doi.org/10.1016/j.ajem.2023.01.041	Intervention - unclear turnaround time for POCT and appears to be undertaken in a laboratory. Relevant outcome data for adult subgroup reported as *post hoc* analysis.
Andrews D, Chetty Y, Cooper BS, Virk M, Glass SK, Letters A, et al. Multiplex PCR point of care testing versus routine, laboratory-based testing in the treatment of adults with respiratory tract infections: a quasi-randomised study assessing impact on length of stay and antimicrobial use. BMC Infect Dis 2017;**17**:1-11.	Study design – not an RCT ('quasi-randomised' study). Includes adult inpatients and outpatients - only reporting the number of patients discharged without admission separately in outpatients. Unclear if comparator is 'usual care'.
Bjerrum L, Cots JM, Llor C, Molist N, Munck A. Effect of intervention promoting a reduction in antibiotic prescribing by improvement of diagnostic procedures: a prospective, before and after study in general practice. Eur J Clin Pharmacol 2006;**62**:913–8.	Study design – not an RCT (before-after study/audit). Unclear population age.
Boere TM, Hopstaken RM, van Tulder MW, Schellevis FG, Verheij TJM, Hertogh Cmpm, et al. Implementation and Use of Point-of-Care C-Reactive Protein Testing in Nursing Homes. Journal of the American Medical Directors Association 2022;**23**(6):968-975.e3.	Outcomes - qualitative outcome data only.
Boere TM, van Buul LW, Hopstaken RM, Veenhuizen RB, van Tulder MW, Cals JWL, et al. Using point-of-care C-reactive protein to guide antibiotic prescribing for lower respiratory tract infections in elderly nursing home residents (UPCARE): study design of a cluster randomized controlled trial. BMC health services research 2020;**20**(1):149. https://doi.org/10.1186/s12913-020-5006-0	Publication type - conference abstract only and no results reported.
Bouzid D, Casalino E, Mullaert J, Laurent O, Duval X, Lescure FX, et al. Added value of rapid respiratory syndromic testing at point of care versus central laboratory testing: a controlled clinical trial. J Antimicrob Chemother 2021;**76** suppl 3:iii20–iii27.	Study design – not an RCT (retrospective observational study). POCT and results turnaround time >45 minutes.
Brendish NJ, Malachira A K, Armstrong L, Houghton R, Aitken S, Nyimbili, E, et al. Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial. Lancet Respir Med 2017;**5**:401-11.	Population – includes patients at initial contact (ED) and patients after initial contact (i.e. secondary contact - acute medical unit); outcome data not reported separately for

Full reference	Reason for exclusion
	relevant population (i.e. initial contact).
Brendish NJ, Malachira AK, Beard KR, Ewings S, Clark TW. Impact of turnaround time on outcome with point-of-care testing for respiratory viruses: a post hoc analysis from a randomised controlled trial. The European respiratory journal 2018;**52**(2):1800555.	Population – includes patients at initial contact (ED) and patients after initial contact (i.e. secondary contact - acute medical unit); outcome data not reported separately for relevant population (i.e. initial contact).
Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. Arch Intern Med 2008;**168**:2000–7.	Intervention - not a POCT (laboratory test) and results turnaround time >45 minutes.
Burkhardt O, Ewig S, Haagen U, Giersdorf S, Hartmann O, Wegscheider K, et al. Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection. Eur Respir J 2010 Sep;**36**(3):601- 7.	Intervention – not a POCT and results turnaround time ≤4 h.
Busson L, Mahadeb B, De Foor M, Vandenberg O, Hallin M. Contribution of a rapid influenza diagnostic test to manage hospitalized patients with suspected influenza. Diagn Micro-biol Infect Dis 2017;**87**:238-42.	Study design - not an RCT (diagnostic accuracy data).
Cals JW, Ament AJ, Hood K, Butler CC, Hopstaken RM, Wassink GF, et al. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. J Eval Clin Pract 2010;**17**:1059–69.	Study design – not an RCT (economic evaluation).
Cals J, Butler C, Hopstaken R, Hood K, Dinant GJ. Effect of C-reactive protein point of care testing and clinical communication skills training on antibiotic use and patient recovery in lower respiratory tract infections: a cluster randomised trial. European respiratory society annual congress, Berlin, Germany, October 4-8, 2008:[P3500].	Publication type – conference abstract only.
Carter JA, Burke HB. CRP-Guided Antibiotic Therapy for Acute COPD Exacerbation: a Randomized Control Trial. Journal of general internal medicine 2021;**36**(7):2194-2196.	Population – unclear population age; unclear results turnaround time for POCT.
Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay M, Huber P, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet (London, England) 2004;**363**:600–7.	Intervention - turnaround time for results >45 mins.
Christ-Crain M, Stolz D, Bingisser R, Muller C, Miedinger D, Huber P, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 2006;**174**:84–93.	Intervention – not a POCT (laboratory test).
Clark TW, Beard KR, Brendish NJ, Malachira AK, Mills S, Chan C, et al. Clinical impact of a routine, molecular, point-of-care, test-	Population – includes patients at initial contact (ED) and

Full reference	Reason for exclusion
and-treat strategy for influenza in adults admitted to hospital (FluPOC): a multicentre, open-label, randomised controlled trial. Lancet respiratory medicine 2021;**9**(4):419-429.	patients after initial contact (i.e. secondary contact - acute medical unit); outcome data not reported separately for relevant population (i.e. initial contact).
Clark TW, Mills S, Brendish N. The impact of syndromic molecular point-of-care testing for respiratory viruses on antibiotic use in adults presenting to hospital with exacerbation of airways disease: further analysis from a randomized controlled trial. Open forum infectious diseases 2019;**6**:S988.	Publication type - conference abstract only. Not an RCT and compares patients testing positive versus negative for viruses versus controls
Diederichsen HZ, Skamling M, Diederichsen A, Grinsted P, Antonsen S, Petersen PH, et al. A randomized controlled trial of the use of CRP rapid test as a guide to treatment of respiratory infections in general practice. Ugeskrift for laeger 2001;**163**(27): 3784-3787.	Language – non-English.
Drks, Influence of a guideline and an additional rapid test for group A Streptococci on antibiotic prescriptions for patients presenting with sore throat in primary care. https://trialsearch.who.int/Trial2.aspx?TrialID=DRKS00013018, 2017.	Outcomes – clinical trial website; no results posted.
Echavarría M, Marcone DN, Querci M, Seoane A, Ypas M, Videla C, et al. Clinical impact of rapid molecular detection of respiratory pathogens in patients with acute respiratory infection. J Clin Virol 2018;**108**:90–5.	Intervention – not a POCT (laboratory test); results turnaround time approximately 65 minutes.
Eley CV, Sharma A, Lee H, Charlett A, Owens R, McNulty CAM. Effects of primary care C-reactive protein point-of-care testing on antibiotic prescribing by general practice staff: pragmatic randomised controlled trial, England, 2016 and 2017. Euro surveillance 2020;**25**(44):1900408.	Intervention – practices in the intervention arm used a diagnostic score to decide whether a CRP test was needed; only one third of the intervention arm received a POCT.
Fally M, Corti C, Fabricius-Bjerre A, Mortensen K, Jensen BN, Andreassen H. Point-of-care procalcitonin test to reduce antibiotics in COPD exacerbation: a quasi-randomised control trial. European respiratory journal 2015;**46**:OA4752.	Population - patients hospitalised with COPD exacerbation. Unclear turnaround time for POCT results. Conference abstract only.
Fawsitt C, Lucey D, Harrington P, Jordan K, Marshall L, O'Brien KK, Teljeur C. A cost-effectiveness and budget impact analysis of C-reactive protein point-of-care testing to guide antibiotic prescribing for acute respiratory tract infections in primary care settings in Ireland: a decision-analytic model. Family Practice 2022;**39**:389-97.	Study design - not an RCT; cost-effectiveness data sourced from an NMA of 7 RCTs.
Gelfer G, Leggett J, Myers J, Wang L, Gilbert DN. The clinical impact of the detection of potential etiologic pathogens of	Intervention – results turnaround time >45 minutes.

Full reference	Reason for exclusion
community-acquired pneumonia. Diagn Microbiol Infect Dis 2015;**83**:400-6.	
Gilbert D, Gelfer G, Wang L, Myers J, Bajema K, Johnston M, et al. The potential of molecular diagnostics and serum procalcitonin levels to change the antibiotic management of community-acquired pneumonia. Diagn Microbiol Infect Dis 2016;**86**:102-7.	Intervention – results turnaround time >45 minutes.
Gomez S, Prieto C, Folgueira L. A prospective study to assess the diagnostic performance of the Sofia((R)) Immunoassay for Influenza and RSV detection. J Clin Virol 2016;**77**:1-4.	Population - includes hospitalised patients of mixed ages (adults and children). Diagnostic accuracy study.
Gonzales R, Aagaard EM, Camargo CA Jr, Ma OJ, Plautz M, Maselli JH, et al. C-reactive protein testing does not decrease antibiotic use for acute cough illness when compared to a clinical algorithm. J Emerg Med 2011;**41**(1):1– 7.	Comparator - not usual care; both intervention and comparator groups had a detailed clinical algorithm placed in their medical chart.
Gonzales R, Anderer T, McCulloch CE, Maselli JH, Bloom FJ, Graf TR, et al. A cluster-randomized trial of decision support strategies for reducing antibiotic use for acute bronchitis. JAMA Intern Med 2013;**173**:267–73.	Intervention - not a POCT (compares printed intervention versus computerised versus control).
Hazelton B, Gray T, Ho J, Ratnamohan VM, Dwyer DE, Kok J. Detection of influenza A and B with the Alere i Influenza A & B: a novel isothermal nucleic acid amplification assay. Influ-enza Other Respir Viruses 2015;**9**:151-4.	Study design – not an RCT (diagnostic accuracy study).
Hazelton B, Nedeljkovic G, Ratnamohan VM, Dwyer DE, Kok J. Evaluation of the Sofia Influenza A + B fluorescent immuno-assay for the rapid diagnosis of influenza A and B. J Med Virol 2015;**87**:35-8.	Study design – not an RCT (diagnostic accuracy study).
Holm A, Nexoe J, Bistrup LA, Pedersen SS, Obel N, Nielsen LP, Pedersen C. Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. Br J Gen Pract 2007;**57**:547–554.	Study design - not an RCT (observational study); not a POCT.
Holmes EAF, Harris SD, Hughes A, Craine N, Hughes DA. Cost-Effectiveness Analysis of the Use of Point-of-Care C-Reactive Protein Testing to Reduce Antibiotic Prescribing in Primary Care. Antibiotics (Basel, Switzerland) 2018;**7**(4):106.	Study design - cost-effectiveness study based on non-RCT clinical data.
Huang DT, Yealy DM, Filbin MR, Brown AM, Chang CH, Doi Y, et al. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. New England Journal of Medicine 2018;**379**(3):236-49. [DOI: 10.1056/NEJMoa1802670]	Intervention - rapid assay test appears to be conducted in a laboratory.
Hunter R. Cost-effectiveness of point-of-care C-reactive protein tests for respiratory tract infection in primary care in England. Advances in Therapy 2015;**32**(1):69-85.	Study design - cost-effectiveness study (clinical data based on Cals 2013 RCT).
Isa HM, Mohroofi AD, Alkhan FN, Hasan AZ, Alkubis MM, Alhewaizem SS, et al. C-reactive protein levels in children with acute bronchiolitis. International Journal of Pediatrics 23 May 2022;eCollection:1311936. [DOI: 10.1155/2022/1311936]	Population – children under 16 years.

Full reference	Reason for exclusion
Isrctn, Molecular point-of-care 'test and treat' for influenza (FluPOC). https://trialsearch.who.int/Trial2.aspx?TrialID=ISRCTN17197293, 2017.	Population – protocol to Clark 2021; includes both patients at initial contact (ED) and secondary contact (acute medical unit); outcome data not reported separately for relevant population (i.e. initial contact).
Jakobsen KA, Melbye H, Kelly MJ, Ceynowa C, Molstad S, Hood K, Butler CC. Influence of CRP testing and clinical findings on antibiotic prescribing in adults presenting with acute cough in primary care. Scand J Prim Health Care 2010;**28**(4):229-36.	Study design - not an RCT (observational data from practices in different countries).
Jung CY, Choe YH, Lee SY, Kim WJ, Lee JD, Ra SW, et al. Use of serology and polymerase chain reaction to detect atypical respiratory pathogens during acute exacerbation of chronic obstructive pulmonary disease. The Korean journal of internal medicine 2018;**33**(5):941-951.	Intervention - *post hoc* analysis of an RCT; assesses differences between patients with and without atypical respiratory pathogens; no relevant outcomes reported.
Kaku N, Urabe T, Iida T, Yun C, Nishida Y, Onitsuka Y, et al., Gargle sample is an effective option in a novel fully automated molecular point-of-care test for influenza: a multicenter study. Virology Journal 2023;**20**(1):41.	Study design – not an RCT. Includes adults and children with outcomes not reported separately in adults.
Klepser ME, Hagerman J, Klepser DG, Klepser SA, Bergman SJ. Evaluation of a community pharmacy-based influenza screening and management program versus pharmacy screening and referral to standard of care. Pharmacotherapy 2011;**31**(10):323e.	Publication type – conference abstract only.
Kristoffersen KB, Sogaard OS, Wejse C, Black FT, Greve T, Tarp B, et al. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission – a randomized trial. Clin Microbiol Infect 2009;**15**:481–7.	Intervention – not a POCT; test results were available on the following day, except for weekends.
Lee CK, Cho CH, Woo MK, Nyeck AE, Lim CS, Kim WJ. Evaluation of Sofia fluorescent immunoassay analyzer for influenza A/B virus. J Clin Virol 2012;**55**:239-43.	Study design – not an RCT (diagnostic accuracy study).
Leonardi GP, Wilson AM, Zuretti AR. Comparison of conven-tional lateral-flow assays and a new fluorescent immunoas-say to detect influenza viruses. J Virol Methods 2013;**189**:379- 82.	Study design – not an RCT (diagnostic accuracy study).
Lewandrowski K, Tamerius J, Menegus M, Olivo PD, Lollar R, Lee-Lewandrowski E. Detection of influenza A and B viruses with the Sofia analyzer: a novel, rapid immunofluorescence-based in vitro diagnostic device. Am J Clin Pathol 2013;**139**: 684-9.	Outcomes - diagnostic accuracy study; not a POCT (laboratory test). Includes mixed age population.
Limper M, van der Does Y, Brandjes DP, De Kruif MD, Rood PP, van Gorp EC. Procalcitonin guided antibiotic therapy in patients presenting with fever in the emergency department. Journal of infection 2014;**69**(4):410-412.	Study design – letter.

Full reference	Reason for exclusion
Little P, Hobbs FDR, Moore M, Mant D, Williamson I, McNulty C, et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). BMJ 2013;**347**:f5806.	Population – includes adults and children; outcomes not reported separately in adults.
Little P, Hobbs R, Moore M, Mant D, Williamson I. PRImary Care Streptococcal Management Study (PRISM): in vitro study, diagnostic cohorts, and a pragmatic adaptive randomised controlled trial with nested qualitative study and cost-effectiveness study. Health Technology Assessment 2014;**18**(6):1-101. [DOI: 10.3310/hta18060]	Population - in vitro study, diagnostic cohorts and RCT which includes a mixed age population; outcomes not reported separately in adults.
Llor C, Bjerrum L, Munck A, Cots JM, Hernández S, Moragas A. Access to point-of-care tests reduces the prescription of antibiotics among antibiotic-requesting subjects with respiratory tract infections. Respiratory Care 2014;**59**:1918-23.	Population - age of patients not specified (appears to be any age). Not an RCT (before-after study). No relevant comparator.
Llor C, Cots JM, Gonzalez Lopez-Valcarcel B, de Dios Alcantara J, Garcia G, Arranz J, et al. Effect of two interventions on reducing antibiotic prescription in pharyngitis in primary care. Journal of Antimicrobial Chemotherapy 2011;**66**:210-5.	Study design – not an RCT (before-after study). No relevant comparator.
Llor C, Sierra N, Hernandez S et al. Impact of C-reactive protein testing on adherence to thrice-daily antibiotic regimens in patients with lower respiratory tract infection. Prim Care Respir J 2010;**19**:358–62.	Study design – not an RCT (before-after study).
Long W, Deng X, Zhang Y, Lu G, Xie J, Tang J. Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community-acquired pneumonia. Respirology (Carlton, Vic.) 2011;**16**(5):819-824.	Population - some included patients had been in the ED observation unit for up to 24 hours. Test 'measured within 1 hour'.
Lubell Y, Do NTT, Nguyen KV, Ta NTD, Tran NTH, Than HM, et al. C-reactive protein point of care testing in the management of acute respiratory infections in the Vietnamese primary healthcare setting - a cost benefit analysis. Antimicrob Resist Infect Control 2018;**7**:119.	Outcomes – cost-benefit study.
Madurell J, Balague M, Gomez M, Cots JM, Llor C. Impact of rapid antigen detection testing on antibiotic prescription in acute pharyngitis in adults. FARINGOCAT STUDY: a multicentric randomized controlled trial. BMC Family Practice 2010;**11**:25.	Outcomes – protocol only; no outcomes reported.
May L, Tatro G, Poltavskiy E, Mooso B, Hon S, Bang H, et al. Rapid multiplex testing for upper respiratory pathogens in the emergency department: a randomized controlled trial. Open forum infectious diseases 2019;**6**(12):ofz481.	Intervention – not a POCT (onsite laboratory test).
Montassier E, Javaudin F, Moustafa F, Nandjou D, Maignan M, Hardouin JB, et al. Guideline-based clinical assessment versus procalcitonin-guided antibiotic use in pneumonia: a pragmatic randomized trial. Annals of Emergency Medicine 2019;**74**(4):580-91.	Intervention – not a POCT (onsite laboratory test).

Full reference	Reason for exclusion
Na, J.O., et al., Detection of atypical respiratory pathogens in acute exacerbations of chronic obstructive pulmonary disease by serology and PCR. American journal of respiratory and critical care medicine, 2015. 191(no pagination).	Publication type – conference abstract only.
Nct, Rapid Diagnostics for Upper Respiratory Infections in the Emergency Department. https://clinicaltrials.gov/show/NCT02957136, 2016.	Intervention – not a POCT (onsite laboratory test). Linked to May 2019.
Nct, Stratified TreAtment to Reduce Risk in COPD. https://clinicaltrials.gov/show/NCT04458636, 2020.	Outcomes – trial record with no results posted.
NCT03744832. Point of care streptococcal pharyngitis testing. clinicaltrials.gov/ct2/show/NCT03744832.	Population – children under 16 years. Trial record with no results posted.
Nicholson KG, Abrams KR, Batham S, Medina MJ, Warren FC, Barer M, et al. Randomised controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and Streptococcus pneumoniae infection on the management of acute admissions in the elderly and high-risk 18-to 64-year-olds. Health Technol Assess. 2014;**18**:1–viii.	Population – inpatients.
Noh JY, Choi WS, Lee J, Kim HL, Song JY, Cheong HJ, et al. Clinical performance of the Sofia Influenza A+B FIA in adult patients with influenza-like illness. Diagn Microbiol Infect Dis 2015;**83**:130-2.	Comparator - not usual care. Diagnostic accuracy study.
Ntr, Bedside testing for lower respiratory tract infections in nursing homes. https://trialsearch.who.int/Trial2.aspx?TrialID=NTR7452, 2018.	Outcomes – trial record with no results posted.
Onwunduba A, Ekwunife O, Onyilogwu E. Impact of point-of-care c-reactive protein testing intervention on non-prescription dispensing of antibiotics for respiratory tract infections in private community pharmacies in Nigeria: a cluster randomized controlled trial. International journal of infectious diseases 2023;**127**:137-143.	Population – simulated patients.
Oosterheert JJ, van Loon AM, Schuurman R, Hoepelman AI, Hak E, Thijsen S, et al. Impact of rapid detection of viral and atypical bacterial pathogens by real-time polymerase chain reaction for patients with lower respiratory tract infection. Clinical infectious diseases 2005;**41**(10):1438-1444.	Population – inpatients. Not near patient test and results within 48 hours.
Oppong R, Jit M, Smith RD, Butler CC, Melbye H, Mölstad S, et al. Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions. Br J Gen Pract 2013; **63**(612):e465–e471.	Study design – not an RCT (observational data).
Orda U, Mitra B, Orda S, Fitzgerald M, Gunnarsson R, Rofe G, et al. Point of care testing for group A streptococci in patients presenting with pharyngitis will improve appropriate antibiotic prescription. Emergency Medicine Australasia 2016;**28**:199-204.	Population – children under 16 years. Not an RCT.

Full reference	Reason for exclusion
Papastergiou J, Trieu CR, Saltmarche D, Diamantouros A. Community pharmacist-directed point-of-care group A Streptococcus testing: evaluation of a Canadian program. Journal of the American Pharmacists Association 2018;**58**:450-6.	Study design – not an RCT (retrospective analysis of aggregate billing data).
Ramakrishnan S, Jeffers H, Langford-Wiley B, Davies J, Mahdi M. A'Court C. et al. Point of care blood eosinophil guided oral prednisolone for COPD exacerbations: a multicentre double blind randomised controlled trial (The STARR2 trial). Thorax 2022;**77**:A3-A4.	Publication type – conference abstract only.
Ramakrishnan S, Jeffers H, Langford-Wiley B, Davies J, Mahdi M. A'Court C. et al. Point of care blood eosinophil guided oral prednisolone for COPD exacerbations: a multi-centre double blind randomised controlled trial(The STARR2 trial). European respiratory journal, 2022. 60.	Publication type – conference abstract only.
Rogers JH, Casto AM, Nwanne G, Link AC, Martinez MA, Nackviseth C, et al. Results from a test-and-treat study for influenza among residents of homeless shelters in King County, WA: a stepped-wedge cluster-randomized trial. Influenza and other respiratory viruses 2023;**17**(1):e13092.	Population – includes adults and children; outcomes not reported separately in adults.
Ryu SW, Lee JH, Kim J, Jang MA, Nam JH, Byoun MS, et al. Comparison of two new generation influenza rapid diagnostic tests with instrument-based digital readout systems for influenza virus detection. Br J Biomed Sci 2016;**73**:115-20.	Comparator – not usual care. Diagnostic accuracy study.
Ryu SW, Suh IB, Ryu SM, Shin KS, Kim HS, Kim J, et al. Comparison of three rapid influenza diagnostic tests with digital readout systems and one conventional rapid influenza diagnostic test. J Clin Lab Anal 2018;**32**:e22234.	Comparator – not usual care. Diagnostic accuracy study.
Schechter-Perkins EM, Mitchell PM, Nelson KP, Liu JH, Shannon A, Ahern J, et al. Point-of-care influenza testing does not significantly shorten time to disposition among patients with an influenza-like illness. American Journal of Emergency Medicine 2019;**37**(5):873-8. [DOI: 10.1016/j.ajem.2018.08.005.]	Population - mixed age population; outcomes not reported separately in adults. Influenza POCT versus core laboratory testing.
Schechter-Perkins EM, et al. Point-of-care influenza testing does not significantly shorten time to disposition among emergency department patients with an influenza-like illness. Annals of emergency medicine 2017;**70**(4):S61.	Publication type – conference abstract only.
Schot MJ, Van den Bruel A, Broekhuizen BD, Cals JW, Noteboom EA, Balemans W, et al. Point-of-care C-reactive protein to assist in primary care management of children with suspected non-serious lower respiratory tract infection: a randomised controlled trial. BJGP Open 2018;**2**(3):1-10. [DOI: 10.3399/bjgpopen18X101600]	Population – children under 16 years.
Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA 2009;**302**:1059–66.	Intervention – not near patient test (central laboratory test).

Full reference	Reason for exclusion
Schuetz P, Christ-Crain M, Thomann R, Falconnier C. Effect of procalcitonin-based guidelines compared with standard guidelines on antibiotic use in lower respiratory tract infections: the randomized-controlled multicenter ProHOSP trial. Critical care (London, England) 2009;**13** Suppl:1P386 (Abstract number).	Publication type – conference abstract only.
Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, et al. Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. BMC health services research 2007;**7**:102.	Outcomes – protocol only; no outcomes reported.
Schuetz P, Grolimund E, Kutz A, Haubitz S, Mueller B, et al. Procalcitonin-guided antibiotic therapy in patients with congestive heart failure and suspicion of lower respiratory tract infection: results from a randomized trial. Critical care (London, England) 2013;**17**:S12.	Publication type – conference abstract only.
Selove W, Rao LV. Performance of rapid SOFIA Influenza A+B test compared to Luminex x-TAG respiratory viral panel assay in the diagnosis of influenza A, B, and subtype H3. J Investig Med 2016;**64**:905-7.	Population – includes adults and children; outcomes not reported separately in adults. Not an RCT.
Shaikh N, Martin, JM. Randomised controlled trial: delayed prescription worsens reported symptoms and increases antibiotic use compared with clinical score with or without rapid antigen testing in patients with sore throat. Evidence-based medicine 2014;**19**(3):117.	Publication type – commentary.
Steurer J, Held U, Spaar A, Bausch B, Zoller M, Hunziker R, Bachmann LM, et al. A decision aid to rule out pneumonia and reduce unnecessary prescriptions of antibiotics in primary care patients with cough and fever. BMC Med 2011;**9**:56.	Study design – not an RCT. No relevant comparator.
Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Müller C, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest 2007;**131**:9–19.	Population - patients hospitalised for COPD exacerbation (i.e. inpatients).
Takemura Y, Ishida H, Saitoh H, Kure H, Kakoi H, Ebisawa K, et al. Antibiotic selection patterns in acutely febrile new outpatients with or without immediate testing for C reactive protein and leucocyte count. Journal of Clinical Pathology Journal of Clinical Pathology 2005;**58**(7):729–733.	Population - age not reported; therefore could include children.
Tang J, Long W, Yan L, Zhang Y, Xie J, Lu G, et al., Procalcitonin guided antibiotic therapy of acute exacerbations of asthma: a randomized controlled trial. BMC infectious diseases 2013;**13**:596.	Intervention – test does not appear to be a POCT (laboratory test).
Temte J, Checovich M, Mundt M, Barlow S, Hamrick I, Reisdorf E. Rapid Detection of Influenza Outbreaks in Long Term Care Facilities Reduces Emergency Room Visits and Hospitalization. Annals of family medicine 2023;**21** Suppl 1.	Publication type – conference abstract only.
Thornton HV, Turner KME, Harrison S, Hammond A, Hawcroft C, Hay AD. Assessing the potential of upper respiratory tract point-	Study design – systematic review of prognostic studies.

Full reference	Reason for exclusion
of-care testing: a systematic review of the prognostic significance of upper respiratory tract microbes. Clin Microbiol Infect 2019;**25**:1339–1346.	
True BL, Carter BL, Driscoll CE, House JD. Effect of a rapid diagnostic method on prescribing patterns and ordering of throat cultures for streptococcal pharyngitis. Journal of Family Practice 1986;**23**:215-9.	Population – includes adults and children; outcomes not reported separately in adults. Not an RCT.
Urbiztondo, I., et al., Decreasing inappropriate use of antibiotics in primary care in four countries in south America—cluster randomized controlled trial. Antibiotics, 2017. 6(4).	Intervention – not a POCT (no tests involved)
Van Buul LW, Boere TM, Hopstaken RM, Van Tulder MW, Twisk JWMR, Verheij TJM, et al. CRP Point-of-care Testing To Reduce Antibiotic Prescribing For Lower Respiratory Tract Infections In Nursing Home Residents. European geriatric medicine 2022;**13**:S338.	Publication type – conference abstract only.
van der Does Y, Limper M, Jie KE, Schuit SCE, Jansen H, Pernot N, et al. Procalcitonin-guided antibiotic therapy in patients with fever in a general emergency department population: a multicentre non-inferiority randomized clinical trial (HiTEMP study). Clinical microbiology and infection 2018;**24**(12):1282-1289.	Intervention – not a POCT (laboratory test).
van Vugt SF, Broekhuizen BD, Lammens C, Zuithoff NP, de Jong PA, Coenen S, et al. Use of serum C reactive protein and procalcitonin concentrations in addition to symptoms and signs to predict pneumonia in patients presenting to primary care with acute cough: Diagnostic study. BMJ 2013;**346**:f2450.	Comparator – no relevant comparator. Not an RCT (diagnostic accuracy study).
Wächtler H, Kaduszkiewicz H, Kuhnert O, Malottki KA, Maaß S, Hedderich J,.et al. Influence of a guideline or an additional rapid strep test on antibiotic prescriptions for sore throat: the cluster randomized controlled trial of HALS (Hals und Antibiotika Leitlinien Strategien). BMC primary care 2023;**24**(1):75.	Population – includes adults and children; outcomes not reported separately in adults. Not all patients in the intervention group received a POCT.
Yang JH, Huang PY, Shie SS, Yang S, Tsao KC, Wu TL, et al. Di-agnostic performance of the Sofia(R) influenza A+B fluores-cent immunoassay in adult outpatients in Northern Taiwan. J Med Virol 2018;**90**:1010-8.	Comparator – no relevant comparator. Not an RCT (diagnostic accuracy study).
Yoo J, Jung CY, Na JO, Kim TH, Oh YM, Ra SW. Bacterial etiology and pneumococcal urinary antigen in moderate exacerbation of chronic obstructive pulmonary disease. Journal of thoracic disease 2022;**14**(7):2532-2543.	Study design - not an RCT (*post hoc* analysis of an RCT but groups not randomised to interventions). No relevant comparator.
Yoon J, Yun SG, Nam J, Choi SH, Lim CS. The use of saliva specimens for detection of influenza A and B viruses by rapid influenza diagnostic tests. J Virol Methods 2017;**243**:15-9.	Comparator – no relevant comparator. Not an RCT (diagnostic accuracy study).
Zhang K, Xie K, Zhang C, Liang Y, Chen Z, Wang H. C-reactive protein testing to reduce antibiotic prescribing for acute	Study design – systematic review (reference list checked).

Full reference	Reason for exclusion
respiratory infections in adults: a systematic review and meta-analysis. Journal of Thoracic Disease 2022;**14**(1):123-134.	

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Appendix 8: 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 adjustment described above, our numbers differed slightly to those presented in the Smedemark review [16] for some trials.[25, 27, 37] 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: 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*	-	-	-	-	8	8	-	-	-
Andreeva [29]	Hospital admission (timeframe unclear)*	-	-	-	-	8	9	-	-	-
Boere [27]	Antibiotic use at index consultation	84[b]	162	65	79	6	5	21.9	0.175	4.66
Boere [27]	Hospital admission 3 weeks	10	139	5	77	6	5	19.6	0.175	4.26
Boere [27]	Mortality rate within 3 weeks	5	143	1	77	6	5	20.0	0.175	4.33
Boere [27]	Antibiotic use at index consultation; COPD patients	20	45	23	29	6	5	4.33	0.175	2.00
Cals [26, 35]	Antibiotics prescribed at index consultation	70	227	108	204	10	10	21.6	0.12	3.47
Cals [26, 35]	Antibiotics prescribed within 28 days	102	227	119	204	10	10	21.6	0.12	3.47
Cals [26, 35]	Number of re-consultations within 28 days	79	227	62	204	10	10	21.6	0.12	3.47
Cals [26, 35]	Hospital admission 28 days[a]	0	227	0	204	10	10	21.6	0.12	3.47
Cals [26, 35]	Mortality rate within 3 weeks[a]	0	227	0	204	10	10	21.6	0.12	3.47
Little [25]	Antibiotics prescribed within 3 months	368	1062	508	870	58	53	17.4	0.05[c]	1.82

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
Little [25]	New or worse symptoms within 28 days	207	760	102	861	58	53	14.6	0.05[c]	1.68
Little [25]	Hospital admissions (timeframe unclear)[a]	10	1062	2	870	58	53	17.4	0.05[c]	1.82
Little [25]	Mortality (timeframe unclear)[a]	0	1062	0	870	58	53	17.4	0.05[c]	1.82

n = number of events; N = total number in arm; CRP = C-reactive protein; M = average cluster size; ICC = intracluster correlation

*Raw data not presented in paper.

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

[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.[27] N=84 used for consistency with Smedemark review.

[c]See appendix of Little.[25]

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 (timeframe unclear)*	-	-	-	-	0	49	0	38
Boere [27]	Antibiotic use at index consultation	18	35	14	17	18	35	14	17
Boere [27]	Hospital admission within 3 weeks	2	33	1	18	1	32	1	17
Boere [27]	Mortality rate within 3 weeks	1	33	1	18	2	32	1	17
Boere [27]	Antibiotic use at index consultation; COPD patients	10	22	11	14	-	-	-	-
Cals [26, 35]	Antibiotics prescribed at index consultation	20	65	31	59	20	65	31	59
Cals [26, 35]	Antibiotics prescribed within 28 days	29	65	34	59	29	65	34	59
Cals [26, 35]	Number of re-consultations within 28 days	23	65	18	59	23	65	18	59
Cals [26, 35]	Hospital admission 28 days[a]	0	65	0	59	0	65	0	59
Cals [26, 35]	Mortality rate within 3 weeks[a]	0	65	0	59	0	65	0	59
Little [25]	Antibiotics prescribed within 3 months[b]	202	583	279	478	-	-	-	-

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]
Little [25]	Antibiotics prescribed at index consultation	-	-	-	-	304	920	407	884
Little [37]	Antibiotics prescribed at index consultation	-	-	-	-	476	1068	468	1024
Little [25]	New or worse symptoms within 28 days[b]	123	452	61	512	165	894	149	812
Little [25]	Hospital admissions (timeframe unclear)[a, b]	5	583	1	478	4	920	1	844
Little [25]	Mortality (timeframe unclear)[a, b]	0	583	0	478	0	920	0	844

n = number of events; N = total number in arm; CRP = C-reactive protein; M = average cluster size; ICC = intracluster correlation

[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.

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] didn't 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 reivew also included two additonal outcomes ('Number of re-consultations within 14 days' and 'Hospital admission (timeframe 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 [27] 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 negligble 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.[27] In the abstract, the paper reports n=84 patients prescribed antibiotics at index consultaiton in the C-reative protein (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 consulation 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 [26, 35] 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 ususal care group).

The Little [25, 37] study used a 2x2 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+communicaiton 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 supplementary data given in Little 2013 [25] 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 timeframe for the primary outcome (antibiotic prescribing) is unclear from the Little 2013[25] 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[37] 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 1,062) at 3 months". These values match those presented in the Little 2013 [25] publication supplementary material. We therefore exclude Little 2013 [25] 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 supplementary material Little 2013 [25]). Finally, we extracted data for outcomes 'Hospital admissions (timeframe unclear)' and 'Mortality (timeframe unclear)' from the text of Little 2013 [25] ("30 patients were reported as being admitted to hospital (two in the usual-care group, ten 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 [25, 37] study. No additional outcome data was obtained from the Little 2019 [37] publication.

Appendix 9: Quality assessment of included RCTs

Table 17: Risk of bias: C-reactive protein tests

Study	Random sequence generation [a]	Allocation conceal-ment[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 Althaus 2019 [30]	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 [27] Boere 2022, #4647}	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 [24]	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 [26, 35]	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 [28]	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[31]	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
Do 2016 [33]	Low risk	Low risk	High risk	1. Unclear risk 2. N/A	Low risk	1. Unclear risk 2. N/A	High risk	Low risk	Low risk

				3. N/A		3. N/A			
Little 2013[25] **Little 2019[37]**	Low risk	Unclear risk	High risk	1. Low risk 2. NA 3. Low risk	Low risk	1. Low risk 2. NA 3. Low risk	Unclear risk	Low risk	High risk
Melbye 1995[32] [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

[a]RoB 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), 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. N/A – not applicable.

Table 18: 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[38]	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]RoB 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), 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 19: Risk of bias: Group A streptococcus 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 [39]	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 [40]	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

[a] Reviewer's judgement on key protocol outcomes: 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 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). N/A – not applicable.

Table 20: 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 [41]	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

[a] Reviewer's judgement on key protocol outcomes: 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 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). N/A – not applicable.

Table 21: Justification for risk of bias judgements

Bias	Reviewer's Judgement	Justification for Reviewer's judgement
Althaus 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. 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.

Bias	Reviewer's Judgement	Justification for Reviewer's judgement
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[27, 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. Low risk 2. N/A 3. Low risk	Data on clinical status, additional diagnostics, and management decisions were collected for all participants on initial consultation and one week and three weeks later; treating physicians filled out electronic case report forms that were integrated into the nursing home electronic patient record system. These forms were automatically uploaded (in real time) to the secure database portal of the research team.
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.

Bias	Reviewer's Judgement	Justification for Reviewer's judgement
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 two participants for the outcome antibiotic prescribing at baseline and for 25 participants for the outcome full recovery at 3 weeks.
Butler 2019[24]		
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[26, 35]		
Blinding of key outcome assessment (detection bias) 1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission),	1. Low risk 2. N/A 3. Low risk	Data were obtained from the medical records of patients for the 28 days follow-up.

Bias	Reviewer's Judgement	Justification for Reviewer's judgement
3. hospital admission (immediately after triage or at 28 days)		
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 [28]		
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.
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[31]		
Blinding of key outcome assessment (detection bias)	1. N/A	

Bias	Reviewer's Judgement	Justification for Reviewer's judgement
1. 7- or 28-day mortality, 2. escalation of care (including unplanned admission), 3. hospital admission (immediately after triage or at 28 days)	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[33]		
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[38]		

Bias	Reviewer's Judgement	Justification for Reviewer's judgement
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 member of the study team (blinded to study arm) conducted a standardised phone interview of all participants on day 7 and day 28 and recorded clinical outcomes (presence or recurrence of LRTIs symptoms), additional medical visits, additional antibiotic prescription, number of days during which activities (work or recreation) were restricted, antibiotic side effects, secondary hospital admission and patient satisfaction.
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 member of the study team (blinded to study arm) conducted a standardised phone interview of all participants on day 7 and day 28 and recorded additional medical visits, additional antibiotic prescription, and secondary hospital admission.
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.
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 2013a [25]		
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 documented on a case-report form created specifically for the study, and data were uploaded centrally by network facilitators. After randomisation a more detailed case-report form was used in follow-up consultations that included the same details as the index form plus medical history, current medications, smoking status, findings of structured examination, whether CRP was tested, and whether the booklet was used.

Bias	Reviewer's Judgement	Justification for Reviewer's judgement
Blinding of other outcome assessment (detection bias) Antibiotic/antiviral use, follow-up consultation/ongoing monitoring, time to clinical cure/resolution of symptoms	Low risk	Data were documented on a case-report form created specifically for the study, and data were uploaded centrally by network facilitators. After randomisation a more detailed case-report form was used in follow-up consultations that included the same details as the index form plus medical history, current medications, smoking status, findings of structured examination, whether CRP was tested, and whether the booklet was used.
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 [41]		
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.

Bias	Reviewer's Judgement	Justification for Reviewer's judgement
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.
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 [39]		
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

Bias	Reviewer's Judgement	Justification for Reviewer's judgement
		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.
Worrall 2007 [40]		
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.

Bias	Reviewer's Judgement	Justification for Reviewer's judgement
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.

CRP – C-reactive protein; eCRF - electronic case report forms; ED – emergency department; HRQoL – health related quality of life; iRDT – influenza rapid diagnostic test; ITT – intention-to-treat; LRTI – lower respiratory tract infection; N/A – not applicable; RADT – rapid antigen detection test; SR – systematic review.

Appendix 10: GRADE tables

GRADE evidence tables are presented below for C-reactive protein, procalcitonin and influenza rapid antigen tests. No evidence for the relevant outcomes was identified for Group A streptococcus rapid antigen tests.

Table 22: Clinical evidence profile for comparison of C-reactive POCT versus usual care in adults with suspected ARI

QUALITY					Summary of findings			Quality[o]	Importance
					No of patients		Effect		
No of studies (design)	Limitations	Inconsistency	Indirectness	Imprecision	CRP	Usual care	Result (95%CI)		
Hospital admission immediately after triage									
NR									
Hospital admission at 3 weeks to 6 months									
1 cluster-RCT[a]	Very serious[g]	NA	No serious indirectness	Not calculable	0/49	0/38	Not reported	VERY LOW	CRITICAL
1 cluster-RCT[b]	Very serious[h]	NA	No serious indirectness	Very serious imprecision[i]	2/33	1/18	RR 1.09 (95% CI 0.11, 11.22)	VERY LOW	CRITICAL
1 cluster-RCT[c]	Very serious[g]	NA	Serious indirectness[j]	Not calculable	0/65	0/59	Not reported	VERY LOW	CRITICAL
1 cluster-RCT[d]	Very serious[g]	NA	No serious indirectness	Very serious imprecision[i]	5/583	1/478	RR 4.10 (95% CI 0.48, 34.97)	VERY LOW	CRITICAL
1 RCT[e]	Very serious[g]	NA	No serious indirectness	Very serious imprecision[i]	35/304	34/301	RR 1.02 (95% CI 0.65, 1.59)	VERY LOW	CRITICAL
1 RCT[f]	Very serious[g]	NA	No serious indirectness	Not calculable	0/129	0/129	Not reported	VERY LOW	CRITICAL
Escalation of care: re-consultation/appointment									

QUALITY					Summary of findings			Quality[o]	Importance
					No of patients		Effect		
No of studies (design)	Limitations	Inconsistency	Indirectness	Imprecision	CRP	Usual care	Result (95%CI)		
3 cluster-RCTs/1 RCT[k]	Very serious[g]	Serious inconsistency[l]	Serious indirectness[j]	Serious imprecision[m]	180/695	103/738	RR 1.61 (95% CI 1.07, 2.41)	VERY LOW	CRITICAL
Escalation of care: virtual ward									
NR									
Escalation of care: emergency department visit									
NR									
Escalation of care: unplanned hospital admission									
NR									
Mortality at 7 days									
NR									
Mortality at 28 days									
1 cluster-RCT[b]	Very serious[h]	NA	No serious indirectness	Very serious imprecision[i]	1/33	0/19	RR 1.68 (95% CI 0.07, 39.16)	VERY LOW	CRITICAL
1 cluster-RCT[c]	Very serious[g]	NA	Serious indirectness[j]	Not calculable	0/65	0/59	Not reported	VERY LOW	CRITICAL
1 cluster-RCT[d]	Very serious[g]	NA	No serious indirectness	Not calculable	0/583	0/478	Not reported	VERY LOW	CRITICAL
1 RCT[e]	Very serious[g]	NA	No serious indirectness	Very serious imprecision[i]	0/325	2/324	RR 0.20 (95% CI 0.01, 4.14)	VERY LOW	CRITICAL
1 RCT[f]	Very serious[g]	NA	No serious indirectness	Not calculable	0/129	0/129	Not reported	VERY LOW	CRITICAL
1 RCT[n]	Very serious[h]	NA	Serious indirectness[j]	Not calculable	0/507	0/501	Not reported	VERY LOW	CRITICAL

[a] Andreeva 2014.[29]

[b] Boere 2021.[27]
[b] Cals 2009.[26]
[d] Little 2013.[25]
[e] Butler 2019.[24]
[f] Cals 2010.[28]
[g] Very serious limitations due to uncertainties around selection bias and high risk of bias due to lack of blinding.
[h] Very serious limitations due to uncertainties around selection bias and high risk of bias due to lack of blinding and incomplete outcome data reporting.
[i] Very serious imprecision because the 95% CI for the RR crosses 0.8 and 1.25.
[j] Serious indirectness as test(s) not currently available in the UK.
[k] Andreeva 2014,[29] Cals 2009,[26] Little 2013[25] and Cals 2010.[28]
[l] Serious inconsistency due to moderate heterogeneity (I^2=56.6%).
[m] Serious imprecision because the 95% CI for the RR crosses 1.25.
[n] Do 2016.[33]
[o] 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.

Table 23: Clinical evidence profile for comparison of procalcitonin POCT versus usual care in adults with suspected ARI

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

Abbreviations: CI – confidence interval; CRP – C-reactive protein; NR – not reported; RCT – randomised controlled trial; RR – relative risk.

[a] Lhopitallier 2021 [38]

[b] Very serious limitations due to lack of blinding and unclear allocation concealment.

[c] Very serious limitations due to lack of blinding, unclear allocation concealment and incomplete outcome data.
[d] Very serious imprecision because the 95% CI for the RR crosses 0.8 and 1.25.
[e] 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.

Table 24: Clinical evidence profile for comparison of rapid antigen tests for influenza versus usual care in adults with suspected ARI

QUALITY					Summary of findings			Quality[d]	Importance
					No of patients		Effect		
No of studies (design)	Limitations	Inconsistency	Indirectness	Imprecision	RADT	Usual care	Result (95%CI)		
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: emergency department visit									
NR									
Escalation of care: unplanned hospital admission									
NR									
Mortality at 7 days									
NR									
Mortality during study (follow-up not reported)									
1 RCT[a]	Very serious[b]	NA	Serious indirectness[c]	Not calculable	0/60	0/33	Not reported	VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; CRP – C-reactive protein; NR – not reported; RCT – randomised controlled trial.									

[a] Berthod 2015. [41, 42]

[b] Very serious limitations due to high risk of selection bias and lack of blinding.
[c] Serious indirectness as the test is not currently available in the UK.
[d] 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.

Appendix 11: 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[24] and the COPD subgroup of Boere 2021[27])*	Antibiotics prescribed at index consultation	2	165/347	236/338	0.68 (0.60, 0.77)	0	0%
Sensitivity analyses							
Excluding Butler 2019[24] *(AECOPD)*	Antibiotics prescribed at index consultation	8	742/1894	822/1529	0.76 (0.67, 0.86)	0.015	55.7%
	Antibiotic prescribed within 28 days	5	464/805	587/817	0.80 (0.73, 0.89)	0.003	21.9%
Excluding Boere 2021[27] *(nursing home setting)*	Antibiotics prescribed at index consultation	8	879/2139	1033/1836	0.76 (0.68, 0.85)	0.013	58.4%
Excluding studies with tests unavailable in the UK *(Althaus 2019,[30] Cals 2009,[26] Diederichsen 2000,[31] Do 2016,[33] Melbye 1995[32])*	Antibiotics prescribed at index consultation	4	247/538	335/508	0.69 (0.62, 0.77)	0	0%
	Antibiotic prescribed within 28 days	3	273/491	363/483	0.74 (0.67, 0.83)	0.002	13.2%
	Escalation of care: number of re-consultations	3	157/630	85/679	1.87 (1.27, 2.77)	0.046	37.8%

n = number of events; N = total number in arm; CRP = C-reactive protein; RR = risk ratio

Appendix 12: Critical appraisal of included systematic reviews of cost-effectiveness studies

Critical appraisal tool used: JBI critical appraisal checklist for systematic reviews and research syntheses

Study reference: van der Pol, S., Garcia, P. R., Postma, M. J., Villar, F. A., & van Asselt, A. D. I. (2021). Economic Analyses of Respiratory Tract Infection Diagnostics: A Systematic Review. PharmacoEconomics, 39(12), 1411–1427. https://doi.org/10.1007/s40273-021-01054-1

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 e.g. 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, B. L., Merlo, G., Ghahreman-Falconer, N., Hall, L., & Comans, T. (2022). Economic evaluation of antimicrobial stewardship in primary care: a systematic review and quality assessment. The Journal of antimicrobial chemotherapy, 77(9), 2373–2388. https://doi.org/10.1093/jac/dkac185

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

Appendix 13: References of excluded studies at full texts and primary reason for exclusion

Authors	Year	Title	Primary reason for exclusion
Abbasi, M. et al.	2022	Cost-Effectiveness Analysis of Rapid Test Compared to Polymerase Chain Reaction (PCR) in Patients with Acute Respiratory Syndrome	Not triage
Abel, L. et al.	2019	Is stratification testing for treatment of chronic obstructive pulmonary disease exacerbations cost-effective in primary care? an early cost-utility analysis	Test not available yet
Bank, S. et al.	2013	A cost-effectiveness analysis of identifying Fusobacterium necrophorum in throat swabs followed by antibiotic treatment to reduce the incidence of Lemierre's syndrome and peritonsillar abscesses	Not rapid test
Barenfanger, J. et al.	2000	Clinical and financial benefits of rapid detection of respiratory viruses: an outcomes study	Not rapid test
Bisno, A. L. et al.	1997	Diagnosis and management of group A streptococcal pharyngitis: a practice guideline. Infectious Diseases Society of America	No economic evaluation
Bisno, A. L. et al.	2002	Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Infectious Diseases Society of America	No economic evaluation
Blitz, S. G. et al.	2002	Diagnostic testing or empirical neuraminidase inhibitor therapy for patients with influenza-like illness: what a difference a day makes	Not rapid test
Boere, T. M. et al.	2022	Cost-effectiveness and return-on-investment of C-reactive protein point-of-care testing in comparison with usual care to reduce antibiotic prescribing for lower respiratory tract infections in nursing homes: a cluster randomised trial	Not cost utility analysis
Carey, R. D. et al.	1991	Evaluation of a rapid diagnostic test for group A beta-haemolytic streptococcus in general practice	No economic evaluation
Chouaid, C. et al.	1993	Cost effectiveness of the induced sputum technique for the diagnosis of Pneumocystis carinii pneumonia (PCP) in HIV-infected patients	Not rapid test
Chouaid, C. et al.	1993	Cost effectiveness of noninvasive oxygen saturation measurement during exercise for	Wrong population

		the diagnosis of Pneumocystis carinii pneumonia	
Chouaid, C. et al.	1995	Use of the polymerase chain reaction technique on induced-sputum samples for the diagnosis of Pneumocystis carinii pneumonia in HIV-infected patients. A clinical and cost-analysis study	Not rapid test
del Rio, C. et al.	1988	Sputum examination in the diagnosis of Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome	Not rapid test
DeNeef, P.	1986	Comparison of tests for streptococcal pharyngitis	Not cost utility analysis
DeNeef, P.	1987	Selective testing for streptococcal pharyngitis in adults	Includes costs only
Diel, R. and Nienhaus, A.	2019	Cost-Benefit Analysis of Real-Time Influenza Testing for Patients in German Emergency Rooms	Not triage
Diel, R. and Nienhaus, A.	2019	Rapid Point-of-Care Influenza Testing for Patients in German Emergency Rooms - A Cost-Benefit Analysis	Not triage
Dinh, A. et al.	2018	Cost effectiveness of pneumococcal urinary antigen in Emergency Department: a pragmatic real-life study	Includes costs only
English, E. C. and Geyman, J. P.	1978	The efficiency and cost effectiveness of diagnostic tests for infectious mononucleosis	Not rapid test
Fawsitt, C. G. et al.	2022	A cost-effectiveness and budget impact analysis of C-reactive protein point-of-care testing to guide antibiotic prescribing for acute respiratory tract infections in primary care settings in Ireland: a decision-analytic model	Not cost utility analysis
Freedberg, K. A. et al.	1992	Optimal management strategies for HIV-infected patients who present with cough or dyspnea: a cost-effective analysis	Not rapid test
Goldfarb, J.	2002	What is the best way to diagnose streptococcal pharyngitis?	Not rapid test
Harris, J. R. et al.	2011	Cost-effectiveness analysis of diagnostic options for pneumocystis pneumonia (PCP)	Not rapid test
Hueston, W. J. and Benich, J. J., 3rd	2004	A cost-benefit analysis of testing for influenza A in high-risk adults	Includes costs only
Lamas-Fernandez, C. et al.	2019	A mathematical model for designing networks of C-Reactive Protein point of care testing	No economic evaluation

Lubell, Y. et al.	2018	C-reactive protein point of care testing in the management of acute respiratory infections in the Vietnamese primary healthcare setting - a cost benefit analysis	Includes costs only
Molicotti, P. et al.	2014	Cost-effectiveness in the diagnosis of tuberculosis: choices in developing countries	Wrong infection
Moore, N.	2016	Rapid point-of-care assays for influenza testing	No economic evaluation
Nshimyumukiza, L. et al.	2016	Cost-effectiveness analysis of antiviral treatment in the management of seasonal influenza A: point-of-care rapid test versus clinical judgment	Not cost utility analysis
Pinsky, B. A. and Hayden, R. T.	2019	Cost-Effective Respiratory Virus Testing	No economic evaluation
Pinto, M. et al.	2016	Cost-effectiveness of the Xpert R MTB/RIF assay for tuberculosis diagnosis in Brazil	Wrong infection
Ryan, M. E. et al.	1997	Cost-effective management of group A streptococcal pharyngitis	Wrong Population
Schuetz, P. et al.	2015	Economic evaluation of procalcitonin-guided antibiotic therapy in acute respiratory infections: a US health system perspective	Includes costs only
Schwarzinger, M. et al.	2003	Bedside rapid flu test and zanamivir prescription in healthy working adults: a cost-benefit analysis	Not cost utility analysis
Siddiqui, M. R. and Edmunds, W. J.	2008	Cost-effectiveness of antiviral stockpiling and near-patient testing for potential influenza pandemic	Not triage
Takemura, Y. et al.	2005	Economic consequence of immediate testing for C-reactive protein and leukocyte count in new outpatients with acute infection	Wrong infection
Tillekeratne, L. G. et al.	2019	Use of clinical algorithms and rapid influenza testing to manage influenza-like illness: a cost-effectiveness analysis in Sri Lanka	Not cost utility analysis
van der Kraan, M. et al.	2021	Performance- and cost-benefit analysis of an influenza point-of-care test compared to laboratory-based multiplex RT-PCR in the emergency department	Includes costs only
Voermans, A. M. et al.	2019	Cost-Effectiveness Analysis of a Procalcitonin-Guided Decision Algorithm for Antibiotic Stewardship Using Real-World U.S. Hospital Data	Not rapid test
Wiwanitkit, V.	2005	Study of the cost-effectiveness of three staining methods for identification of	Not rapid test

		Pneumocystis carinii in bronchoalveolar lavage fluid	
Xie, X. et al.	2017	Evaluating the accuracy and economic value of a new test in the absence of a perfect reference test	Not rapid test
You, J. H. et al.	2012	A cost-effectiveness analysis of "test" versus "treat" patients hospitalized with suspected influenza in Hong Kong	Not rapid test
Datta, B. et al.	2019	Comparison of clinical and cost-effectiveness of two strategies using mobile digital x-ray to detect pulmonary tuberculosis in rural India	Wrong infection
Diomedi, A.	2013	Cost-effectiveness of different screening strategies (single or dual) for the diagnosis of tuberculosis infection in healthcare workers	Wrong infection
Guerra, R. L. et al.	2013	Cost-effectiveness of routine diagnostic evaluation of pulmonary tuberculosis in a primary care unit in Brazil	Wrong infection
Chitpim, N. et al.	2022	Cost-Utility Analysis of Molecular Testing for Tuberculosis Diagnosis in Suspected Pulmonary Tuberculosis in Thailand	Wrong infection
Armina Padmasawitri, T. I. et al.	2018	Disparities in model-based cost-effectiveness analyses of tuberculosis diagnosis: A systematic review	Wrong infection
Benson, M. S. et al.	1991	Erratum: Non-bronchoscopic diagnosis of Pneumocystis carinii pneumonia: Is it cost-effective? (Respiratory Care 1990; 35:1100)	Not retrieved
Van Der Maas, et al.	2017	Procalcitonin Biomarker Algorithm Reduces Antibiotic Prescriptions, Duration of Therapy, and Costs in Chronic Obstructive Pulmonary Disease: A Comparison in the Netherlands, Germany, and the United Kingdom	Not cost utility analysis
Dinh, A. et al.	2016	RESPIR-03 - Relevance and cost effectiveness of pneumococcal urinary antigen test	Full text not in English
Stevenson, M. et al.	2016	Sepsis: The lightcycler septifast test MGRADE, SepsiTestTM and IRIDICA BAC BSI assay for rapidly identifying bloodstream bacteria and fungi - A systematic review and economic evaluation	Wrong infection
Nsengiyumva, N. P. et al.	2021	Triage of Persons With Tuberculosis Symptoms Using Artificial Intelligence-Based Chest Radiograph Interpretation: A Cost-Effectiveness Analysis	Wrong infection
Bates, J. et al.	2017	General practitioner use of a C-reactive protein point-of-care test to help target	Protocol

		antibiotic prescribing in patients with acute exacerbations of chronic obstructive pulmonary disease (the PACE study): study protocol for a randomised controlled trial	
Behnamfar, Z. et al.	2019	Cost and effectiveness analysis of the diagnostic and therapeutic approaches of group A Streptococcus pharyngitis management in Iran	Wrong population
Cals, J. W. et al.	2011	C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial	Not cost utility analysis
Dugas, A. F. et al.	2013	Cost-utility of rapid polymerase chain reaction-based influenza testing for high-risk emergency department patients	Not rapid test
Ruiz, R. et al.	2019	Effectiveness and cost-effectiveness of Improving clinicians' diagnostic and communication Skills on Antibiotic prescribing Appropriateness in patients with acute Cough in primary care in CATalonia (the ISAAC-CAT study): study protocol for a cluster randomised controlled trial	Protocol
Smith, K. J. et al.	2013	Cost-effectiveness of procalcitonin-guided antibiotic use in community acquired pneumonia	Not triage
Stojanovic, I. et al.	2017	Economic evaluation of procalcitonin-guided antibiotic therapy in acute respiratory infections: a Chinese hospital system perspective	Includes costs only

Appendix 14: Applicability of included cost utility studies to our review question

Study identification Bilir, S. P., Kruger, E., Faller, M., Munakata, J., Karichu, J. K., Sickler, J., & Cheng, M. M. (2021). US cost-effectiveness and budget impact of point-of-care NAAT for streptococcus. The American journal of managed care, 27(5), e157–e163. https://doi.org/10.37765/ajmc.2021.88638		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	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 section 2 of the checklist if the study is considered 'not applicable'.	Not applicable	US payer perspective means cost-effectiveness results unlikely to be useful; includes children

Study identification Chew, R., Greer, R. C., Tasak, N., Day, N. P. J., & Lubell, Y. (2022). Modelling the cost-effectiveness of pulse oximetry in primary care management of acute respiratory infection in rural northern Thailand. Tropical medicine & international health: TM & IH, 27(10), 881–890. https://doi.org/10.1111/tmi.13812		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	Partly	Subgroups focus on children <5y, 5-14y 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
1.5 Is the perspective for outcomes appropriate for the review question?	Partly	DALYs but doesn't 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 section 2 of the checklist if the study is considered 'not applicable'.	Not applicable	The test and setting are not applicable to this review

Study identification Francis, N. A., Gillespie, D., White, P., Bates, J., Lowe, R., … Butler, C. C. (2020). C-reactive protein point-of-care testing for safely reducing antibiotics for acute exacerbations of chronic obstructive pulmonary disease: the PACE RCT. Health technology assessment (Winchester, England), 24(15), 1–108. https://doi.org/10.3310/hta24150		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	Yes	Patients with COPD in primary care; test used to guide antibiotic prescribing
1.2 Are the interventions appropriate for the review question?	Yes	C-reactive protein; 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 section 2 of the checklist if the study is considered 'not applicable'.	Directly applicable	

Study identification Fraser, H., Gallacher, D., Achana, F., Court, R., Taylor-Phillips, S., Nduka, C., Stinton, C., Willans, R., Gill, P., & Mistry, H. (2020). Rapid antigen detection and molecular tests for group A streptococcal infections for acute sore throat: systematic reviews and economic evaluation. Health technology assessment (Winchester, England), 24(31), 1–232. https://doi.org/10.3310/hta24310		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	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
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 section 2 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, E. A. F., Harris, S. D., Hughes, A., Craine, N., & Hughes, D. A. (2018). Cost-Effectiveness Analysis of the Use of Point-of-Care C-Reactive Protein Testing to Reduce Antibiotic Prescribing in Primary Care. Antibiotics (Basel, Switzerland), 7(4), 106. https://doi.org/10.3390/antibiotics7040106		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	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	C-reactive protein; 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; 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 section 2 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 R. (2015). Cost-effectiveness of point-of-care C-reactive protein tests for respiratory tract infection in primary care in England. Advances in therapy, 32(1), 69–85. https://doi.org/10.1007/s12325-015-0180-x		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	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	C-reactive protein; 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?	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; 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 section 2 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, P., Hobbs, F. D., Moore, M., Mant, D., Williamson, I., … Mullee, M., & PRISM investigators (2014). PRImary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive randomised controlled trial with nested qualitative study and cost-effectiveness study. Health technology assessment (Winchester, England), 18(6), vii–101. https://doi.org/10.3310/hta18060		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	Partly	Patients aged ≥3y; 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 section 2 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, S., O'Reilly, R., Adhikari, N. K. J., Fowler, R., & Sander, B. (2020). Point-of-care diagnostic tests for influenza in the emergency department: A cost-effectiveness analysis in a high-risk population from a Canadian perspective. PloS one, 15(11), e0242255. https://doi.org/10.1371/journal.pone.0242255		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	Partly	Patients aged 65 with suspected influenza-like illness; ED
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 section 2 of the checklist if the study is considered 'not applicable'.	Not applicable	Canadian payer perspective means cost-effectiveness results unlikely to be useful; disease of interest is influenza

Study identification Michaelidis, C. I., Zimmerman, R. K., Nowalk, M. P., Fine, M. J., & Smith, K. J. (2014). Cost-effectiveness of procalcitonin-guided antibiotic therapy for outpatient management of acute respiratory tract infections in adults. Journal of general internal medicine, 29(4), 579–586. https://doi.org/10.1007/s11606-013-2679-7		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	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	Point of care 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 section 2 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, K. G., Abrams, K. R., Batham, S., Medina, M. J., Warren … & Zambon, M. (2014). Randomised controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and Streptococcus pneumoniae infection on the management of acute admissions in the elderly and high-risk 18- to 64-year-olds. Health technology assessment, 18(36), 1–viii. https://doi.org/10.3310/hta18360		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	Partly	Patients ages >65y or >18y 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 section 2 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, R., Jit, M., Smith, R. D., Butler, C. C., Melbye, H., Mölstad, S., & Coast, J. (2013). Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions. The British journal of general practice : the journal of the Royal College of General Practitioners, 63(612), e465–e471. https://doi.org/10.3399/bjgp13X669185		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	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	C-reactive protein 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 section 2 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

Study identification Rothberg, M. B., Bellantonio, S., & Rose, D. N. (2003). Management of influenza in adults older than 65 years of age: cost-effectiveness of rapid testing and antiviral therapy. Annals of internal medicine, 139(5 Pt 1), 321–329. https://doi.org/10.7326/0003-4819-139-5_part_1-200309020-00007		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	Partly	Adults aged >65y 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 section 2 of the checklist if the study is considered 'not applicable'.	Not applicable	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, M. B., He, S., & Rose, D. N. (2003). Management of influenza symptoms in healthy adults. Journal of general internal medicine, 18(10), 808–815. https://doi.org/10.1046/j.1525-1497.2003.20822.x		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	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 utilities index (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 section 2 of the checklist if the study is considered 'not applicable'.	Not applicable	US-based study and from 2003; unlikely to reflect current UK NHS context; influenza only; cost-effectiveness results unlikely to be applicable

Study identification Smith, K. J., & Roberts, M. S. (2002). Cost-effectiveness of newer treatment strategies for influenza. The American journal of medicine, 113(4), 300–307. https://doi.org/10.1016/s0002-9343(02)01222-6		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	Partly	Adults aged 32y 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 section 2 of the checklist if the study is considered 'not applicable'.	Not applicable	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, J. H. S., Tam, L. P., & Lee, N. L. S. (2017). Cost-effectiveness of molecular point-of-care testing for influenza viruses in elderly patients at ambulatory care setting. PloS one, 12(7), e0182091. https://doi.org/10.1371/journal.pone.0182091		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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?	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
1.8 **Overall judgement:** Directly applicable/partially applicable/not applicable There is no need to use section 2 of the checklist if the study is considered 'not applicable'.	Not applicable	Hong Kong based; influenza only; cost-effectiveness results unlikely to be applicable

Study identification Neuner, J. M., Hamel, M. B., Phillips, R. S., Bona, K., & Aronson, M. D. (2003). Diagnosis and management of adults with pharyngitis. A cost-effectiveness analysis. Annals of internal medicine, 139(2), 113–122. https://doi.org/10.7326/0003-4819-139-2-200307150-00011		
Guidance topic: Cost-effectiveness of rapid and point of care testing for ARIs		**Question no:** RQ1.3
Checklist completed by: KS		
Section 1: 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 section 2 of the checklist if the study is considered 'not applicable'.	Not applicable	US-based study and from 2003; unlikely to reflect current UK NHS context; question eligibility of index test; population and setting unclear