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Research Article

Diagnostic accuracy of point-of-care tests for acute respiratory infection: a systematic review of reviews

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Abstract

Background: Acute respiratory infections are a common reason for consultation with primary and emergency healthcare services. Identifying individuals with a bacterial infection is crucial to ensure appropriate treatment. However, it is also important to avoid overprescription of antibiotics, to prevent unnecessary side effects and antimicrobial resistance.

We conducted a systematic review to summarise evidence on the diagnostic accuracy of symptoms, signs and point-of-care tests to diagnose bacterial respiratory tract infection in adults, and to diagnose two common respiratory viruses, influenza and respiratory syncytial virus.

Methods: The primary approach was an overview of existing systematic reviews. We conducted literature searches (22 May 2023) to identify systematic reviews of the diagnostic accuracy of point-of-care tests. Where multiple reviews were identified, we selected the most recent and comprehensive review, with the greatest overlap in scope with our review question. Methodological quality was assessed using the Risk of Bias in Systematic Reviews tool. Summary estimates of diagnostic accuracy (sensitivity, specificity or area under the curve) were extracted.

Where no systematic review was identified, we searched for primary studies. We extracted sufficient data to construct a 2 × 2 table of diagnostic accuracy, to calculate sensitivity and specificity. Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies version 2 tool. Where possible, meta-analyses were conducted. We used GRADE to assess the certainty of the evidence from existing reviews and new analyses.

Results: We identified 23 reviews which addressed our review question; 6 were selected as the most comprehensive and similar in scope to our review protocol. These systematic reviews considered the following tests for bacterial respiratory infection: individual symptoms and signs; combinations of symptoms and signs (in clinical prediction models); clinical prediction models incorporating C-reactive protein; and biological markers related to infection (including C-reactive protein, procalcitonin and others). We also identified systematic reviews that reported the accuracy of specific tests for influenza and respiratory syncytial virus. No reviews were found that assessed the diagnostic accuracy of white cell count for bacterial respiratory infection, or multiplex tests for influenza and respiratory syncytial virus. We therefore conducted searches for primary studies, and carried out meta-analyses for these index tests.

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Overall, we found that symptoms and signs have poor diagnostic accuracy for bacterial respiratory infection (sensitivity ranging from 9.6% to 89.1%; specificity ranging from 13.4% to 95%). Accuracy of biomarkers was slightly better, particularly when combinations of biomarkers were used (sensitivity 80–90%, specificity 82–93%). The sensitivity and specificity for influenza or respiratory syncytial virus varied considerably across the different types of tests. Tests involving nucleic acid amplification techniques (either single pathogen or multiplex tests) had the highest diagnostic accuracy for influenza (sensitivity 91–99.8%, specificity 96.8–99.4%).

Limitations: Most of the evidence was considered low or very low certainty when assessed with GRADE, due to imprecision in effect estimates, the potential for bias and the inclusion of participants outside the scope of this review (children, or people in hospital).

Future work: Currently evidence is insufficient to support routine use of point-of-care tests in primary and emergency care. Further work must establish whether the introduction of point-of-care tests adds value, or simply increases healthcare costs.

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Background

Rates of acute respiratory infection have increased since the COVID-19 pandemic.[1] In response, NHS England has established new acute respiratory infection (ARI) hubs and ARI virtual wards.[2,3] These are intended to reduce pressure on other parts of the health service by providing care for people with respiratory infections. This review was prepared to inform national guidance on the initial assessment and management of acute respiratory infection in people aged over 16 in England, published by the National Institute for Health and Care Excellence (NICE).[4] The NICE guideline (NG237) has a broader scope than the present review and the reader should refer to that document for recommendations from NICE.

Epidemiology and burden of acute respiratory infections

Acute respiratory infections comprise any infection of the upper or lower respiratory tract, including the nose (common cold), sinuses (sinusitis), middle ear (acute otitis media), larynx (laryngitis) and pharynx (pharyngitis/tonsillitis), as well as the lower airways (acute bronchitis) and lung (pneumonia). They can affect all individuals, but are particularly common in children, older adults and people with pre-existing lung disease. Acute respiratory infections represent a major cause of illness across the UK and worldwide. Estimates from the World Health Organization (WHO) suggest that there were 17.2 billion upper respiratory tract infections[5] and 488.9 million cases of lower respiratory tract infection[6] globally in 2019, accounting for approximately 2.4 million deaths worldwide.[6] Acute respiratory infections therefore have a high burden on the healthcare system, with significant associated healthcare and societal costs. One study estimated direct annual medical costs associated with acute respiratory infections in the UK at £86M,[7] including costs of general practitioner (GP) consultations, prescribed medications and any required hospital admissions. The causes of ARI are varied, but predominantly involve viruses (such as influenza, respiratory syncytial virus, parainfluenza, rhinovirus, adenovirus, coronavirus and human metapneumovirus[8]) or bacteria (including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Staphylococcus aureus*, *Bordetella pertussis*, Gram-negative rods and *Legionella*[9]).

Presentation of acute respiratory infections

The symptoms of respiratory infections can vary from relatively mild, self-limiting problems to more severe symptoms requiring urgent assessment and potentially hospital admission. They often include a combination of symptoms including sore throat, runny nose, cough, fever and shortness of breath. Many people with acute respiratory infections will manage their own symptoms without seeking advice from a healthcare professional. Among individuals who present to a professional, distinguishing between those in whom symptoms are likely to resolve without treatment and those in whom symptoms may deteriorate and require intervention is key. Ideally this distinction would be made rapidly, using information available at the time of the consultation, such as readily available symptoms and signs. This could also include a point-of-care diagnostic test.

Diagnostic pathway for suspected acute respiratory infections

Clinical diagnosis of an acute respiratory infection is the norm, based on the typical symptoms and signs of disease. Identification of a specific causative pathogen

is frequently not required, especially if symptoms are mild and considered likely to resolve spontaneously. However, it is important to identify people whose symptoms may not resolve without intervention. This includes those with severe symptoms, who may require admission to hospital for escalation of care. It may also include those with a bacterial infection, where symptoms are less likely to be self-limiting and may require antibiotics.

In some instances, a clinical diagnosis may be supplemented with laboratory confirmation of a bacterial or viral infection. These tests can be used as an 'add-on' to clinical diagnosis, or to help triage people who may require additional care. Tests could be based on the measurement of substances that fluctuate with the presence of different types of infection. These biological markers ('biomarkers') may include proteins produced by the body in response to an infection (such as C-reactive protein, CRP) or levels of certain cell types (including white cell counts). Point-of-care tests measuring these biomarkers are known as 'host-response' point-of-care tests. Alternatively, diagnosis may be based on isolation of a specific bacterium or virus, known as 'microbiological' point-of-care tests. Identification of the causative pathogen can be challenging, however, because many of the species responsible for infections can be carried as commensal organisms. Consequently, identification of an organism does not definitively mean that this is the cause of the individual's symptoms, so a false positive test result may be produced. Conversely, there may be low rates of shedding for some pathogens, or the sampling technique may be inadequate. This can lead to false-negative test results. Furthermore, standard microbiological diagnosis often takes too long to influence immediate management in primary care because samples may need to be transported to a central laboratory, and identification of an organism may require culture for several days. Decisions regarding initial treatment are therefore frequently taken without the benefit of a microbiological result. The lack of a 'gold standard' diagnostic test to distinguish between bacterial and viral infection means that it can be difficult to diagnose these conditions, and also makes it difficult to assess the accuracy of new tests.

Treatment pathway for suspected acute respiratory infections

The initial treatment of acute respiratory infections is determined by two key features. First, treatment depends on the severity of the symptoms at presentation – including an assessment of whether the individual is unwell enough to require hospital admission, or management in an intermediate care facility (such as a virtual ward). Second, treatment depends on the anticipated prognosis for the illness – with consideration of whether the infection is likely to resolve or deteriorate without intervention. The likely prognosis will depend on features specific to the individual (such as their age and the presence of comorbidities) as well as features of the infection itself (including whether a bacterial or viral cause is suspected).

Despite most acute respiratory infections being caused by viruses, antibiotics are frequently prescribed for these conditions. The reasons for this are multifactorial but may include patient expectations, time pressures, diagnostic uncertainty and concerns about medico-legal consequences of perceived undertreatment.[10,11]

Relevant health inequalities

People on lower incomes and with poorer living situations are at higher risk of infectious diseases.[12] In the UK, the incidence of pneumonia in people over 65 is 70% higher in those living in the lowest socioeconomic quintile compared with the highest quintile.[13] These higher rates of ARI are linked to increased rates of domestic damp and mould,[14] air pollution,[15] functional impairment, unhealthy lifestyles and comorbidities.[16] Therefore, rapid and accurate diagnostic tests that enable early treatment could play a role in reducing the inequalities in morbidity and mortality from ARIs.

People living in deprived areas are also at increased risk of carrying resistant bacteria.[17] Antibiotic prescribing is higher in deprived areas and for people on low incomes.[18,19] This is partly due to the higher incidence of infections. However, clinician antibiotic prescribing is influenced by many factors including uncertainty, fear of negative outcomes and perceived and actual patient expectation.[20,21] This can lead to high antibiotic prescribing becoming the norm in some areas.[22] Tests that reduce diagnostic uncertainty are an important tool to reduce unnecessary prescription of antibiotics in deprived communities, which in turn could contribute to reduced carriage of resistant bacteria.

Aims and objectives

This systematic review aimed to determine the accuracy of the following tests in adults (>16 years) who present in an acute care setting:

1. symptoms and signs to diagnose bacterial respiratory infections

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2. rapid, point-of-care tests to diagnose bacterial or viral respiratory infections
3. rapid, point-of-care tests to diagnose influenza and respiratory syncytial virus (RSV).

Methods

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023427097. There were no changes to the protocol during the review process. The principal approach used was an overview of systematic reviews.

Search strategy

We undertook systematic literature searches to identify published clinical evidence relevant to the review question. Database searches used subject headings, free-text terms and, where appropriate, study design filters. We conducted two main sets of searches, the first to identify systematic reviews of diagnostic test accuracy studies (up to 22 May 2023) and the second to identify primary diagnostic test accuracy studies (up to 6 June 2023), where there were gaps in the available evidence. We searched for systematic reviews in the following databases: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, NIHR Journals Library and Epistemonikos. We searched for primary studies in MEDLINE and EMBASE. A pragmatic search of the International Trials Registers (ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform) was also conducted but did not yield any relevant results.

The searches were iterative, with the initial search structured around broad, top-level terms for the index tests (rapid point-of-care tests or clinical prediction rules) combined with terms for the target condition or causative agents of respiratory tract infections. Later searches included the addition of relevant host-response biomarkers or named tests (devices), as the retrieval of relevant research evidence evolved. No date restrictions were placed on the searches.

Details of the search strategies (reviews and primary studies) can be found in *Appendix 1*. Searches for grey literature or unpublished literature were not undertaken.

Eligibility criteria

Systematic reviews that fulfilled the following criteria were eligible for inclusion. Where no systematic reviews were identified, primary studies that fulfilled the same criteria were included.

Population

We included reviews (or primary studies) of participants aged 16 years or over with suspected acute respiratory infection. We included remote settings (such as via telephone or video call) and face-to face settings (e.g. care homes, community pharmacies, primary care, emergency departments or outpatient settings). We excluded reviews or primary studies where more than one quarter of the participants had a diagnosis of COVID-19; were inpatients in hospital; had a respiratory infection during end-of-life care; had aspiration pneumonia, bronchiectasis, cystic fibrosis or known immunosuppression; or had symptoms of otitis media or sinusitis. We also excluded studies where more than one quarter of participants were children (aged <16 years).

Index tests

We assessed index tests that could be used at point of care to distinguish between bacterial and viral respiratory infections. We included index tests used specifically to identify bacterial infections and those used to specifically identify viral infections, as well as tests which may be able to distinguish between the two types of infection. We intended that any included point-of-care tests could be conducted and provide results within 45 minutes or less. However, it should be noted that the duration of the test was often not reported. If the test duration was not explicit, but after investigation it appeared sufficiently close to this time frame (e.g. likely to be feasible within approximately 1 hour) then we included the test in the review.

We included the following tests:

1. Symptoms and signs of acute respiratory infection, which were either assessed individually, or in combination, as part of a clinical decision tool.
2. Biomarker point-of-care tests including the following:

    - CRP
    - procalcitonin
    - a combination of CRP and myxovirus resistance protein A (MxA)
    - a combination of TNF-related apoptosis-induced ligand (TRAIL), interferon-γ-induced protein-10 (IP-10) and CRP
    - white cell differential count

We included other point-of-care tests that had been assessed in published systematic reviews. However, when it was necessary to expand the search to primary

studies, we only included the specific tests listed above.

We also included:

3. Multiplex or single point-of-care tests for the following viral pathogens:

    - respiratory syncytial virus (RSV)
    - influenza (A or B)

We did not include point-of-care tests that aimed specifically to diagnose SARS-CoV-2 or group A streptococcus, because there is existing guidance from NICE on testing for these organisms. When assessing primary studies, we excluded those where the index test had been performed on frozen/stored samples, as we did not consider this to be conducted 'at point of care'.

Reference standard

We accepted any reference standard that could be used to distinguish viral and bacterial infections, including confirmation of bacterial infection or viral infection through laboratory testing, radiological assessment, expert consensus or a clinical algorithm.

Study design

We primarily included existing systematic reviews. We defined 'systematic' reviews as reviews which (1) stated clear and unambiguous eligibility criteria, (2) undertook a comprehensive search (either stated as their aim or implied by use of two or more bibliographic databases), (3) provided details of the included studies (e.g. with a table of characteristics, and references for all included studies) and (4) used tools to assess the validity of primary studies [e.g. Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2)].[23]

Where no applicable systematic reviews were identified, or where there were evidence gaps (e.g. no evidence on an index test) in the systematic reviews, we conducted searches for diagnostic test accuracy studies. We included diagnostic cross-sectional or diagnostic cohort studies (known as one-gate designs). We excluded diagnostic case-control studies (two-gate designs), which often overestimate accuracy.[24,25]

We also excluded studies not published in English, preprints, dissertations and theses, registry entries for ongoing trials, editorials, letters, news items and commentaries, animal studies, conference abstracts and posters.

Screening and inclusion assessment

Titles and abstracts identified by the searches were independently screened by two reviewers [Katie Webster (KW) and Tom Parkhouse (TP)]. We obtained full copies of all reports considered potentially relevant and these were independently assessed for inclusion by two reviewers (KW, TP). Any disagreements were resolved by consensus, or discussion with additional reviewers (Deborah Caldwell, Julian Higgins and Hayley Jones) where necessary.

Assessment of identified systematic reviews

We selected the most robust and up-to-date evidence for each test, determined by consensus decision of two reviewers (TP, KW). Systematic reviews identified in the search were assessed for their applicability to the review question. Where multiple overlapping reviews were identified, we included the most relevant review, considering the comprehensiveness of the search, date of publication and relevance to the current review question. Reviews with largely overlapping scope were not assessed or extracted if the information had been superseded by a more recent publication. We extracted data from relevant analyses reported in systematic reviews that closely matched the review protocol.

Data extraction

Data were extracted using standardised data extraction forms developed in Microsoft Excel. Data extraction forms were piloted on a small sample of papers and adapted as necessary. Data were extracted by one reviewer and checked in detail by a second reviewer. Any disagreements were resolved by consensus.

We collected the following data, where reported: study design (systematic review or diagnostic accuracy study), funding sources (public, industry, mixed), study location and setting, presentation (symptoms), sex, age, inclusion criteria, rapid point-of-care test details (manufacturer, target condition/organism), reference standard test(s).

We collected data from systematic reviews on diagnostic accuracy measures, including sensitivity, specificity or area under the curve (AUC). For primary studies, we extracted data as 2×2 tables where possible, comparing the index test with the reference standard. When measures of accuracy (e.g. sensitivity, specificity, AUC) were reported without providing the information needed to calculate 2×2 tables, we extracted these data.

Risk-of-bias assessment

We assessed the risk of bias in results of systematic reviews using the Risk of Bias in Systematic Reviews (ROBIS) tool.[26] For additional primary test accuracy studies, we assessed risk of bias and applicability using QUADAS-2.[23] Quality assessment was undertaken by one reviewer and checked by a second reviewer. Any disagreements were resolved by consensus, or through discussion with a third reviewer (Penny Whiting).

Evidence synthesis

Having identified suitable systematic reviews for inclusion, we present an overview of reviews, according to methods reported in the *Cochrane Handbook for Systematic Reviews of Interventions*.[27] We summarised data reported within the included systematic reviews, including results of analyses presented by the original review authors.

Statistical analysis

For tests where no suitable systematic reviews were identified, we performed meta-analyses of sensitivity and specificity using data from primary diagnostic test accuracy studies. Where at least four studies were available, we fitted bivariate random effects models with binomial likelihoods, using the 'metandi' function in Stata version 17 (StataCorp LLC, College Station, Los Angeles, CA, United States).[28–30] Where fewer than four studies were available, univariate meta-analyses of sensitivity and specificity were conducted. Subgroup analyses were performed by device/manufacturer. We use coupled forest plots of sensitivity and specificity, allowing visual assessment of heterogeneity, and summary estimates with 95% confidence intervals (CIs). Study-level and summary results were also plotted in receiver operating characteristic (ROC) space, with 95% confidence ellipses around summary estimates representing the joint uncertainty in sensitivity and specificity. Heterogeneity across studies is quantified using τ^2 statistics. These are estimates of the variance across studies of sensitivity and specificity on the log-odds scale. Ninety-five per cent prediction ellipses are also shown on the summary ROC plots.

Analysis of subgroups

We sought data pertaining to the following subgroups of interest: setting of study; age of patients; presence of chronic comorbidity; people who are pregnant/post-partum; and different reference standards.

Interpretation of test accuracy

To aid in the interpretation of results, we identified test accuracy thresholds for sensitivity and specificity that we considered to represent an accurate test (75%) and a very accurate test (90%). We recognise that these thresholds are arbitrary, but used them to assist in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the results, and interpretation of the findings.

Assessment of the certainty of the evidence

We performed GRADE[31] assessments on all syntheses, both those extracted from systematic reviews and those we undertook ourselves. However, this approach was adapted slightly to accommodate the inclusion of data from systematic reviews. For example, we were unable to determine a rating of inconsistency for many of the analyses reported in a systematic review – as no information on heterogeneity was provided. Consequently, the reported GRADE ratings may overestimate the certainty of the evidence for some outcomes, as this domain was not assessed.

Where possible, we examined the risk-of-bias assessments for the specific studies included in each analysis. Where the majority of studies were rated at unclear or high risk of bias for at least one domain, we downgraded the certainty of evidence. If risk of bias assessments for individual studies were not provided by the review authors, we assessed the studies directly using the QUADAS-2 tool. In some instances it was not possible to determine exactly which studies were included in a specific analysis. Our judgement of risk of bias was then based on the overall set of studies, rather than the specific studies included in each analysis.

Patient and public involvement or community engagement, and involvement

Due to the limited time available, we did not directly involve patients, the public or the community in the review. However, the draft scope for this review was developed by NICE with the input of a guideline committee that included patient and public representatives. In addition, the guideline scope was subject to a consultation and engagement process (https://www.nice.org.uk/guidance/gid-ng10376/documents/draft-scope-comments-and-responses).

Equality, diversity and inclusion

The review team included a representative for equality, diversity and inclusion (Christie Cabral).

Ethics

Ethical approval was not required for this project, as it is a secondary analysis of data already in the public domain.

Results

Systematic reviews

Results of the search

The systematic search for potentially relevant systematic reviews found 4450 references. The full texts of 163 articles were retrieved for closer inspection; 23 of these studies met the inclusion criteria for this review (see *Appendix 2*, *Table 2* for a summary of these studies). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is shown in *Figure 1*.

Six relevant systematic reviews were identified as being most aligned with the scope of this overview. Details of these six reviews are reported in *Table 1*, and the summary risk of bias assessment is shown in *Figure 2*. Details of all reviews and publications excluded after full text assessment – along with the main reason for exclusion – are given in *Report Supplementary Material 1, Table S1*.

Symptoms and signs for the diagnosis of bacterial pneumonia

Four recent systematic reviews were identified which assessed the accuracy of individual symptoms and signs or combinations of symptoms and signs in diagnosing bacterial pneumonia.[33,34,36,37] The total number of studies included in each review ranged from 8[34,37] to 421.[33] The reviews were all considered to be at low risk of bias overall, although we had some concerns regarding the synthesis for one review[33] (as the high risk of bias in the primary studies was not addressed in the synthesis, there was no information on heterogeneity and some subgroup analyses were not reported) and some concerns over the identification of studies for two other reviews[34,37] (as a single author was involved in sifting studies). Of note, none of the reviews explicitly stated that case-control studies were excluded – the inclusion of such studies may result in overestimates of diagnostic test accuracy.

The reviews included primary studies of participants with symptoms of acute respiratory infection,[33] cough or lower respiratory tract infection[34,37] or an exacerbation of COPD.[36] One review included both adults and children[33] but presented some subgroup data for adults and children. Where possible, we extracted data which related exclusively to adults. All of the studies specifically included participants in appropriate settings (primary, ambulatory or emergency care settings), although one review also included some hospitalised participants.[36] The target condition was pneumonia for two studies,[34,37] bacterial pneumonia for one study[33] and a bacterial exacerbation of COPD for the final study.[36]

Individual symptoms and signs

Overall, the estimated accuracy of symptoms and signs in the diagnosis of bacterial pneumonia was poor (*Figure 3*). Data were available from a single review by Gentilotti and colleagues, for symptoms closely associated with acute respiratory infection (such as cough, sore throat and a runny nose), generic symptoms (including myalgia and diarrhoea) and a variety of clinical signs (including tachycardia, hypotension and low oxygen saturation).[33] The certainty of the evidence ranged from very low to moderate certainty (see *Appendix 3*, *Table 3*). Concerns were predominantly due to the risk of bias in the primary studies, and wide confidence intervals that crossed our prespecified thresholds for 'accurate' or 'very accurate' tests.

Subgroup analysis: People with chronic obstructive pulmonary disease

We identified one review which provided some data on the presence of purulent sputum to identify those with bacterial exacerbations of COPD.[36] In keeping with data for the general population, the estimated sensitivity and specificity were poor [71%, 95% CI 42 to 90.3 studies, 259 participants (very-low-certainty evidence due to risk of bias and wide confidence interval) and 51%, 95% CI 30 to 73.3 studies, 259 participants (moderate-certainty evidence due to a risk of bias), respectively, see *Appendix 3*, *Table 3*]. We did not identify any additional information on the subgroups of interest in this review.

Combinations of symptoms and signs

Schierenberg's[37] review included an analysis of clinical prediction models used to detect bacterial pneumonia – including combinations of symptoms and signs. Across the six models considered, the area under the curve (AUC) ranged from 0.53 to 0.79. This was considered very-low-certainty evidence due to heterogeneity between the individual estimates which ranged from not useful to useful, and a risk of publication bias (see *Appendix 3*, *Table 3*).

The same authors[34] performed a separate review which investigated the addition of CRP to the models. When using a combination of CRP, symptoms and signs, the AUC was found to increase by 0.075 (95% CI 0.044 to 0.107). They also reported the accuracy of combinations of symptoms and signs plus CRP for diagnosing bacterial pneumonia at two risk thresholds: 2.5% and 20% (i.e. where individuals with a predicted risk of either ≥ 2.5% or ≥ 20% were classed as having bacterial pneumonia).

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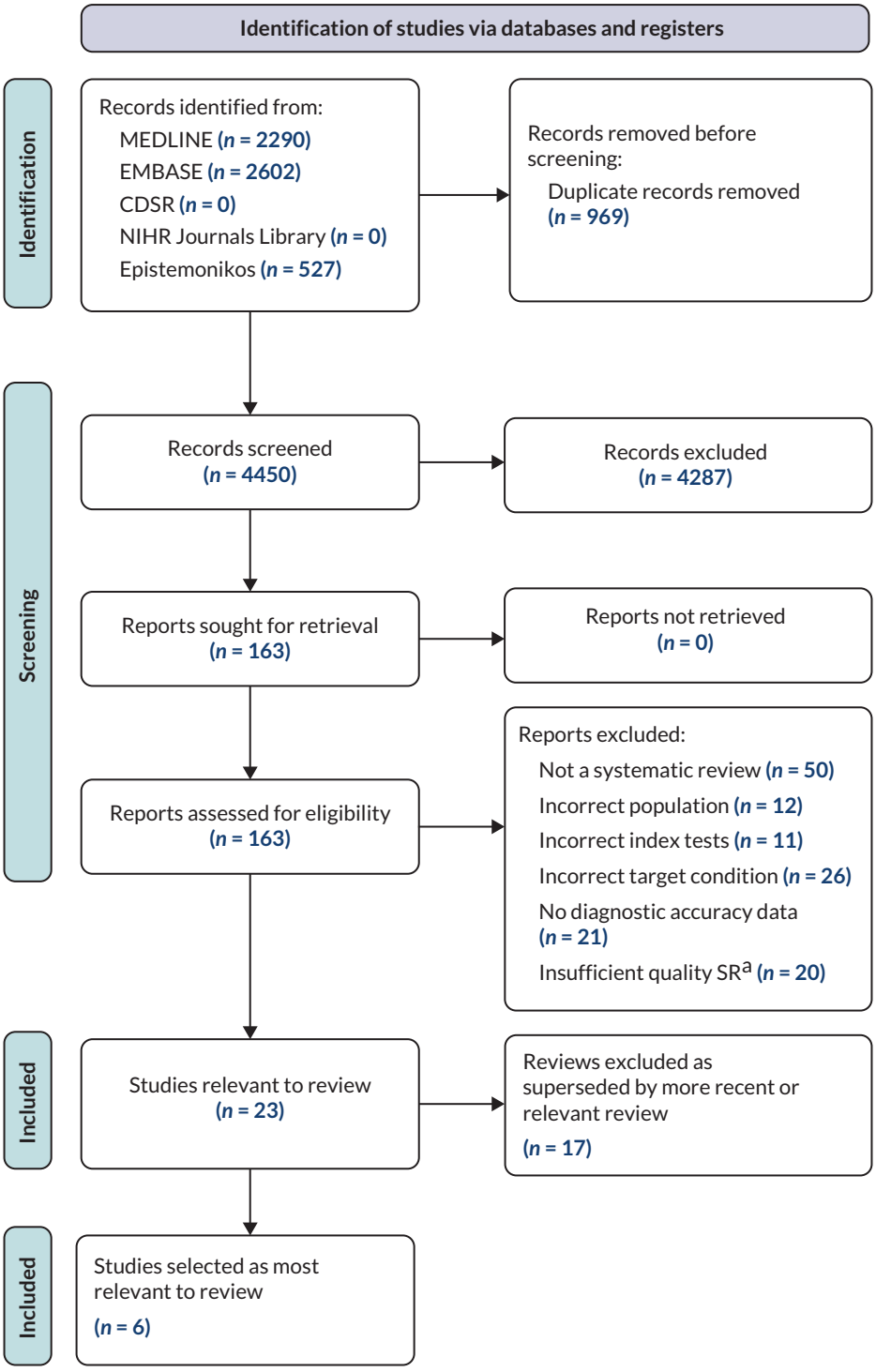

FIGURE 1 Identification of relevant systematic reviews. [a]Systematic review that searched only one database, or did not provide an assessment of methodological quality for included studies.

Across the eight studies included in the review, the lower threshold was estimated to have high sensitivity (97%, 95% CI 95 to 98, moderate-certainty evidence) but the estimated specificity was poor (36%, 95% CI 34 to 37, moderate-certainty evidence). Raising the risk threshold to 20% resulted in much higher estimated specificity (90%, 95% CI 89 to 91, moderate-certainty evidence), but the estimated sensitivity dropped to 70% (95% CI 66 to 73, low-certainty evidence) (see *Appendix 3*, *Table 3*).

TABLE 1 Included systematic reviews

Reference	Population	Clinical features	Setting	Target condition assessed	Index tests	Reference standard
Carlton 2021[32]	Adults and children. Different analyses included different populations	People presenting with symptoms of acute respiratory tract infection	Primary, emergency or secondary care	Bacterial respiratory tract infection and viral respiratory tract infection	Combinations of biomarkers (at least two included). TRAIL, IP-10 and CRP (ImmunoXpert) CRP and MxA (FebriDx) CRP and neopterin	Any reference standard, including expert consensus, clinical algorithms and microbiology
Gentilotti 2022[33]	Adults and children. Where possible, summary (subgroup) estimates were extracted which relate to adults only	Symptoms consistent with acute respiratory infection	All included studies relating to primary/emergency care settings, including primary care, emergency department, outpatient clinics and long-term care facilities. Where possible, summary (subgroup) estimates were extracted to show the effect in these different settings	Bacterial pneumonia and influenza	Symptoms and signs, host biomarkers (CRP and procalcitonin) and single pathogen tests for influenza	Any reference standard was permitted including X-ray, bacterial or viral culture, PCR, rapid antigen tests, lung ultrasound, composite analyses, expert opinion, microbiological diagnosis and rapid influenza tests
Minnaard 2017[34]	Adults	Suspected lower respiratory tract infection	Primary healthcare, ambulatory care or emergency department settings	Pneumonia	Combination of symptoms and signs plus CRP measurement	Chest X-ray
Onwuchekwa 2023[35]	Adults and children. Extracted data relate to adults only	No information provided	Primary care, emergency care and hospitalised participants	RSV	Direct immunofluorescence and rapid antigen tests	RT PCR
Pazmany 2021[36]	Adults with COPD	Presenting with an acute exacerbation of COPD	Primary care, emergency care and hospitalised participants	Bacterial acute exacerbation of COPD	Presence of purulent sputum	Microbiological culture
Schierenberg 2017[37]	Adults	Immunocompetent adults who self-referred with an acute or worsened cough or lower respiratory tract infection	Primary care, ambulatory care or emergency departments	Pneumonia	Combinations of symptoms and signs (clinical prediction models)	Chest X-ray, CT or MRI

COPD, chronic obstructive pulmonary disease; CT, computed tomography; MRI, magnetic resonance imaging; MxA, myxovirus resistance protein; PCR, polymerase chain reaction; RT PCR, real-time polymerase chain reaction.

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Review	Phase 2				Phase 3
	1. STUDY ELIGIBILITY CRITERIA	2. IDENTIFICATION AND SELECTION OF STUDIES	3. DATA COLLECTION AND STUDY APPRAISAL	4. SYNTHESIS AND FINDINGS	RISK OF BIAS IN THE REVIEW
Carlton 2021[32]	☺	☺	☺	☺	☺
Gentilotti 2022[33a]	☺	☺	☺	☹	☺
Minnaard 2017[34b]	☺	☹	☺	☺	☺
Onwucheckwa 2023[35]	☺	☺	☺	☺	☺
Pazmany 2021[36]	☺	☺	☺	☺	☺
Schierenberg 2017[37b]	☺	☹	☺	☺	☺

☺ Low risk
☹ High risk
? Unclear risk

[a] *Rated at high risk of bias for synthesis and findings as some pre-specified subgroup analyses were not reported, no information was available regarding heterogeneity, and the high/unclear risk of bias in many primary studies was not addressed in the synthesis.*

[b] *A single author was involved in sifting studies for eligibility.*

FIGURE 2 ROBIS assessment for included systematic reviews. [a]Rated at high risk of bias for synthesis and findings as some prespecified subgroup analyses were not reported, no information was available regarding heterogeneity, and the high/unclear risk of bias in many primary studies was not addressed in the synthesis. [b]A single author was involved in sifting studies for eligibility.

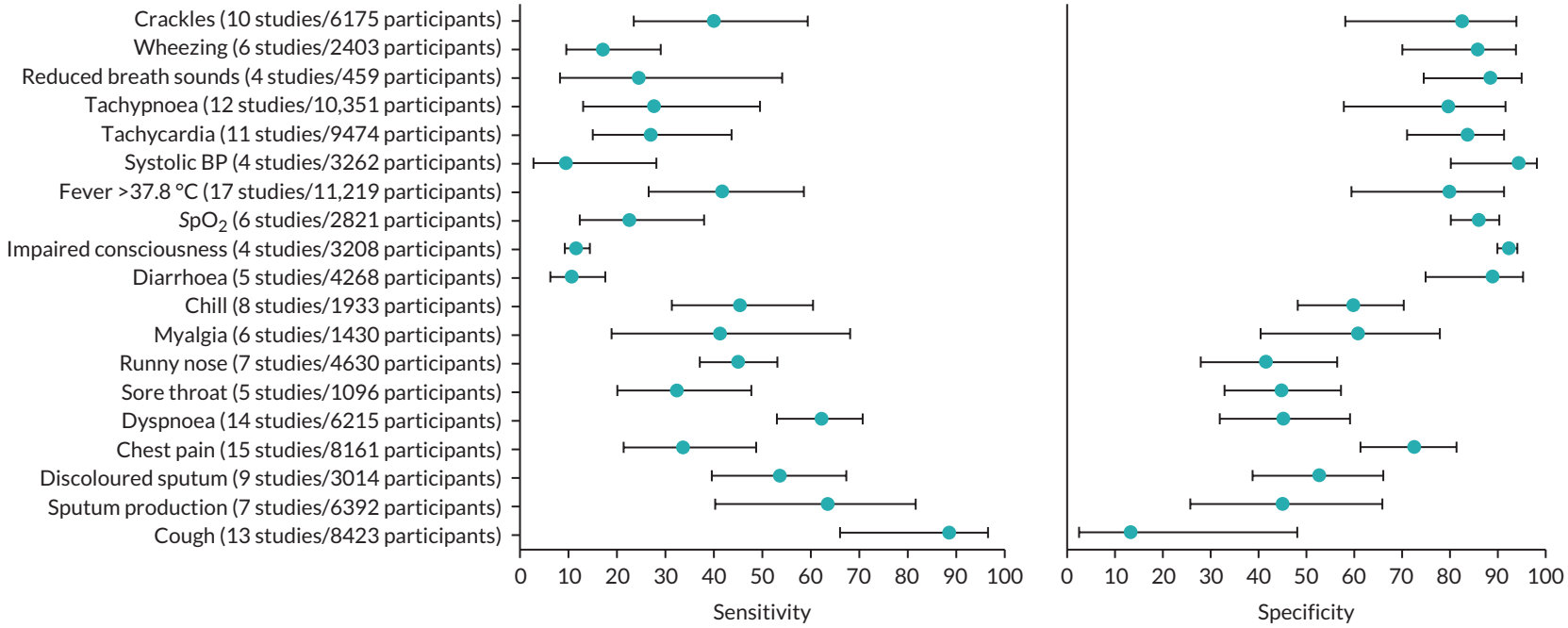

FIGURE 3 Sensitivity and specificity of individual symptoms and signs to diagnose bacterial pneumonia. Pooled estimates from random effects meta-analyses.[33]

Biomarker point-of-care tests to detect bacterial or viral respiratory tract infection

Two recent systematic reviews were identified which investigated the use of host biomarkers.[32,33]

C-reactive protein

Data were identified from one review.[33] Sensitivity and specificity of CRP to detect bacterial infection varied across the different thresholds assessed. These ranged from 10 mg/l [4 studies, 944 participants; estimated sensitivity 92% (95% CI 56 to 99) very-low-certainty evidence; estimated specificity 43% (95% CI 22 to 66) moderate-certainty evidence] to 100 mg/l [6 studies, 4418 participants; estimated sensitivity 52% (95% CI 31 to 72) moderate-certainty evidence; estimated specificity 91% (95% CI 79 to 97) low-certainty evidence] (see *Appendix 3*, *Table 4*).

Procalcitonin

Accuracy of procalcitonin to detect bacterial infection was assessed at three thresholds, by a single review.[33] Test accuracy varied across these thresholds. At > 0.1 mcg/ml the sensitivity and specificity were 74% (95% CI 38% to 93% and 36% to 94%) respectively; 4 studies; 1092 participants; very-low-certainty evidence). At > 0.25 mcg/ml the sensitivity was 44% (95% CI 14% to 79%) and specificity was 89% (95% CI 50% to 98%; 5 studies; 4019 participants; low- and very-low-certainty evidence). At > 0.5 mcg/ml the sensitivity was 44% (95% CI 19% to 73%) and specificity was 93% (95% CI 43% to 100%; 4 studies; 1195 participants; low- and very low-certainty evidence).

TNF-related apoptosis-induced ligand, IP-10 and CRP (ImmunoXpert)

The diagnostic accuracy of ImmunoXpert for bacterial infections had an estimated sensitivity of 85% (95% CI 75% to 91%) and estimated specificity of 86% (95% CI 73% to 93%; 4 studies; 1291 participants).[32] However, the evidence was again considered very low certainty (see *Appendix 3*, *Table 4*).

C-reactive protein and MxA (FebriDx)

FebriDx had an estimated sensitivity of 84% (95% CI 75 to 90; low-certainty evidence) and estimated specificity of 93% (95% CI 90 to 95; moderate-certainty evidence; 4 studies; 598 participants)[32] (see *Appendix 3*, *Table 4*).

Other host biomarkers

The Carlton review[32] identified one study (198 participants) which examined the combination of CRP and neopterin to diagnose bacterial infection. This was shown to have an estimated sensitivity of 80% (95% CI 71 to 86) and estimated specificity of 82% (95% CI 71 to 89), though there was very low certainty in the evidence for both estimates (see *Appendix 3*, *Table 4*).

Single pathogen tests for influenza and RSV

Influenza

The Gentilotti[33] review assessed the accuracy of various single pathogen tests for influenza. However, of the six single pathogen tests included, only immunochromatography had an estimate for an adult-specific population. Estimates for the remaining tests are taken from studies that included both adults and children, and we therefore had serious concerns about indirectness in the GRADE assessment. This should be taken into consideration when interpreting the findings.

Most of the tests that rely on direct antigen detection (immunochromatography, direct immunofluorescence, optical immunoassays and MariPOC) showed adequate sensitivity (ranging from 56% to 82%) and high specificity (range 88–99%), although the certainty of the evidence was considered to be very low or low. This was due to concerns over the potential for bias, indirectness for some estimates (where analyses included children) and wide confidence intervals. Tests using a chemiluminescent neuraminidase assay showed adequate sensitivity (81%, 95% CI 51% to 94%, 787 participants, 4 studies) and specificity (82%, 95% CI 65% to 91%, 787 participants, 4 studies), but the certainty of the evidence was also very low due to the risk of bias and the inclusion of children in the analysis (see *Appendix 3*, *Table 5*).

Overall, the diagnostic accuracy of tests based on nucleic acid amplification (both PCR-based and non-PCR-based) appeared higher than those based on antigen detection, with sensitivity ranging from 91% to 95.1% and specificity from 97.5% to 98%. However, the certainty of the evidence was again considered low or very low due to the risk of bias, inclusion of children in the analyses and confidence intervals that crossed our pre-specified threshold for a useful test (90%) (see *Appendix 3*, *Table 5*).

Respiratory syncytial virus

A recent systematic review was identified which investigated the use of single pathogen tests for diagnosing RSV.[35] The vast majority of included studies were focused on children. However, we did identify two studies[38,39] within this review that considered an adult population, and assessed tests that could be used in a point-of-care setting (direct immunofluorescence and rapid antigen testing). Both of these tests showed high specificity, but poor sensitivity for

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the detection of RSV, and the certainty of the evidence was low and very low (see *Appendix 3*, *Table 5*).

Primary studies

White cell differential count

We identified no systematic reviews that considered white cell differential count for the diagnosis of bacterial respiratory infection. Therefore we undertook a search for primary studies. Four hundred and fifty-five references were identified by the search. We retrieved the full texts of 48 studies for closer inspection, and included four studies (see *Appendix 4*, *Figure 4* for the PRISMA flow diagram, *Appendix 4*, *Table 6* for details of the included studies and *Appendix 4*, *Figure 5* for the QUADAS-2 assessments of included studies). Details of all primary studies excluded at full text, along with the main reason for exclusion are given in the *Report Supplementary Material 1, Table S2*.

Three studies assessed the accuracy of total white cell count in diagnosing pneumonia,[40–42] while the remaining study[43] looked at diagnostic accuracy for bacterial pharyngitis. Participants were heterogeneous, and included people with symptoms of lower respiratory tract infection[41] and those who already had a diagnosis of community-acquired pneumonia.[42] It should be noted that the results of these studies may not be fully applicable to primary or emergency care settings, as white cell counts were not conducted at point of care and therefore would be unlikely to provide results within 45 minutes. We had additional concerns regarding one study[40] that incorporated white cell counts as part of the reference standard, and another study[41] that excluded people with more severe illness or malignancy.

Pneumonia

Two studies including a total of 864 participants[41,42] reported sensitivity estimates ranging from 10.1% to 71.1%, and specificity estimates ranging from 31.3% to 94.6%, depending on the threshold used (see *Appendix 4*, *Table 6* for further details). One study of 284 participants[40] reported an area under the curve of 0.65. The evidence was considered very low certainty (see *Appendix 5*, *Table 7*).

Bacterial pharyngitis

A single study of 179 participants[43] was identified that looked at the use of white cell count to diagnose bacterial pharyngitis. The study simply reported an AUC of 0.68 (no confidence intervals were reported). This was low-certainty evidence (see *Appendix 5*, *Table 7*).

Multiplex tests

We did not identify an existing systematic review addressing multiplex tests that could be used in the point-of-care setting, so we undertook a search for primary studies. Five hundred and eighty-seven references were identified by the search. We retrieved the full texts of 130 studies for closer inspection. Twelve of these studies met the criteria specified in the review protocol. See *Appendix 6* for the PRISMA flow diagram (see *Appendix 6*, *Figure 6*), details of the included studies (see *Appendix 6*, *Table 8*) and QUADAS-2 assessments of the included studies (see *Appendix 6*, *Figure 7*). Most of the studies included were considered to be at low risk of bias for at least five of the seven QUADAS-2 domains. The main concerns were regarding the use of an inappropriate reference standard (such as the use of a rapid antigen test, or incorporation of index test results as part of the reference standard), concerns over participant flow and timing (high numbers of excluded participants), and poor applicability of the index test (if samples were not analysed in a point-of-care setting). Details of all primary studies excluded at full text, along with the main reason for exclusion are given in the supplementary information (see *Report Supplementary Material 1, Table S3*). Twelve diagnostic accuracy studies were identified. All considered the accuracy of the tests to diagnose at least two viruses, including influenza A, influenza B and RSV.

Influenza A

Eight studies, across seven papers (2212 participants), reported on the detection of influenza A.[44–50] The diagnostic accuracy of these tests was very high, with an estimated sensitivity of 98% (95% CI 91% to 100%) and specificity of 99% (95% CI 97% to 99%), respectively. However, the certainty of the evidence was low. Sufficient data were available to analyse two specific multiplex tests separately: Cobas Liat and Xpert Xpress. See *Appendix 7*, *Table 9* for the overall results and GRADE assessment, *Appendix 7*, *Figure 8* for the results of the meta-analysis, and *Appendix 7*, *Figure 9* for the results of the individual studies shown in ROC space.

Influenza B

Six studies, across five papers (1823 participants), assessed detection of influenza B.[44,46,48–50] The pooled estimate for sensitivity was 95% (95% CI 89% to 98%) and for specificity was 99% (95% CI 98% to 99.6%). While potentially useful, the evidence was considered very low and low certainty, respectively. Again, separate analyses were conducted for Cobas Liat and Xpert Xpress. See *Appendix 8*, *Table 10* for the overall results and GRADE assessment, *Appendix 8*, *Figure 10* for the meta-analysis, and *Appendix 8*, *Figure 11* for the results of the individual studies shown in ROC space.

Influenza A and/or B

Seven papers[46,48,50–54] reported on the detection of influenza A and/or B, as a combined measure (2162 participants). However, in two of these papers,[53,54] the multiplex test

of interest was used as the reference standard, not as the index test. As such, we did not include these studies in the analysis, but instead presented the results as the percentage positive agreement and percentage negative agreement between tests (see entries for these studies in *Appendix 6*, *Table 8*). We were able to include two further studies[44,49] which assessed detection of influenza A and B separately. In total, the analysis included eight studies, across the seven included papers. The pooled estimate for sensitivity was 97% (95% CI 93% to 99%) and for specificity was 97% (95% CI 95% to 98%). Both estimates were considered to be low-certainty evidence. Separate analyses were also conducted for Cobas Liat and Xpert Xpress. See *Appendix 9*, *Table 11* for the overall results and GRADE assessment, *Appendix 9*, *Figure 12* for the meta-analysis, and *Appendix 9*, *Figure 13* for the results of the individual studies shown in ROC space.

Respiratory syncytial virus

Five studies assessed RSV (2273 participants).[44,45,47,49,55] There was moderate-certainty evidence that the specificity of these tests was very high. The pooled estimate was 99.5% (95% CI 99% to 100%). Sensitivity was also relatively high, with a pooled estimate of 85% (95% CI 74% to 92%). However, in this case, the evidence was considered very low certainty, owing to a serious risk of bias in the studies and very serious imprecision. Separate analyses were also conducted for Cobas Liat and Xpert Xpress. See *Appendix 10*, *Table 12* for the overall results and GRADE assessment, *Appendix 10*, *Figure 14* for the meta-analysis, and *Appendix 10*, *Figure 15* for the results of the individual studies shown in ROC space.

Discussion

The evidence identified in this review shows limited diagnostic accuracy for symptoms and signs of bacterial infection and for point-of-care tests that rely on a single biomarker (such as CRP or procalcitonin). Point-of-care tests that include multiple biomarkers may have slightly higher diagnostic accuracy. However, the evidence was predominantly assessed as low or very low certainty, due to limitations which include the risk of bias in primary studies, indirectness of the evidence and imprecision of the effect estimates.

We identified several tests used to diagnose influenza in an adult population, including tests that detect the presence of influenza antigens and those that detect nucleic acids. Diagnostic accuracy appeared highest for nucleic acid amplification tests – either those that test exclusively for influenza or multiplex tests (capable of diagnosing additional pathogens). The evidence was again considered to be predominantly low or very low certainty. The available data on RSV was very limited – the majority of primary studies were conducted in children, and therefore not applicable to this review. Consequently, we are unable to draw conclusions about the accuracy of direct antigen tests for RSV. The specificity of multiplex tests for RSV is probably high. However, the sensitivity may be lower, and the evidence was low certainty.

We used rigorous methods and extensive searches to ensure that all relevant evidence was identified for this review. Nonetheless, the majority of the evidence identified was considered to be low or very low certainty when assessed with the GRADE framework. In part, this was due to concerns over the potential for bias in the primary studies, and some concerns over indirectness in the included populations (where analyses included children, or some participants who were hospitalised). However, many of the concerns were due to imprecision in the effect estimates – as the confidence intervals crossed thresholds that we considered to represent an accurate or very accurate test (taken to be a sensitivity or specificity of 75% and 90%, respectively). We acknowledge that these thresholds are arbitrary and that readers, or different authors, may consider different thresholds to represent a useful test. This would impact on the certainty in the estimates. Furthermore, we noted that most systematic reviews did not report any information on heterogeneity in the primary studies included in their analyses. Consequently, we were unable to assess inconsistency when applying GRADE, and our assessment of evidence certainty may be considered optimistic.

In this review we primarily sought evidence about the accuracy of tests to distinguish between viral and bacterial causes of ARI that take no more than 45 minutes to yield a result. Symptoms and signs of infection are part of routine clinical assessment and therefore would add no time to the decision-making process. Many of the diagnostic tests identified give results within 10 to 15 minutes, making them suitable for use in a primary care setting or emergency department. However, multiplex tests typically require more time, with many taking up to 1 hour or longer. The extent to which such tests would fit into routine clinical practice needs careful consideration. However, the clear benefit of the multiplex platforms is the possibility of testing a single sample for multiple viral and bacterial pathogens, as well as the apparent increase in diagnostic accuracy.

It should be noted that most of the evidence identified in this review looked at the diagnostic accuracy of tests in isolation – that is the accuracy of a single

test to determine the cause of a respiratory infection. In reality, clinical diagnosis involves assessment of a constellation of symptoms and signs, as well as the results of specific tests. We identified only one review that assessed the incremental benefit of assessing CRP in conjunction with symptoms and signs of infection.[34] The addition of CRP showed a small increase in diagnostic accuracy as compared to symptoms and signs alone. Due to a lack of published evidence, it is currently unclear whether this is also the case for tests that examine other biomarkers.

Symptoms and signs of respiratory infection are often used to determine eligibility for studies of test accuracy. For example, many studies will enrol individuals with a fever or cough for further testing. Consequently, it is possible that estimates of accuracy for individual symptoms and signs could be artificially high – as the prevalence of these symptoms is high in the study population. Nonetheless, this situation does reflect routine clinical practice, where healthcare professionals are using these features to determine who requires further testing.

We accepted any reference standard to diagnose bacterial infection. This was partly because there is no agreement on what constitutes an ideal reference test. Microbiological testing may be regarded as an essential component of determining a viral or bacterial cause of an infection. However, these tests are likely to detect the presence of commensal organisms and are known to produce false-negative results (due to inadequacy of sampling technique or culture methods).[56,57] Consequently, a variety of reference standards were used in the studies included in this review – ranging from radiological imaging, microbiological assessment (such as culture and/or PCR) and consensus opinion of an expert panel.

For some tests, there were similarities between the index test and the reference standard used. In particular, a number of pathogen-specific tests used PCR techniques as both the index test and the reference standard. Given the similar methods used, the results of these tests are likely to be correlated, and therefore the accuracy of the index tests may be overestimated.[58]

Cost-effectiveness was not assessed as part of this review. However, the cost of different types of tests varies and some may be prohibitively expensive for use in a primary care setting. This will need careful consideration before implementing a new testing strategy.

This review focused only on the diagnostic accuracy of tests. For patients and clinicians, the most important questions are likely to be about the impact of using these tests on health outcomes. For example, does testing for bacterial infections result in better health than relying on clinical judgement alone? Will more people avoid side effects from the prescription of unnecessary antibiotics? Will hospital admissions be reduced, or people suffer fewer complications from severe bacterial infections? Assessing these outcomes requires studies that consider the implementation of these tests followed by clinical management based on the test results.

It is recognised that prescription and use of antibiotics may be affected by factors commonly associated with health inequalities, such as age and ethnicity.[59] Testing to help determine who needs antibiotics could help to reduce these inequities in health care, but only if the tests themselves are used appropriately. CRP is one of the only tests for which there is evidence in relation to equity of use. Despite their limited diagnostic accuracy, the use of CRP tests for people with ARI may reduce antibiotic prescribing without increasing negative health outcomes,[60] in part because they may enable clinicians to communicate a 'no antibiotic' treatment decision more easily.[59,61] A study from Denmark (where CRP tests are widely used) found that clinicians were less likely to use a CRP test when prescribing antibiotics for those who were unemployed or receiving disability pension, immigrants or children of immigrants.[62] It is not clear why this happens, but consequently these groups may still be more likely to be prescribed unnecessary antibiotics. For these tests to help address (rather than reproduce) inequities, there needs to be clear guidance and monitoring of use with respect to underserved groups.

At present there is an absence of evidence regarding diagnostic accuracy to support current clinical practice (where symptoms and signs are used to diagnose bacterial infection) or to justify the introduction of microbiological or host-response point-of-care tests. Policy makers should resist seeing point-of-care tests as the 'silver bullet' to solve healthcare system pressures until there is adequate evidence to demonstrate they are safe, clinically effective and cost-effective. There are concerns that introduction of point-of-care tests may unintentionally increase healthcare demand, as patients' illnesses become 'medicalised' with attendances for testing.

We recommend further research to define an adequate reference standard for respiratory infection diagnosis. This could be based on a better understanding of the natural history of the microbiology, and/or prognosis, of infections. In addition, it should be established whether point-of-care tests add diagnostic value over and above current practice

– the use of symptoms and signs to identify individuals at risk of more severe illness, or who require additional treatment. There is a lack of high-quality evidence regarding the diagnostic accuracy of point-of-care tests for ARI in the community and emergency department setting. The diagnostic accuracy of such point-of-care tests should be assessed specifically in this setting where the population is different – with generally less severe infections and consequently different microbiology and immune responses. This means that data from inpatients cannot necessarily be extrapolated to the outpatient setting, as the diagnostic accuracy of the test may vary according to disease severity. Finally, it will be important to assess if the use of point-of-care tests will medicalise illness and lead to unintended increased demand for NHS care for ARIs.

Conclusion

The majority of the evidence identified in this review was considered to be low or very low certainty, highlighting that future studies may change the overall estimates of accuracy. Nonetheless, from the evidence identified in this review it appears that individual symptoms and signs, or existing clinical prediction models (incorporating multiple symptoms and signs) are unlikely to be sufficiently accurate to distinguish between bacterial and viral infections. Diagnostic accuracy of individual host biomarkers also appears to be insufficient, although certain combinations of biomarkers may have higher sensitivity and specificity. As may be expected, the accuracy of different types of rapid tests for influenza and RSV varied. The highest diagnostic accuracy was seen with tests that rely on amplification of viral nucleic acid (including PCR and non-PCR-based techniques).

Further work is required to determine the optimum reference standard, and whether the introduction of point-of-care tests may add value to current diagnostic pathways. It remains to be seen whether additional testing would improve health outcomes for patients, or simply lead to an increase in healthcare consultations and resource costs.

Additional information

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Data-sharing statement

This is secondary research and therefore the data generated are not suitable for sharing beyond that contained within the manuscript. Further information can be obtained from the corresponding author.

Ethics statement

Ethical approval was not required for this secondary research project.

Information governance statement

No identifiable data were used as part of this review.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/JLCP4570.

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Study registration

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List of abbreviations

AECOPD	acute exacerbation of chronic obstructive pulmonary disease
ARI	acute respiratory infection
AUC	area under the curve
BP	blood pressure
CDSR	Cochrane Database of Systematic Reviews
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	computed tomography
DFA	direct fluorescence antigen
DTA	diagnostic test accuracy
EU	European Union
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HSROC	hierarchical summary receiver operating characteristic
ICU	intensive care unit
IP-10	interferon-γ-induced protein-10
IQR	interquartile range
LRTI	lower respiratory tract infection
mPCR	multiplex polymerase chain reaction

MRI	magnetic resonance imaging
MxA	myxovirus resistance protein A
NAAT	nucleic acid amplification test
NICE	National Institute for Health and Care Excellence
PCR	polymerase chain reaction
POCT	point-of-care test
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies version 2
RADT	rapid antigen detection tests
RFT	rapid flu test
RIDT	rapid influenza diagnostic test
ROBIS	Risk of Bias in Systematic Reviews
ROC	receiver operating characteristic
RSV	respiratory syncytial virus
RTI	respiratory tract infection
RT PCR	real-time polymerase chain reaction
SD	standard deviation
SpO_2	oxygen saturations
TRAIL	TNF-related apoptosis-induced ligand
URTI	upper respiratory tract infection
WHO	World Health Organization

List of supplementary material

Report Supplementary Material 1 Supplementary material

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/JLCP4570).

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

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Appendix 1

Searches for systematic reviews

Database: Ovid MEDLINE(R) ALL <1946 to May 22, 2023>
Final search strategy

1	[Respiratory Tract Infection (RTI)]
2	exp Respiratory Tract Infections/
3	exp Otorhinolaryngologic Diseases/
4	((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (infect* or coinfect* or inflamm*)).tw,kf.
5	((chest or lung? or lobar or pleura?) adj3 (absces* or infect* or coinfect* or inflamm*)).tw,kf.
6	(bronchit* or bronchiolit* or allergic bronchopulmon* or bronchopneumon* or common cold* or coryza or croup or empyem* or epipharyngit* or epiglottit* or epiglotit* or flu or influenza or laryngit* or laryngotracheobronchit* or laryngo tracheo bronchit* or laryngo tracheobronchit* or laryngotracheit* or nasopharyngit* or otitis media or parainfluenza or pharyngit* or pleurisy or pneumoni* or pleuropneumoni* or rhinit* or rhinopharyngit* or rhinosinusit* or severe acute respiratory syndrome or SARS or sinusit* or sore throat* or throat infection* or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit* or whooping cough or pertussis or pertusis).mp.
7	((acute* or exacerbat* or flare*) adj3 (asthma* or copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).mp.
8	((acute* or subacute* or exacerbat* or prolonged) adj3 cough*).mp.
9	(RTI or LRTI or URTI or ARTI or AURI or ALRI).tw,kf.
10	or/2-9
11	[RTI Viral Infection]
12	exp Respiratory System/ and (exp Viruses/ or exp Virus Diseases/)
13	exp Pneumonia, Viral/ or *Orthomyxoviridae Infections/ or Influenza, Human/
14	((airway* or respiratory or pulmonary or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (nonbacter* or viral* or virus* or adenovir*)).tw,kf.
15	(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.

16 or/12-15

17 [RTI Bacterial Infection]

18 exp Respiratory System/ and (exp Bacteria/ or exp Bacterial Infections/)

19 Pneumonia, Bacterial/ or Chlamydial Pneumonia/ or Pneumonia, Mycoplasma/ or Pneumonia, Pneumococcal/ or Pneumonia, Staphylococcal/

20 ((airway* or respiratory or pulmonary or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir* or pathogen*)).tw,kf.

21 (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.

22 ((strep* adj3 (throat* or pharyn* or tonsil*)) or (strep* and (airway* or pulmonary or brochopulmonar* or brocho-pulmonar* or respiratory* or (ear adj3 nose adj3 throat) or ENT or Otorhinolaryng*))).mp.

23 (GABHS or ("group a" adj3 strep*)).tw,kf.

24 strep* pyogen*.mp.

25 or/18-24

26 [Rapid Tests]

27 Point-of-Care Systems/

28 (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 anti*)))).tw,kf.

29 (point adj2 care).ti,kf.

30 (((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 anti*)).tw,kf.

31 (((near adj2 patient) or nearpatient or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 rapid*).tw,kf.

32 Rapid Diagnostic Tests/

33 (rapid* adj3 (detect* or diagnos* or screen*)).tw,kf.

34 (time-to-result? or ((quick* or rapid* or short* or time*) adj3 (turnaround or turn-around))).tw,kf.

35 (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.

36 (RADT or RADTs or RDT or RDTs).tw,kf.

37 (biomarker* or bio* marker* or ((biologic* or bacteri* or viral or virus or immuno* or inflammat* or molecular or protein or serum) adj marker*)).tw,kf.

38 ((rapid adj3 (molecular or PCR or polymerase chain reaction)) or singleplex* or single-plex* or multiplex* or multi-plex*).mp.

39 lab-on-a-chip.tw,kf.

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

41 (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.

42 ((chemiluminescen* or chemi-luminescen*) adj (immuno-assay* or immuno-assay* or assay*)).mp.

43 (((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.

44 or/27-43

45 (10 or 16 or 25) and 44

46 [Systematic Review Filter]

47 (systematic review or meta-analysis).pt.

48 systematic review/ or meta-analysis/ or network meta-analysis/

49 (meta-analys* or metaanalys* or meta-synth* or meta-synth*).tw,kf.

50 (((systematic* or quantitativ* or methodologic*) adj5 (review* or overview*)) or (systematic* adj3 analys*)).tw,kf.

51 (systematic or structured or evidence or diagnostic or predicti* or trials or studies).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)

52 (quantitativ$ adj5 synthes*).tw,kf.

53 ((research adj3 (integrati* or overview*)) or (integrative adj2 review*) or research integration).tw,kf.

54 scoping review?.ti,kf. or (review.ti,kf,pt. and (trials as topic or studies as topic).hw.)

55 ((diagnostic or evidence) adj3 review*).tw,kf.

56 review.pt. and (medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).tw,kf,hw.

57 exp technology assessment, biomedical/

58 (technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).tw,kf.

59 (0266-4623 or 1469-493X or 1366-5278 or 1530-440X or 2046-4053).is.

60 or/47-59

61 [DTA Filter]

62 Diagnosis/

63 "Diagnostic Techniques and Procedures"/

64 Diagnostic Test Approval/

65 Diagnostic Tests, Routine/

66 Molecular Diagnostic Techniques/

67 exp Reagent Kits, Diagnostic/

68 (diagnos* adj3 (analys* or assay* or immunoassay* or classif* or differenti* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test*)).ab.

69 diagnos*.ti,kf,hw.

70 "sensitivity and specificity"/ or "predictive value of tests"/ or roc curve/ or signal-to-noise ratio/ or "limit of detection"/

71 false negative reactions/ or false positive reactions/

72 (sensitivity or specificity).tw,kf.

73 likelihood ratio.tw,kf.

74 (predict* adj4 val*).tw,kf. or predict*.ti.

75 ((accura* or reliab* or valid*) and (point-of-care or POC or (rapid adj2 (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*)))).tw,kf.

76 ((accura* or reliab* or valid*) and (bacteri* and (viral or virus*) and (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*))).tw,kf.

77 area under curve/

78 (observer adj variation*).tw,kf.

79 (roc adj curve*).tw,kf.

80 likelihood functions/

81 (false adj (positiv* or negativ*)).tw,kf.

82 QUADAS*.mp.

83 Diagnosis, Differential/

84 (codetect* or co-detect* or codiagnos* or co-diagnos*).tw,kf.

85 ((discriminat* or differenti* or dual*) adj (detect* or diagnos*)).mp.

86 (bacteri* adj5 (viral or virus*) adj5 (analys* or assay* or immunoassay* or classif* or detect* or codetect* or determin* or diagnos* or codiagnos* or differenti* or discriminat* or distinguish* or identif* or method* or misdiagnos* or predict* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf,hw.

87 or/62-86

88 45 and 60 and 87

89 [Other]

90 (bacteri* adj5 (viral or virus*) adj5 (detect* or diagnos* or differenti* or predict* or screen* or test*)).tw,kf.

91 (bacteri* and (viral or virus*) and (codetect* or co-detect* or codiagnos* or co-diagnos*)).tw,kf.

92 (10 or 16 or 25) and 60 and (90 or 91)

93 (((prescribing or prescription?) adj guideline?) or ((antibiotic? or antimicrobial) adj stewardship?)).mp.

94 ((guide or guiding or predict* or ration* or reduc* or steward*) adj3 (antibiotic* or antivir* or anti-vir* or antimicrob* or anti-microb*)).tw,kf.

95 45 and 60 and (93 or 94)

96 88 or 92 or 95

97 remove duplicates from 96

98 [Symptoms & Signs]

99 Symptom Assessment/

100 Patient Acuity/

101 ((sign? adj3 symptom*) or ((sign? or symptom*) adj2 (score* or scoring))).tw,kf.

102 ((patient* or sign? or symptom* or illness* or disease* or disorder* or infection*) adj3 acuity).tw,kf.

103 exp Vital Signs/

104 (peak flow or oxygen saturation or sats).mp.

105 Clinical Decision Rules/

106 (clinic* predicti* or (clinic* adj5 (decision* or predicti*) adj5 (aid? or algorithm? or characteristic? or criteri* or evaluation? or index or indices or marker? or method* or model* or panel? or parameter? or rule or rules or score? or scoring or screen* or signs or symptoms or system? or technique? or test* or tool? or value? or variable*))).mp.

107 (clinical* adj (predicti* or predictor*)).tw,kf.

108 (rule in or ruled in or rule out or ruled out).tw,kf.

109 ((predict* or prognos* or cluster*) adj3 (sign? or symptom*)).tw,kf.

110 ((detect* or diagnos*) adj5 (sign? or symptom*)).tw,kf.

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111 or/99-110

112 (10 or 16 or 25) and 111 and 60 and 87

113 [Host-response biomarkers]

114 Procalcitonin/

115 (procalcitonin or pro-calcitonin or calcitonin precursor polyprotein or calcitonin related polypeptide alpha or calcitonin-1).mp. or PCT.tw,kf.

116 C-Reactive Protein/

117 C-reactive protein.mp. or (CRP or HSCRP).tw,kf.

118 Myxovirus Resistance Proteins/

119 (myxovirus resistance protein* or mx-protein* or MxA or (interferon adj2 induc* protein) or IP-10).mp.

120 (myxovirus resistance protein* or mx-protein* or MxA or (interferon adj2 induc* protein)).mp.

121 (FebriDx* or Febri-Dx*).mp.

122 TNF-Related Apoptosis-Inducing Ligand/

123 ((tumor necrosis factor or TNF) adj2 related apoptosis adj2 ligand).tw,kf.

124 TRAIL.tw,kf.

125 Chemokine CXCL10/

126 (ImmunoXpert* or Immuno-Xpert*).tw,kf.

127 (Interferon gamma inducible protein-10 or IFN-gamma-inducible protein-10 or IP-10 or IP10 or CXCL10 or CXCL-10).tw,kf.

128 (ImmunoXpert* or Immuno-Xpert* or MeMedBV* or MeMed-BV*).mp.

129 leukocyte count/ or lymphocyte count/ or cd4 lymphocyte count/ or cd4-cd8 ratio/

130 ((WBC or white blood cell? or lymphocyte? or leukocyte? or CD4 or eosinophil? or neutrophil?) adj3 (count? or number? or ratio?)).tw,kf.

131 *leukocytes/ or exp *granulocytes/ or exp *leukocytes, mononuclear/

132 *interleukins/ or interleukin-5/ or interleukin-6/ or interleukin-10/

133 (il-5 or interleukin 5 or b-cell-growth-factor-ii or bcgf-ii or eosinophil differentiation factor or t-cell replacing factor).tw,kf.

134 (il-6 or interleukin-6 or b-cell differentiation factor or b-cell stimulatory factor-2 or bsf-2 or (differentiation-inducing protein adj1 myeloid) or hybridoma growth factor or plasmacytoma growth factor or hepatocyte stimulating factor or interferon beta-2 or ifn-beta-2 or mgi-2).tw,kf.

135 (il-10 or interleukin-10 or cytokine synthesis inhibitory factor or csif-10).tw,kf.

136 (interleukin*.tw,kf. or exp Interleukins/) and ((diagnos* or detect*).ti,kf,hw. or diagnosis.fs.)

137 or/114-136

138 (10 or 16 or 25) and 137 and 60 and 87

139 HEMATOLOGIC TESTS/

140 ((h?em* or blood or plasma or serum) adj2 (test* or marker?)).tw,kf.

141 exp Cell Count/

142 ((blood or RBC or red cell? or erythrocyt* or normocyt* or platelet* or thrombocyt*) adj3 (count* or distribution? or number* or paramet* or ratio?)).tw,kf.

143 Blood Sedimentation/

144 (((blood or RBC or red cell? or erythrocyt*) adj2 sedimentation) or ESR).tw,kf.

145 exp BLOOD GAS ANALYSIS/

146 blood gas*.tw,kf.

147 Oxygen/an, bl [Analysis, Blood]

148 Carbon Dioxide/an, bl [Analysis, Blood]

149 Sodium Bicarbonate/an, bl [Analysis, Blood]

150 (ABG or O2sat* or O2-sat* or O2CT or PaO2 or PaCO2 or HCO3 or (blood adj3 pH)).tw,kf.

151 (partial pressure and oxygen).hw.

152 (partial pressure adj3 (oxygen or O2)).tw,kf.

153 Sodium/bl [Blood]

154 ((blood or plasma or serum) adj2 (sodium or Na)).tw,kf.

155 ((blood or plasma or serum) adj2 marker?).tw,kf.

156 Fibrin Fibrinogen Degradation Products/

157 (fibrin* adj2 degradation).tw,kf.

158 fibrinogen.tw,kf. or *fibrinogen/ or Fibrinogen/an, bl, ur [Analysis, Blood, Urine]

159 (d-dimer? or ddimer?).tw,kf.

160 Urine/an [Analysis]

161 (((urin* or urea) adj2 (analys* or test* or marker?)) or UAT).tw,kf.

162 Nitrogen/ur [Urine]

163 ((nitrogen or nitrate? or nitrite? or “N” or N2) adj3 (urea or urin*)).tw,kf.

164 Adrenomedullin/

165 (adrenomedullin or proadrenomedullin or ADM or proADM).tw,kf.

166 exp Aspartate Aminotransferases/

167 ((aspartat* adj3 (aminotrans* or amino-trans* or apoaminotrans* or apo-aminotrans* or apo-amino-trans* or apoamino-trans* or transaminas* or trans-aminas*)) or ((glutam* aspart* or glutam* oxaloacet*) adj3 (transaminas* or trans-aminas*)) or sgot).tw,kf.

168 Alanine Transaminase/

169	((alanine adj3 (aminotrans* or amino-trans* or transamin* or trans-amin*)) or (glutam* adj3 pyruvic adj3 trans*) or sgpt).tw,kf.
170	((lipopolysac* or lipo-polysac* or lipo-poly-sac* or lipopoly-sac* or LPS) adj3 (bind* or bound*)).tw,kf.
171	Chitinases/ or Chitinase-3-like protein 1/
172	(kitinase-3-like-1 or chitinase-3-like-1 or chitinase-3-like-protein-1 or CHI3L1).tw,kf.
173	Antibodies, Bacterial/an, bl [Analysis, Blood]
174	Antibodies, Viral/an, bl [Analysis, Blood]
175	Blood Proteins/an
176	Immunoglobulins/an
177	("immunoglobulin M" or IgM or "immunoglobulin G" or IgG).tw,kf,hw.
178	*Serologic Tests/
179	(((point adj2 care) or poc or (near adj2 patient) or nearpatient or rapid* or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 (serolog* or antibody or antibodies or immunoglobulin* or immune globulin*)).tw,kf.
180	((serolog* or antibody or antibodies or immunoglobulin* or immune globulin*) 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 rapid or routine* or screen* or system* or technique* or test*)).ti,kf.
181	or/139-180
182	(10 or 16 or 25) and 181 and 60 and 87
183	97 or 112 or 138 or 182

Database: Ovid EMBASE <1974 to 2023 May 24>

1	Respiratory Tract Infection/ or exp Influenza/ or Laryngotracheobronchitis/ or Parainfluenza Virus Infection/ or Respiratory Syncytial Virus Infection/ or Viral Respiratory Tract Infection/ or Lower Respiratory Tract Infection/ or Chest Infection/ or Pertussis/ or Lung Infection/ or exp Infectious Pneumonia/ or Lung Abscess/ or exp Lung Mycosis/ or exp Viral Bronchiolitis/ or Upper Respiratory Tract Infection/ or exp Nose Infection/ or Oropharynx Candidiasis/ or Peritonsillar Abscess/ or Viral Upper Respiratory Tract Infection/
2	Ear Nose Throat Disease/di or Otorhinolaryngology/ or exp Ear Infection/ or exp Otitis/
3	((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (infect* or coinfect* or inflamm*)).tw,kf.
4	((chest or lung? or lobar or pleura?) adj3 (absces* or infect* or coinfect* or inflamm*)).tw,kf.
5	(bronchit* or bronchiolit* or allergic bronchopulmon* or bronchopneumon* or common cold* or coryza or croup or empyem* or epipharyngit* or epiglottit* or epiglotit* or flu or influenza or laryngit* or laryngotracheobronchit* or laryngo tracheo bronchit* or laryngo tracheobronchit* or laryngotracheit* or nasopharyngit* or otitis media or parainfluenza or pharyngit* or pleurisy or pneumoni* or pleuropneumoni* or rhinit* or rhinopharyngit* or rhinosinusit* or severe acute respiratory syndrome or SARS or sinusit* or sore throat* or throat infection* or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit* or whooping cough or pertussis or pertusis).mp.
6	((acute* or exacerbat* or flare*) adj3 (asthma* or copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).mp.
7	((acute* or subacute* or exacerbat* or prolonged) adj3 cough*).mp.
8	(RTI or LRTI or URTI or ARTI or AURI or ALRI).tw,kf.
9	or/1-8
10	exp Respiratory System/ and exp Virus Infection/
11	((airway* or respiratory or pulmonary or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (nonbacter* or viral* or virus* or adenovir*)).tw,kf.
12	Rhinovirus/ or exp Human Rhinovirus/ or exp Rhinovirus Infection/
13	exp Influenza Virus/ or Orthomyxovirus Infection/
14	Respirovirus/ or Human Parainfluenza virus 1/ or Human Parainfluenza Virus 3/ or Respirovirus Infection/
15	exp Virus Pneumonia/
16	Pneumovirus/ or Pneumovirus Infection/ or exp Human Respiratory Syncytial Virus/ or Respiratory Syncytial Virus Infection/
17	Metapneumovirus/ or Metapneumovirus Infection/ or Human Metapneumovirus/ or Human Metapneumovirus Infection/
18	(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.
19	or/10-18
20	exp Respiratory System/ and (exp Bacterium/ or exp Bacterial Infection/)
21	((airway* or respiratory or pulmonary or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir* or pathogen*)).tw,kf.

22	Bacterial Pneumonia/ or Chlamydial Pneumonia/ or Mycoplasma Pneumonia/ or Staphylococcal Pneumonia/ or exp Streptococcus Pneumonia/
23	(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.
24	((strep* adj3 (throat* or pharyn* or tonsil*)) or (strep* and (airway* or pulmonary or brochopulmonar* or brocho-pulmonar* or respiratory* or (ear adj3 nose adj3 throat) or ENT or Otorhinolaryng*))).mp.
25	Streptococcus Infection/ or Streptococcus Group A/ or exp Group A Streptococcal Infection/ or Streptococcal Pharyngitis/
26	(GABHS or ("group a" adj3 strep*)).tw,kf.
27	strep* pyogen*.mp.
28	or/20-27
29	"systematic review"/ or meta analysis/ or network meta-analysis/
30	review.pt. and (evidence based adj (medicine or practice)).mp.
31	(systematic or structured or evidence or diagnostic or predicti* or trials or studies).ti. and ((review or overview or look or examination or update* or summary).ti. or review.pt.)
32	(0266-4623 or 1469-493X or 1366-5278 or 1530-440X or 2046-4053).is.
33	(systematic review? or evidence report* or technology assessment?).jw.
34	(meta-analys* or metaanalys* or meta-synth* or meta-synth*).ti,ab,kf,hw.
35	(((systematic* or methodologic*) adj3 (analys* or review* or overview*)) or (quantitativ* adj3 (review* or synthes*))).tw,kf.
36	(diagnostic test accuracy study or validation study or cohort analysis or cross-sectional study or case control study).hw. and review.ti,kf,pt.
37	((integrative adj2 review*) or research integration).tw,kf. or scoping review?.ti,kf.
38	((diagnostic or evidence) adj3 review*).tw,kf.
39	review.pt. and (medline or medlars or embase or pubmed or scisearch or psychinfo or psycinfo or psychlit or psyclit or cinahl or electronic database* or bibliographic database* or computeri#ed database* or online database* or pooling or pooled or mantel haenszel or peto or dersimonian or der simonian or fixed effect or ((hand adj2 search*) or (manual* adj2 search*))).ti,ab,kf,hw.
40	biomedical technology assessment/
41	(technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).tw,kf.
42	or/29-41
43	Gold Standard/
44	(reference standard? or gold standard?).tw,kf.
45	clinical diagnosis.mp.
46	Diagnostic Test Accuracy Study/
47	Diagnostic Accuracy/
48	(DTA or (diagnos* adj2 accura*)).tw,kf.
49	Validation Study/
50	"Sensitivity and Specificity"/
51	specificity.tw,kf.
52	Receiver Operating Characteristic/
53	Reliability/
54	Internal Validity/
55	Internal Consistency/
56	(validat* or validity).tw,kf.
57	likelihood ratio*.tw,kf.
58	Predictive Value/
59	(predict* adj4 val*).tw,kf. or predict*.ti.
60	((re-test or retest or test-retest) adj reliability).tw,kf.
61	Diagnostic Error/ or False Negative Result/ or False Positive Result/ or Missed Diagnosis/
62	(false adj (positiv* or negativ*)).tw,kf.
63	receiver operating characteristic*.tw,kf.
64	ROC.tw,kf.
65	Area Under the Curve/
66	Observer Variation/
67	(observer adj variation*).tw,kf.
68	((degree? or rate* or rating) adj3 agreement?).tw,kf.
69	Diagnosis/
70	diagnos*.ti,kf.
71	(diagnos* adj3 (analys* or assay* or immunoassay* or classif* or differenti* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test*)).ab.
72	Diagnostic Procedure/ or Diagnostic Test/ or Diagnostic Test Approval/ or exp Diagnostic Kit/ or Diagnosis Time/
73	Laboratory Diagnosis/
74	Molecular Diagnosis/
75	((accura* or reliab* or valid*) and (point-of-care or POC or (rapid adj2 (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*)))).tw,kf.

76	((accura* or reliab* or valid*) and (bacteri* and (viral or virus*) and (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*))).tw,kf.
77	"quality assessment of diagnostic accuracy studies"/
78	QUADAS*.mp.
79	Differential Diagnosis/
80	(codetect* or co-detect* or codiagnos* or co-diagnos*).tw,kf.
81	((discriminat* or differenti* or dual*) adj (detect* or diagnos*)).mp.
82	(bacteri* adj5 (viral or virus*) adj5 (analys* or assay* or immunoassay* or classif* or detect* or codetect* or determin* or diagnos* or codiagnos* or differenti* or discriminat* or distinguish* or identif* or method* or misdiagnos* or predict* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf,hw.
83	or/43-82
84	42 and 83
85	Diagnostic Accuracy/ and Review/
86	84 or 85
87	(9 or 19 or 28) and 86
88	(COVID19 or COVID-19 or COVID2019 or COVID-2019 or 2019 nCoV or 2019nCoV or 2019-novel CoV or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2" or 2019 nCoV or 2019nCoV or 2019-novel CoV or "SARS coronavirus 2" or "Severe Acute Respiratory Syndrome Coronavirus-2").ti.
89	87 not 88
90	((neonat* or infant* or child* or p?ediatri*) not adult*).ti.
91	89 not 90
92	"Point of Care System"/
93	(POCT or POCTs or (((point adj2 care) or poc) adj3 (analys* or antigen? or assay* or device? or immuno-assay* 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 anti*)))). tw,kf.
94	(point adj2 care).ti,kf.
95	(((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 anti*)).tw,kf.
96	(((near adj2 patient) or nearpatient or bedside? or bed-side? or extra-laboratory or extralaboratory) adj3 rapid*). tw,kf.
97	Rapid Test/ or Influenza A Rapid Test/ or Streptococcus Group A Rapid Test/
98	(rapid test* or (rapid* adj3 (detect* or diagnos* or screen*))).tw,kf.
99	(time-to-result? or ((quick* or rapid* or short* or time*) adj3 (turnaround or turn-around))).tw,kf.
100	(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.
101	(RADT or RADTs or RDT or RDTs).tw,kf.
102	(biomarker or bio* marker* or ((biologic* or bacteri* or viral or virus or immuno* or inflammat* or molecular or protein or serum) adj marker*)).tw,kf.
103	Multiplex Analyzer/
104	exp Multiplex Polymerase Chain Reaction/
105	Singleplex Polymerase Chain Reaction/
106	((rapid adj3 (molecular or PCR or polymerase chain reaction)) or singleplex* or single-plex* or multiplex* or multi-plex*).mp.
107	lab-on-a-chip.tw,kf.
108	((lateral flow adj (assay* or immunoassay* or test*)) or LFA or LFIA).tw,kf.
109	(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.
110	((chemiluminescen* or chemi-luminescen*) adj (immuno-assay* or immuno-assay* or assay*)).mp.
111	(((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.
112	or/92-111
113	91 and 112
114	(bacteri* adj5 (viral or virus*) adj5 (detect* or diagnos* or differenti* or predict* or screen* or test*)).tw,kf.
115	(bacteri* and (viral or virus*) and (codetect* or co-detect* or codiagnos* or co-diagnos*)).tw,kf.
116	(9 or 19 or 28) and 42 and (114 or 115)
117	116 not (88 or 90)
118	113 or 117
119	limit 118 to conference abstract status
120	118 not 119
121	Health Status Indicator/ or Patient Acuity/

122	Symptom Assessment/
123	Symptomatology/
124	*Symptom/
125	((sign? adj2 symptom*) and (score* or scoring)).tw,kf.
126	((patient* or sign? or symptom* or illness* or disease* or disorder* or infection*) adj3 acuity).tw,kf.
127	Vital Sign/
128	Decision Support System/ or Clinical Decision Rule/
129	(clinic* predicti* or (clinic* adj5 (decision* or predicti*) adj5 (aid? or algorithm? or characteristic? or criteri* or evaluation? or index or indices or marker? or method* or model* or panel? or parameter? or rule or rules or score? or scoring or screen* or signs or symptoms or system? or technique? or test* or tool? or value? or variable*))).tw,kf.
130	(clinical* adj (predicti* or predictor*)).tw,kf.
131	("rule in" or "ruled in" or "rule out" or "ruled out").tw,kf.
132	((predict* or prognos* or cluster*) adj3 (sign? or symptom*)).tw,kf.
133	((detect* or diagnos*) and (sign? or symptom*)).ti,kf.
134	or/121-133
135	91 and 134
136	limit 135 to conference abstract status
137	135 not 136
138	Procalcitonin Test Kit/
139	*Procalcitonin/ or Procalcitonin/ec [Endogenous Compound]
140	(procalcitonin or pro-calcitonin or calcitonin precursor polyprotein or calcitonin related polypeptide alpha or calcitonin-1 or PCT).tw,kf.
141	*C reactive protein/ or C reactive protein/ec [Endogenous Compound]
142	(c-reactive protein or CRP or HSCRP).tw,kf.
143	Myxovirus Resistance Protein/
144	(myxovirus resistance protein* or mx-protein* or MxA or (interferon adj2 induc* protein) or IP-10).tw,kf.
145	(FebriDx* or Febri-Dx*).af.
146	Tumor Necrosis Factor Related Apoptosis Inducing Ligand/
147	((tumor necrosis factor or TNF) adj2 related apoptosis adj2 ligand).tw,kf.
148	TRAIL.tw,kf.
149	C Reactive Protein/ and Endogenous Compound/
150	Procalcitonin/ and Endogenous Compound/
151	Gamma Interferon Inducible Protein 10/
152	(Interferon gamma inducible protein-10 or IFN-gamma-inducible protein-10 or IP-10 or IP10 or CXCL10 or CXCL-10).tw,kf.
153	(ImmunoXpert* or Immuno-Xpert* or MeMedBV* or MeMed-BV*).af.
154	or/138-153
155	91 and 154
156	limit 155 to conference abstract status
157	155 not 156
158	exp *Blood Cell Count/
159	((WBC or white blood cell? or white cell? or lymphocyte? or leukocyte? or monocyte? or CD4* or eosinophil? or neutrophil?) adj3 (count* or distribution? or number* or paramet* or ratio?)).tw,kf.
160	((whole blood or blood cell or RBC or red cell? or erythrocyt* or normocyt* or platelet* or thrombocyt*) adj3 (count* or distribution? or number* or paramet* or ratio?)).tw,kf.
161	((h?em* or blood or plasma or serum) adj2 (test* or marker?)).tw,kf.
162	*erythrocyte sedimentation rate/
163	(((blood or RBC or red cell? or erythrocyt*) adj2 sedimentation) or ESR).tw,kf.
164	or/158-163
165	91 and 164
166	limit 165 to conference abstract status
167	165 not 166
168	Blood Gas Analysis/
169	blood gas*.tw,kf.
170	Oxygen Saturation/
171	(ABG or O2sat* or O2-sat* or O2CT or PaO2 or PaCO2 or HCO3 or (blood adj3 pH)).tw,kf.
172	((oxygen adj2 (concentration or saturation)) or sats).tw,kf.
173	(partial pressure and oxygen).hw.
174	(partial pressure adj3 (oxygen or O2)).tw,kf.
175	or/168-174
176	91 and 175
177	((blood or plasma or serum) adj2 (sodium or Na)).tw,kf.
178	electrolyte blood level/ or sodium blood level/
179	(177 or 178) and 91

180	(il-5 or interleukin 5 or b-cell-growth-factor-ii or bcgf-ii or eosinophil differentiation factor or t-cell replacing factor or il-6 or interleukin-6 or b-cell differentiation factor or b-cell stimulatory factor-2 or bsf-2 or (differentiation-inducing protein adj1 myeloid) or hybridoma growth factor or plasmacytoma growth factor or hepatocyte stimulating factor or interferon beta-2 or ifn-beta-2 or mgi-2 or il-10 or interleukin-10 or cytokine synthesis inhibitory factor or csif-10).tw,kf.
181	180 and 91
182	fibrinogen/
183	fibrinogen.tw,kf.
184	fibrin degradation product/
185	(fibrin* adj2 degradation).tw,kf.
186	d dimer/
187	(d-dimer? or ddimer?).tw,kf.
188	or/182-187
189	91 and 188
190	(((urin* or urea) adj2 (analys* or test* or marker?)) or UAT).tw,kf.
191	((nitrogen or nitrate? or nitrite? or "N" or N2) adj3 (urea or urin*)).tw,kf.
192	urea nitrogen blood level/
193	urea/ec
194	or/190-193
195	194 and 91
196	Adrenomedullin/
197	(adrenomedullin or adrenomedullin or proadrenomedullin or proadrenomedullin or ADM or proADM).tw,kf.
198	(196 or 197) and 91
199	Enzyme Blood Level/
200	Aspartate Aminotransferase Blood Level/ or Aspartate Aminotransferase Level/
201	((aspartat* adj3 (aminotrans* or amino-trans* or apoam-inotrans* or apo-aminotrans* or apo-amino-trans* or apoamino-trans* or transaminas* or trans-aminas*)) or ((glutam* aspart* or glutam* oxaloacet*) adj3 (transami-nas* or trans-aminas*)) or sgot).tw,kf.
202	*Aspartate Aminotransferase/ or Aspartate Aminotransferase/ec [Endogenous Compound]
203	Alanine Aminotransferase Level/ or Alanine Aminotransferase Blood Level/
204	*Alanine Aminotransferase/ or Alanine Aminotransferase/ec [Endogenous Compound]
205	((alanine adj3 (aminotrans* or amino-trans* or transamin* or trans-amin*)) or (glutam* adj3 pyruvic adj3 trans*) or sgpt).tw,kf.
206	or/199-205
207	91 and 206
208	Lipopolysaccharide Binding Protein/ec [Endogenous Compound]
209	((lipopolysac* or lipo-polysac* or lipo-poly-sac* or lipopoly-sac* or LPS) adj3 (bind* or bound*)).tw,kf.
210	(208 or 209) and 91
211	Chitinase 3 Like Protein 1/
212	(kitinase-3-like-1 or chitinase-3-like-1 or chitinase-3-like-protein-1 or CHI3L1).tw,kf.
213	(211 or 212) and 91
214	(176 or 179 or 181 or 189 or 195 or 198 or 207 or 210 or 213)
215	limit 214 to conference abstract status
216	214 not 215
217	120 or 137 or 157 or 167 or 216

Database: Cochrane Database of Systematic Reviews

https://www.cochranelibrary.com/cdsr/reviews

Issue 5 of 12, May 2023 (searched 18 May 2023)

Records screened in situ for potentially relevant reviews

S1	All-Text: * Limit CDSR to Review Type: <Diagnostic>
S2	All-Text: * Limit CDSR to Protocol Type: <Diagnostic>

Database: NIHR Journal Library

https://www.journalslibrary.nihr.ac.uk/advancedsearch/

Browsed online, using NHIR Library indexing categories to help identify relevant DTA reviews. A series of short iterative searches were also conducted. Records were screened in situ (30 May 2023).

Browsing

S1	NIHR Programme: <Systematic Reviews> Limited by: (i) HRCS Health Category: <Respiratory> or (ii) HRCS Health Category: <Infection>
S2	NIHR Programme: <HTA> Limited by:(i) HRCS Health Category: <Respiratory> or (ii) HRCS Health Category: <Infection>

S3	Research Type: <Evidence Synthesis> Limited by: (i) HRCS Health Category: <Respiratory> or (ii) HRCS Health Category: <Infection>
S4	Research Type: NICE DAR (Diagnostic Assessment Report)

Searching

S1	diagnos* AND review
S2	diagnos* AND accuracy
S3	diagnos* AND test*
S4	rapid* AND test*
S5	"point of care"

Database: Epistemonikos

https://www.epistemonikos.org/en/advanced_search

S1a	(respiratory OR "ear nose and throat" OR ENT OR otorhinolaryng* OR RTI OR LRTI OR URTI OR ARTI OR AURI OR ALRI OR airway* OR bronchopulmonar* OR broncho-pulmonar* OR tracheobronch* OR tracheo-bronch* OR "pulmonary tract" OR ((chest OR lung OR lungs OR lobar OR pleura*) AND (absces* OR infect* OR coinfect* OR inflamm*)) OR bronchit* OR bronchiolit* OR bronchopneumon* OR "common cold" OR coryza OR croup OR empyem* OR epipharyngit* OR epiglottit* OR epiglotit* OR flu OR influenza OR laryngit* OR laryngotracheobronchit* OR (laryngo AND tracheo AND bronchit*) OR (laryngo AND tracheobronchit*) OR laryngotracheit* OR nasopharyngit* OR "otitis media" OR parainfluenza OR pharyngit* OR pleurisy OR pneumoni* OR pleuropneumoni* OR rhinit* OR rhinopharyngit* OR rhinosinusit* OR sinusit* OR "sore throat" OR (throat AND infection*) OR supraglottit* OR supraglotit* OR tonsillit* OR tonsilit* OR tracheit* OR "whooping cough" OR pertussis OR pertussis OR asthma* OR "COPD" OR "COAD" OR "chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "chronic obstructive airways disease" OR "chronic obstructive lung disease" OR ((acute or subacute* or exacerbat* or prolonged) AND cough*)) Limit-1: Publication Type: <Systematic Review> AND Type of Study:<Diagnostic Accuracy> OR Limit-2: Publication Type: <Systematic Review> AND Type of Study: <Prediction (Diagnostic)>
S1b	SARS OR "severe acute respiratory syndrome" Limit-1: Publication Type: <Systematic Review> AND Type of Study: <Diagnostic Accuracy> [All SARS-CoV2, records not downloaded] Limit-2: Publication Type: <Systematic Review> AND Type of Study: <Prediction (Diagnostic)>
S1c	(rhinovir* OR (rhino* AND vir*) OR coryzavir* OR (coryza* AND vir*) OR influenzavir* OR (influenza* AND vir*) OR (H1N1 OR H3N2) OR parainfluenzavir* OR (parainfluenza* AND vir*) OR pneumovir* OR (pneumo* AND vir*) OR metapneumovir* OR meta-pneumovir* OR HMPV OR RSV OR ("respiratory syncytial" AND vir*) OR (strep* AND pneumon*) OR (diplococ* AND pneumon*) OR pneumococ* OR (staph* AND pneumon*) OR (chlamyd* AND pneumon*) OR (myco* AND pneumon*) OR (influenza AND bacil*) OR (bacteri* AND influenza*) OR (hemophil* AND influenza*) OR (haemophil* AND influenza*) OR (strep* AND (throat* OR pharyn* OR tonsil* OR airway* OR pulmonary OR brochopulmonar* OR brocho-pulmonar* OR respiratory*)) OR GABHS or ("group a" AND strep*) OR (strep* AND pyogen*)) Limit-1: Publication Type: <Systematic Review> AND Type of Study: <Diagnostic Accuracy> OR Limit-2: Publication Type: <Systematic Review> AND Type of Study: <Prediction (Diagnostic)>
S2a	(("diagnostic accuracy" OR "diagnostic test accuracy" OR (diagnostic AND studies)) AND ((rapid* AND (detect* or method* or molecular or test*)) OR "near patient" OR "point of care" OR POCT* OR biomarker* OR panel OR panels) AND ("respiratory tract" or (respiratory AND infection*) OR "ear nose and throat" OR "ENT" OR otorhinolaryng* OR "RTI" OR "LRTI" OR "URTI" OR "ARTI" OR "AURI" OR "ALRI" OR airway* OR bronchopulmonar* OR broncho-pulmonar* OR tracheobronch* OR tracheo-bronch* OR "pulmonary tract" OR (pulmonary AND infection*) OR ((chest OR lung OR lungs OR lobar OR pleura*) AND (absces* OR infect* OR coinfect* OR inflamm*)) OR bronchit* OR bronchiolit* OR bronchopneumon* OR "common cold" OR coryza OR croup OR empyem* OR epipharyngit* OR epiglottit* OR epiglotit* OR flu OR influenza OR laryngit* OR laryngotracheobronchit* OR (laryngo AND tracheo AND bronchit*) OR (laryngo AND tracheobronchit*) OR laryngotracheit* OR nasopharyngit* OR "otitis media" OR parainfluenza OR pharyngit* OR pleurisy OR pneumoni* OR pleuropneumoni* OR rhinit* OR rhinopharyngit* OR rhinosinusit* OR sinusit* OR "sore throat" OR (throat AND infection*) OR supraglottit* OR supraglotit* OR tonsillit* OR tonsilit* OR tracheit* OR "whooping cough" OR pertussis OR pertussis OR asthma* OR "COPD" OR "COAD" OR "chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "chronic obstructive airways disease" OR "chronic obstructive lung disease" OR ((acute or subacute* or exacerbat* or prolonged) AND cough*))) Limit: Publication Type: <Systematic Review>

S2b ((diagnos* OR detect*) AND ("clinical decision rule" OR "clinical decision rules" OR "prediction model" OR "prediction models" OR "predictive model" OR "predictive models" OR "prediction rule" OR "prediction rules" OR "predictive rule" OR "predictive rules") AND ("respiratory tract" or (respiratory AND infection*) OR "ear nose and throat" OR "ENT" OR otorhinolaryng* OR "RTI" OR "LRTI" OR "URTI" OR "ARTI" OR "AURI" OR "ALRI" OR airway* OR bronchopulmonar* OR broncho-pulmonar* OR tracheobronch* OR tracheo-bronch* OR "pulmonary tract" OR (pulmonary AND infection*) OR ((chest OR lung OR lungs OR lobar OR pleura*) AND (absces* OR infect* OR coinfect* OR inflamm*)) OR bronchit* OR bronchiolit* OR bronchopneumon* OR "common cold" OR coryza OR croup OR empyem* OR epipharyngit* OR epiglottit* OR epiglotit* OR flu OR influenza OR laryngit* OR laryngotracheobronchit* OR (laryngo AND tracheo AND bronchit*) OR (laryngo AND tracheobronchit*) OR laryngotracheit* OR nasopharyngit* OR "otitis media" OR parainfluenza OR pharyngit* OR pleurisy OR pneumoni* OR pleuropneumoni* OR rhinit* OR rhinopharyngit* OR rhinosinusit* OR sinusit* OR "sore throat" OR (throat AND infection*) OR supraglottit* OR supraglotit* OR tonsillit* OR tonsilit* OR tracheit* OR "whooping cough" OR pertussis OR pertussis OR asthma* OR "COPD" OR "COAD" OR "chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "chronic obstructive airways disease" OR "chronic obstructive lung disease" OR ((acute or subacute* or exacerbat* or prolonged) AND cough*)))
Limit: Publication Type: <Systematic Review>

S2c (("diagnostic accuracy" OR "diagnostic test accuracy" OR (diagnostic AND studies)) AND ((rapid* AND (detect* or method* or molecular or test*)) OR "near patient" OR "point of care" OR POCT* OR biomarker* OR panel OR panels) AND (rhinovir* OR (rhino* AND vir*) OR coryzavir* OR (coryza* AND vir*) OR influenzavir* OR (influenza* AND vir*) OR (H1N1 OR H3N2) OR parainfluenzavir* OR (parainfluenza* AND vir*) OR pneumovir* OR (pneumo* AND vir*) OR metapneumovir* OR meta-pneumovir* OR HMPV OR RSV OR ("respiratory syncytial" AND vir*) OR (strep* AND pneumon*) OR (diplococ* AND pneumon*) OR pneumococ* OR (staph* AND pneumon*) OR (chlamyd* AND pneumon*) OR (myco* AND pneumon*) OR (influenza AND bacil*) OR (bacteri* AND influenza*) OR (hemophil* AND influenza*) OR (haemophil* AND influenza*) OR (strep* AND (throat* OR pharyn* OR tonsil* OR airway* OR pulmonary OR brochopulmonar* OR brocho-pulmonar* OR respiratory*)) OR GABHS or ("group a" AND strep*) OR (strep* AND pyogen*)))
Limit: Publication Type: <Systematic Review>

S2d ((diagnos* OR detect*) AND ("clinical decision rule" OR "clinical decision rules" OR "prediction model" OR "prediction models" OR "predictive model" OR "predictive models" OR "prediction rule" OR "prediction rules" OR "predictive rule" OR "predictive rules") AND (rhinovir* OR (rhino* AND vir*) OR coryzavir* OR (coryza* AND vir*) OR influenzavir* OR (influenza* AND vir*) OR (H1N1 OR H3N2) OR parainfluenzavir* OR (parainfluenza* AND vir*) OR pneumovir* OR (pneumo* AND vir*) OR metapneumovir* OR meta-pneumovir* OR HMPV OR RSV OR ("respiratory syncytial" AND vir*) OR (strep* AND pneumon*) OR (diplococ* AND pneumon*) OR pneumococ* OR (staph* AND pneumon*) OR (chlamyd* AND pneumon*) OR (myco* AND pneumon*) OR (influenza AND bacil*) OR (bacteri* AND influenza*) OR (hemophil* AND influenza*) OR (haemophil* AND influenza*) OR (strep* AND (throat* OR pharyn* OR tonsil* OR airway* OR pulmonary OR brochopulmonar* OR brocho-pulmonar* OR respiratory*)) OR GABHS or ("group a" AND strep*) OR (strep* AND pyogen*)))
Limit: Publication Type: <Systematic Review>

Searches for primary diagnostic accuracy studies

White cell differential count

A precision maximising search was conducted due to the limited timeframe and inherent noise retrieved when searching for white blood cells and inflammatory infections

Database: Ovid MEDLINE(R) ALL <1946 to June 6, 2023>

1	Diagnosis/
2	"Diagnostic Techniques and Procedures"/
3	Diagnostic Test Approval/
4	Diagnostic Tests, Routine/
5	Molecular Diagnostic Techniques/
6	exp Reagent Kits, Diagnostic/
7	(diagnos* adj3 (analys* or assay* or immunoassay* or classif* or differenti* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test*)).ab.
8	diagnos*.ti,kf,hw.

9	(DTA or (diagnos* adj2 accura*)).tw,kf.
10	"sensitivity and specificity"/ or "predictive value of tests"/ or roc curve/ or signal-to-noise ratio/ or "limit of detection"/
11	(sensitivity or specificity).tw,kf.
12	likelihood ratio*.tw,kf.
13	(predict* adj4 val*).tw,kf. or predict*.ti.
14	((re-test or retest or test-retest) adj reliability).tw,kf.
15	((accura* or reliab* or valid*) and (point-of-care or POC or (rapid adj2 (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*)))).tw,kf.
16	((accura* or reliab* or valid*) and (bacteri* and (viral or virus*) and (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*))).tw,kf.
17	Validation Study/
18	(validat* or validity).tw,kf.
19	area under curve/
20	observer variation/
21	(observer adj variation*).tw,kf.
22	((degree? or rate* or rating) adj3 agreement?).tw,kf.
23	((detect* or diagnos*) and agreement?).tw,kf.
24	Receiver Operating Characteristic/
25	(receiver operating characteristic* or ROC).tw,kf.
26	likelihood functions/
27	diagnostic error/ or false negative result/ or false positive result/ or missed diagnosis/ or false negative reactions/ or false positive reactions/
28	(false adj (positiv* or negativ*)).tw,kf.
29	(QUADAS* or STARD).mp.
30	laboratory diagnosis/
31	(reference standard? or gold standard?).tw,kf.
32	Diagnosis, Differential/
33	(codetect* or co-detect* or codiagnos* or co-diagnos*).tw,kf.
34	((discriminat* or differenti* or dual*) adj (detect* or diagnos*)).mp.
35	(bacteri* adj5 (viral or virus*) adj5 (analys* or assay* or immunoassay* or classif* or detect* or codetect* or determin* or diagnos* or codiagnos* or differenti* or discriminat* or distinguish* or identif* or method* or misdiagnos* or predict* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf,hw.
36	or/1-35
37	(((WBC or white blood cell? or white cell? or lymphocyte? or leukocyte? or monocyte? or CD4* or eosinophil? or neutrophil? or granulocyte?) adj3 (count* or distribution? or level? or number* or paramet* or ratio?)) or NLR).tw,kf.
38	(respiratory or (ear nose adj2 throat) or ENT or otorhinolaryng* or RTI or LRTI or URTI or ARTI or AURI or ALRI or airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonary tract or ((chest or lung or lungs or lobar or pleura*) and (absces* or infect* or coinfect* or inflamm*)) or bronchit* or bronchiolit* or bronchopneumon* or common cold or coryza or croup or empyem* or epipharyngit* or epiglottit* or epiglotit* or flu or influenza or laryngit* or laryngotracheobronchit* or (laryngo and tracheo and bronchit*) or (laryngo and tracheobronchit*) or laryngotracheit* or nasopharyngit* or otitis media or parainfluenza or pharyngit* or pleurisy or pneumoni* or pleuropneumoni* or rhinit* or rhinopharyngit* or rhinosinusit* or sinusit* or sore throat or (throat and infection*) or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit* or whooping cough or pertussis or pertussis or asthma* or COPD or COAD or chronic obstructive pulmonary disease or chronic obstructive airway disease or chronic obstructive airways disease or chronic obstructive lung disease or ((acute or subacute* or exacerbat* or prolonged) and cough*)).ti.
39	36 and 37 and 38
40	(differential diagnos* or codetect* or co-detect*).mp.
41	((bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir*) and (nonbacter* or viral* or virus* or adenovir*)).mp.
42	40 or 41
43	39 and 42
44	(((WBC or white blood cell? or white cell? or lymphocyte? or leukocyte? or monocyte? or CD4* or eosinophil? or neutrophil? or granulocyte?) and (count* or distribution? or level? or number* or paramet* or ratio?)) or NLR).ti.
45	38 and 42 and 44
46	43 or 45
47	(COVID19 or COVID-19 or COVID2019 or COVID-2019 or 2019 nCoV or 2019nCoV or 2019-novel CoV or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2" or 2019 nCoV or 2019nCoV or 2019-novel CoV or "SARS coronavirus 2" or "Severe Acute Respiratory Syndrome Coronavirus-2").ti.
48	46 not 47
49	((neonat* or infant* or child* or p?ediatri*) not adult*).ti.
50	48 not 49

Database: Ovid EMBASE <1980 to 2023 Week 22>

1	Gold Standard/
2	(reference standard? or gold standard?).tw,kf.
3	clinical diagnosis.mp.
4	Diagnostic Test Accuracy Study/

5 Diagnostic Accuracy/

6 (DTA or (diagnos* adj2 accura*)).tw,kf.

7 Validation Study/

8 "Sensitivity and Specificity"/

9 specificity.tw,kf.

10 Receiver Operating Characteristic/

11 Reliability/

12 Internal Validity/

13 Internal Consistency/

14 (validat* or validity).tw,kf.

15 likelihood ratio*.tw,kf.

16 predictive value/

17 (predict* adj4 val*).tw,kf. or predict*.ti.

18 ((re-test or retest or test-retest) adj reliability).tw,kf.

19 diagnostic error/ or false negative result/ or false positive result/ or missed diagnosis/

20 (false adj (positiv* or negativ*)).tw,kf.

21 receiver operating characteristic*.tw,kf.

22 ROC.tw,kf.

23 area under the curve/

24 observer variation/

25 (observer adj variation*).tw,kf.

26 ((degree? or rate* or rating) adj3 agreement?).tw,kf.

27 Diagnosis/

28 diagnos*.ti,kf.

29 (diagnos* adj3 (analys* or assay* or immunoassay* or classif* or differenti* or method* or kit or kits or panel? or predict* or screen* or system* or technique* or test*)).ab.

30 diagnostic procedure/ or diagnostic test/ or diagnostic test approval/ or exp diagnostic kit/ or diagnosis time/

31 laboratory diagnosis/

32 molecular diagnosis/

33 ((accura* or reliab* or valid*) and (point-of-care or POC or (rapid adj2 (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*)))).tw,kf.

34 ((accura* or reliab* or valid*) and (bacteri* and (viral or virus*) and (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*))).tw,kf.

35 "quality assessment of diagnostic accuracy studies"/

36 QUADAS*.mp.

37 differential diagnosis/

38 (codetect* or co-detect* or codiagnos* or co-diagnos*).tw,kf.

39 ((discriminat* or differenti* or dual*) adj (detect* or diagnos*)).mp.

40 (bacteri* adj5 (viral or virus*) adj5 (analys* or assay* or immunoassay* or classif* or detect* or codetect* or determin* or diagnos* or codiagnos* or differenti* or discriminat* or distinguish* or identif* or method* or misdiagnos* or predict* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf,hw.

41 or/1-40

42 (((WBC or white blood cell? or white cell? or lymphocyte? or leukocyte? or monocyte? or CD4* or eosinophil? or neutrophil? or granulocyte?) adj3 (count* or distribution? or level? or number* or paramet* or ratio?)) or NLR).tw,kf.

43 (respiratory or (ear nose adj2 throat) or ENT or otorhinolaryng* or RTI or LRTI or URTI or ARTI or AURI or ALRI or airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonary tract or ((chest or lung or lungs or lobar or pleura*) and (absces* or infect* or coinfect* or inflamm*)) or bronchit* or bronchiolit* or bronchopneumon* or common cold or coryza or croup or empyem* or epipharyngit* or epiglottit* or epiglotit* or flu or influenza or laryngit* or laryngotracheobronchit* or (laryngo and tracheo and bronchit*) or (laryngo and tracheobronchit*) or laryngotracheit* or nasopharyngit* or otitis media or parainfluenza or pharyngit* or pleurisy or pneumoni* or pleuropneumoni* or rhinit* or rhinopharyngit* or rhinosinusit* or sinusit* or sore throat or (throat and infection*) or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit* or whooping cough or pertussis or pertussis or asthma* or COPD or COAD or chronic obstructive pulmonary disease or chronic obstructive airway disease or chronic obstructive airways disease or chronic obstructive lung disease or ((acute or subacute* or exacerbat* or prolonged) and cough*)).ti.

44 41 and 42 and 43

45 (differential diagnos* or codetect* or co-detect*).mp.

46 ((bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir*) and (nonbacter* or viral* or virus* or adenovir*)).mp.

47 45 or 46

48 44 and 47

49 (((WBC or white blood cell? or white cell? or lymphocyte? or leukocyte? or monocyte? or CD4* or eosinophil? or neutrophil? or granulocyte?) and (count* or distribution? or level? or number* or paramet* or ratio?)) or NLR).ti.

50 43 and 47 and 49

51 48 or 50

52 (COVID19 or COVID-19 or COVID2019 or COVID-2019 or 2019 nCoV or 2019nCoV or 2019-novel CoV or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2" or 2019 nCoV or 2019nCoV or 2019-novel CoV or "SARS coronavirus 2" or "Severe Acute Respiratory Syndrome Coronavirus-2").ti.

53	51 not 52
54	limit 53 to conference abstract status
55	53 not 54
56	((neonat* or infant* or child* or p?ediatri*) not adult*).ti.
57	55 not 56

Multiplex PCR

Database: Ovid MEDLINE(R) ALL <1946 to June 27, 2023> Final search strategy

1	[Target Conditions: RTI]
2	exp Respiratory Tract Infections/
3	exp Otorhinolaryngologic Diseases/
4	((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (infect* or coinfect* or inflamm*)).tw,kf.
5	((chest or lung? or lobar or pleura?) adj3 (absces* or infect* or coinfect* or inflamm*)).tw,kf.
6	(bronchit* or bronchiolit* or allergic bronchopulmon* or bronchopneumon* or common cold* or coryza or croup or empyem* or epipharyngit* or epiglottit* or epiglotit* or flu or influenza or laryngit* or laryngotracheobronchit* or laryngo tracheo bronchit* or laryngo tracheobronchit* or laryngotracheit* or nasopharyngit* or otitis media or parainfluenza or pharyngit* or pleurisy or pneumoni* or pleuropneumoni* or rhinit* or rhinopharyngit* or rhinosinusit* or severe acute respiratory syndrome or SARS or sinusit* or sore throat* or throat infection* or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit* or whooping cough or pertussis or pertusis).mp.
7	((acute* or exacerbat* or flare*) adj3 (asthma* or copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).mp.
8	((acute* or subacute* or exacerbat* or prolonged) adj3 cough*).mp.
9	(RTI or LRTI or URTI or ARTI or AURI or ALRI).tw,kf.
10	or/2-9
11	exp Respiratory System/ and (exp Viruses/ or exp Virus Diseases/)
12	exp pneumonia, viral/ or *orthomyxoviridae infections/ or influenza, human/
13	((airway* or respiratory or pulmonary or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (nonbacter* or viral* or virus* or adenovir*)).tw,kf.
14	(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.
15	or/11-14
16	exp Respiratory System/ and (exp Bacteria/ or exp Bacterial Infections/)
17	pneumonia, bacterial/ or chlamydial pneumonia/ or pneumonia, mycoplasma/ or pneumonia, pneumococcal/ or pneumonia, staphylococcal/
18	((airway* or respiratory or pulmonary or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir* or pathogen*)).tw,kf.
19	(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.
20	((strep* adj3 (throat* or pharyn* or tonsil*)) or (strep* and (airway* or pulmonary or brochopulmonar* or brocho-pulmonar* or respiratory* or (ear adj3 nose adj3 throat) or ENT or Otorhinolaryng*))).mp.
21	(GABHS or ("group a" adj3 strep*)).tw,kf.
22	strep* pyogen*.mp.
23	or/16-22
24	10 or 15 or 23
25	[Index Tests: Rapid Multiplex Tests]
26	(multiplex* and "sample to answer").mp.
27	24 and 26
28	(maripoc* or mari-poc*).af.
29	(Rapid* and Diagnostic* and (MiniLab* or mini-lab*)).af.
30	(QIAstat* or QIA-stat* or (Qiagen* and (Resp* adj3 panel))).af.
31	(Biofire* Respiratory or Biofire* RP*).af.
32	(BioFire* adj (FilmArray* or Film-Array) adj (Respiratory Panel? or RP*)).af.
33	(Biofire* adj (FilmArray* or Film-Array*) adj Pneumo*).af.
34	(Biofire* adj (FilmArray* or Film-Array*)).ti.
35	(Biofire* and "sample to answer").mp.
36	(Biofire* adj5 (rapid or real time or RT-PCR or rRT-PCR)).mp.
37	(34 or 35 or 36) and 24
38	(Spotfire* or Spot-fire*).af.

39	24 and 38
40	(Cobas* adj5 ((lab* adj3 tube*) or liat*)).af.
41	24 and 40
42	(cobas* Influenza A* or cobas* Influenza B* or cobas* RSV or cobas* respiratory sync* virus).af.
43	((Cepheid* adj3 GeneXpert* adj3 Xpress*) or (Cepheid* adj3 Gene-Xpert* adj3 Xpress*)).af.
44	(Xpert* adj3 Xpress* adj3 (influenza or flu or respiratory sync* virus or RSV)).af.
45	(Cepheid* adj3 Xpert* adj3 (influenza or flu or respiratory sync* virus or RSV)).af.
46	(ePlex* RP* or (ePlex* adj3 resp* adj3 panel?)).af.
47	ePlex*.af.
48	24 and 47
49	((GenMark* or Gen-Mark*) and (RP* or (resp* adj3 panel?))).af.
50	(Simplexa* or Liaison* MDX*).af.
51	24 and 50
52	Aries*.mp. not (sheep or lamb or lambs or ram or rams or ewe or ewes or ovine or ovis aries).ti.
53	24 and 52
54	(Savanna* and (quidel* or molecular or multiplex* or rapid or real-time or RTPCR or RT-PCR or rRTPCR or rRT-PCR or test? or device? or panel? or PoCT or Point-of-Care or near-patient?)).mp.
55	24 and 54
56	((RVP4* or RVP-4*) and (Savanna* or Quidel* or molecular or multiplex* or rapid or real-time or RTPCR or RT-PCR or rRTPCR or rRT-PCR or test? or device? or panel? or PoCT or Point-of-Care or near-patient?)).mp.
57	(Respiratory Vir* Panel4* or Respiratory Vir* Panel-4*).af.
58	Verigen*.af.
59	24 and 58
60	Panther* Fusion*.af.
61	24 and 60
62	"Flu A/B/RSV*".af.
63	"AdV/hMPV/RV*".af.
64	"SARS-CoV-2/Flu A/B*".af.
65	"SARS-CoV-2/Flu A/B/RSV*".af.
66	(paraflu or parafluTM or parafluR).af.
67	27 or 28 or 29 or 30 or 31 or 32 or 33 or 37 or 39 or 41 or 42 or 43 or 44 or 45 or 46 or 48 or 49 or 51 or 53 or 55 or 56 or 57 or 59 or 61 or 62 or 63 or 64 or 65 or 66
68	((COVID19 or COVID-19 or COVID2019 or COVID-2019 or 2019 nCoV or 2019nCoV or 2019-novel CoV or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2" or 2019 nCoV or 2019nCoV or 2019-novel CoV or "SARS coronavirus 2" or "Severe Acute Respiratory Syndrome Coronavirus-2") not (rhinovir* or rhino* vir* or coryzavir* or coryza* vir* or influenzavir* or influenza* vir* or (H1N1 or H3N2) or parainfluenza-vir* or parainfluenza* vir* or pneumovir* or pneumo* vir* or human metapneumovir* or human meta-pneumovir* or HMPV or respiratory sync* vir* or RSV)).ti.
69	67 not 68
70	(("SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2" or "SARS coronavirus 2" or "Severe Acute Respiratory Syndrome Coronavirus-2") adj3 Flu* adj3 RSV).af.
71	69 or 70
72	((neonat* or infant* or child* or p?ediatri*) not adult*).ti.
73	71 not 72

Database: EMBASE <1974 to 2023 June 27> Final search strategy

1	[Target Conditions: RTI]
2	respiratory tract infection/ or exp influenza/ or laryngotracheobronchitis/ or parainfluenza virus infection/ or respiratory syncytial virus infection/ or viral respiratory tract infection/ or lower respiratory tract infection/ or chest infection/ or pertussis/ or lung infection/ or exp infectious pneumonia/ or lung abscess/ or exp lung mycosis/ or exp viral bronchiolitis/ or upper respiratory tract infection/ or exp nose infection/ or oropharynx candidiasis/ or peritonsillar abscess/ or viral upper respiratory tract infection/
3	ear nose throat disease/di or otorhinolaryngology/ or exp ear infection/ or exp otitis/
4	((airway* or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or pulmonar* tract or pulmonary or respirat* tract or respiratory or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (infect* or coinfect* or inflamm*)).tw,kf.
5	((chest or lung? or lobar or pleura?) adj3 (absces* or infect* or coinfect* or inflamm*)).tw,kf.

6	(bronchit* or bronchiolit* or allergic bronchopulmon* or bronchopneumon* or common cold* or coryza or croup or empyem* or epipharyngit* or epiglottit* or epiglotit* or flu or influenza or laryngit* or laryngotracheobronchit* or laryngo tracheo bronchit* or laryngo tracheobronchit* or laryngotracheit* or legionnair* disease or legionellos* or middle east respiratory syndrome or MERS or nasopharyngit* or otitis media or parainfluenza or pharyngit* or pleurisy or pneumoni* or pleuropneumoni* or rhinit* or rhinopharyngit* or rhinosinusit* or severe acute respiratory syndrome or SARS or sinusit* or sore throat* or throat infection* or supraglottit* or supraglotit* or tonsillit* or tonsilit* or tracheit* or whooping cough or pertussis or pertusis).mp.
7	((acute* or exacerbat* or flare*) adj3 (asthma* or copd or coad or chronic obstructive pulmonary disease or chronic obstructive airway* disease or chronic obstructive lung disease)).mp.
8	((acute* or subacute* or exacerbat* or prolonged) adj3 cough*).mp.
9	(RTI or LRTI or URTI or ARTI or AURI or ALRI).tw,kf.
10	or/2-9
11	exp respiratory system/ and exp virus infection/
12	((airway* or respiratory or pulmonary or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (nonbacter* or viral* or virus* or adenovir*)).tw,kf.
13	rhinovirus/ or exp human rhinovirus/ or exp rhinovirus infection/
14	exp Influenza virus/ or orthomyxovirus infection/
15	respirovirus/ or human parainfluenza virus 1/ or human parainfluenza virus 3/ or respirovirus infection/
16	exp virus pneumonia/
17	pneumovirus/ or pneumovirus infection/ or exp human respiratory syncytial virus/ or respiratory syncytial virus infection/
18	metapneumovirus/ or metapneumovirus infection/ or human metapneumovirus/ or human metapneumovirus infection/
19	(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 sync* vir*).mp. or RSV.tw,kf.
20	or/11-19
21	exp respiratory system/ and (exp bacterium/ or exp bacterial Infection/)
22	((airway* or respiratory or pulmonary or bronchopulmonar* or broncho-pulmonar* or tracheobronch* or tracheo-bronch* or (ear adj3 nose adj3 throat) or ENT or otorhinolaryng*) adj3 (bacter* or bacilli* or bacili* or corynebac* or mycobac* or nonvir* or pathogen*)).tw,kf.
23	bacterial pneumonia/ or chlamydial pneumonia/ or mycoplasma pneumonia/ or staphylococcal pneumonia/ or exp streptococcus pneumonia/
24	(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.
25	((strep* adj3 (throat* or pharyn* or tonsil*)) or (strep* and (airway* or pulmonary or brochopulmonar* or brocho-pulmonar* or respiratory* or (ear adj3 nose adj3 throat) or ENT or Otorhinolaryng*))).mp.
26	streptococcus infection/ or streptococcus group a/ or exp group a streptococcal infection/ or streptococcal pharyngitis/
27	(GABHS or ("group a" adj3 strep*)).tw,kf.
28	strep* pyogen*.mp.
29	or/21-28
30	10 or 20 or 29
31	[DTA Filter]
32	Gold Standard/
33	(reference standard? or gold standard?).tw,kf.
34	Diagnostic Test Accuracy Study/
35	Diagnostic Accuracy/
36	(DTA or (diagnos* adj2 accura*)).tw,kf.
37	Validation Study/
38	"Sensitivity and Specificity"/
39	(sensitivity or specificity).tw,kf.
40	Receiver Operating Characteristic/
41	Reliability/
42	Internal Validity/
43	Internal Consistency/
44	(validat* or validity).tw,kf.
45	likelihood ratio*.tw,kf.
46	predictive value/
47	(predict* adj4 val*).tw,kf. or predict*.ti.
48	((re-test or retest or test-retest) adj reliability).tw,kf.
49	diagnostic error/ or false negative result/ or false positive result/ or missed diagnosis/
50	(false adj (positiv* or negativ*)).tw,kf.
51	receiver operating characteristic*.tw,kf.
52	ROC.tw,kf.
53	area under the curve/
54	observer variation/

55	(observer adj variation*).tw,kf.
56	((degree? or rate* or rating) adj3 agreement?).tw,kf.
57	((detect* or diagnos*) and agreement?).tw,kf.
58	diagnostic.ti,kf.
59	(diagnos* adj3 (classif* or differenti* or predict* or rapid* or RT-PCR or rRT-PCR)).ab.
60	diagnostic test approval/ or diagnosis time/
61	laboratory diagnosis/
62	molecular diagnosis/
63	((accura* or reliab* or valid*) and (point-of-care or POC or (rapid adj2 (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*)))).tw,kf.
64	((accura* or reliab* or valid*) and (bacteri* and (viral or virus*) and (analys* or assay* or immunoassay* or classif* or detect* or diagnos* or differenti* or predict* or technique* or test*))).tw,kf.
65	"quality assessment of diagnostic accuracy studies"/
66	(QUADAS* or STARD).mp.
67	differential diagnosis/
68	(codetect* or co-detect* or codiagnos* or co-diagnos*).tw,kf.
69	((discriminat* or differenti* or dual*) adj (detect* or diagnos*)).mp.
70	(bacteri* adj5 (viral or virus*) adj5 (analys* or assay* or immunoassay* or classif* or detect* or codetect* or determin* or diagnos* or codiagnos* or differenti* or discriminat* or distinguish* or identif* or method* or misdiagnos* or predict* or kit or kits or panel? or predict* or rapid or routine* or screen* or system* or technique* or test*)).tw,kf,hw.
71	"sample to answer".mp.
72	or/32-71
73	[Index Tests: Rapid Multiplex PCR]
74	rapid test/dc
75	(multiplex* and "sample to answer").mp.
76	(74 or 75) and 30
77	(maripoc* or mari-poc*).mp,ct,dv,dc,dm,mv,my,tn.
78	(Rapid* and Diagnostic* and (MiniLab* or mini-lab*)).mp,ct,dv,dc,dm,mv,my,tn.
79	(QIAstat* or QIA-stat* or (Qiagen* and (Resp* adj3 panel))).mp,ct,dv,dc,dm,mv,my,tn.
80	Biofire* Respiratory.mp,ct,dv,dc,dm,mv,my,tn.
81	BioFire* RP*.mp,ct,dv,dc,dm,mv,my,tn.
82	(Biofire* and "sample to answer"). mp,ct,dv,dc,dm,mv,my,tn.
83	(Biofire* adj5 (rapid or real time or RT-PCR or rRT-PCR)).mp,ct,dv,dc,dm,mv,my,tn.
84	or/77-83
85	(BioFire* adj (FilmArray* or Film-Array) adj (Respiratory Panel? or RP*)).mp,ct,dv,dc,dm,mv,my,tn.
86	(Biofire* adj (FilmArray* or Film-Array*) adj Pneumonia). mp,ct,dv,dc,dm,mv,my,tn.
87	(85 or 86) and 72
88	(Biofire* adj (FilmArray* or Film-Array*)).ti.
89	88 and 30 and 72
90	(Spotfire* or Spot-fire*).mp,ct,dv,dc,dm,mv,my,tn.
91	90 and (30 or 72)
92	(Cobas* adj5 ((lab* adj3 tube*) or liat*)). mp,ct,dv,dc,dm,mv,my,tn.
93	(cobas* Influenza A* or cobas* Influenza B* or cobas* RSV or cobas* respiratory sync* virus). mp,ct,dv,dc,dm,mv,my,tn.
94	(92 and 30 and 72) or 93
95	(Xpert* adj3 Xpress* adj3 (influenza or flu or respiratory sync* virus or RSV)).mp,ct,dv,dc,dm,mv,my,tn.
96	(Cepheid* adj3 Xpert* adj3 (influenza or flu or respiratory sync* virus or RSV)).mp,ct,dv,dc,dm,mv,my,tn.
97	((Cepheid* adj3 GeneXpert* adj3 Xpress*) or (Cepheid* adj3 Gene-Xpert* adj3 Xpress*)).mp,ct,dv,dc,dm,mv,my,tn.
98	((95 or 96) and 72) or 97
99	(ePlex* RP* or (ePlex* adj3 resp* adj3 panel?)). mp,ct,dv,dc,dm,mv,my,tn.
100	ePlex*.mp,ct,dv,dc,dm,mv,my,tn.
101	(100 and 72) or 99
102	((GenMark* or Gen-Mark*) and (RP* or (resp* adj3 panel?))).mp,ct,dv,dc,dm,mv,my,tn.
103	102 and 72
104	76 or 84 or 87 or 89 or 91 or 94 or 98 or 101 or 103
105	(Simplexa* or Liaison* MDX*).mp,ct,dv,dc,dm,mv,my,tn.
106	105 and 30 and 72
107	Aries*.mp,ct,dv,dc,dm,mv,my,tn.
108	(sheep or lamb or lambs or ram or rams or ewe or ewes or ovine or ovis aries).ti.
109	107 not 108
110	109 and 30 and 72

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111	(Savanna* and (quidel* or molecular or multiplex* or rapid or real-time or RTPCR or RT-PCR or rRTPCR or rRT-PCR or test? or device? or panel? or PoCT or Point-of-Care or near-patient?)).mp,ct,dv,dc,dm,mv,my,tn.
112	((RVP4* or RVP-4*) and (Savanna* or Quidel* or molecular or multiplex* or rapid or real-time or RTPCR or RT-PCR or rRTPCR or rRT-PCR or test? or device? or panel? or PoCT or Point-of-Care or near-patient?)).mp,ct,dv,dc,dm,mv,my,tn.
113	(respiratory vir* Panel4* or respiratory vir* Panel-4*).mp,ct,dv,dc,dm,mv,my,tn.
114	(111 or 112 or 113) and 30
115	Verigen*.mp,ct,dv,dc,dm,mv,my,tn.
116	115 and 30 and 72
117	Panther* Fusion*.mp,ct,dv,dc,dm,mv,my,tn.
118	117 and 30 and 72
119	Paraflu*.mp,ct,dv,dc,dm,mv,my,tn.
120	119 and 72
121	"Flu A/B/RSV*".mp,ct,dv,dc,dm,mv,my,tn.
122	"AdV/hMPV/RV*".mp,ct,dv,dc,dm,mv,my,tn.
123	106 or 110 or 114 or 116 or 118 or 120 or 121 or 122
124	104 or 123
125	((COVID19 or COVID-19 or COVID2019 or COVID-2019 or 2019 nCoV or 2019nCoV or 2019-novel CoV or "SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2" or 2019 nCoV or 2019nCoV or 2019-novel CoV or "SARS coronavirus 2" or "Severe Acute Respiratory Syndrome Coronavirus-2") not (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 sync* vir* or RSV)).ti.
126	124 not 125
127	"SARS-CoV-2/Flu A/B*".mp,ct,dv,dc,dm,mv,my,tn.
128	"SARS-CoV-2/Flu A/B*".mp,ct,dv,dc,dm,mv,my,tn.
129	(("SARS-CoV-2" or "SARS-CoV2" or SARSCoV2 or "SARSCoV-2" or "SARS coronavirus 2" or "Severe Acute Respiratory Syndrome Coronavirus-2") adj3 Flu* adj3 RSV).mp,ct,dv,dc,dm,mv,my,tn.
130	or/126-129
131	((neonat* or infant* or child* or p?ediatri*) not adult*).ti.
132	130 not 131
133	limit 132 to conference abstract status
134	132 not 133

Appendix 2

TABLE 2 Systematic reviews meeting inclusion criteria for the overview of reviews

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Bruning 2017[63]	'. . . all available rapid tests for the detection of respiratory viruses in patients of all ages with RTIs' 'Studies were considered for inclusion if they were written in English or Dutch and reported original data regarding the accuracy of a rapid test for ≥ 1 respiratory virus compared with PCR'	MEDLINE and EMBASE (January 2016)	QUADAS-2	179	Any rapid test	RSV	2	Adults and children	Not stated	Not stated	Funded by EU's Seventh Framework People Programme. The authors declare no conflicts of interest	Both studies for RSV in mixed population. Excluded, as data superseded by more recent reviews (Gentilotti 2022[33] and Onwuchekwa 2023[35])
					Any rapid test	Influenza A and/or B	11	Adults	Not stated	Not stated		
Carlton 2021[32]	'Our review included diagnostic accuracy studies, reporting on point-of-care and rapid diagnostic tests consisting of more-than-one biomarker to identify bacterial or viral aetiology, in the general population presenting to primary or secondary care with acute RTI symptoms'	MEDLINE, EMBASE, Web of Science (February 2021)	QUADAS-2	20	Immuno-Xpert (TRAIL, IP-10 and CRP)	Bacterial or viral	4	Adults and children	Features of acute RTI	'... the general population presenting to primary or secondary care'	Conducted as part of lead author's undergraduate research project, without dedicated funding. Otherauthors' time supported by NIHR ARC West. The authors declare no conflicts of interest	Included
					FebriDx (CRP and MxA)	Bacterial or viral	4	Adults and children	Features of acute RTI	'... the general population presenting to primary or secondary care'		
					CRP and neopterin	Bacterial or viral	1	Adults	Features of acute RTI	'... the general population presenting to primary or secondary care'		

continued

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TABLE 2 Systematic reviews meeting inclusion criteria for the overview of reviews (*continued*)

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Chartrand 2012[64]	'Studies were included if they assessed the accuracy of an RIDT [rapid influenza diagnostic test] against 1 of the 2 accepted reference standards. [. . .] Acceptable reference standards included viral culture or RT-PCR'	PubMed, EMBASE, BIOSIS and Web of Science (December 2011)	QUADAS	159	Any rapid test	Influenza A and/or B	17	Adults	Not stated	Not stated	Supported in part by the Canadian Institutes of Health Research Authors declare no conflicts of interest	Superseded by more recent review (Gentilotti 2022[33])
Chartrand 2015[65]	'Studies were considered for inclusion if they assessed the diagnostic accuracy of a commercial rapid immunoassay for RSV in patients with suspected ARI'	PubMed and EMBASE (April 2015)	QUADAS-2	71	Any rapid test	RSV	4	Adults	People with suspected ARI	Any setting	No funding information or conflicts of interest reported	Not specific to primary/ emergency care settings Superseded by more recent review (Onwuchekwa 2023[35])
Engel 2012[66]	'Studies using adult patients (> 16 years of age) consulting their GP with a probable LRTI were included if CRP was measured in (a part) of those patients'	MEDLINE, EMBASE and the Cochrane Library (July 2010)	QUADAS and the 'Cochrane Validity Score'	10	CRP	Bacterial LRTI and pneumonia	Narrative synthesis of 5 relevant articles	Adults (> 16 years)	Suspected LRTI. People with URTI/ confirmed pneumo-nia were excluded	Primary care	No funding received. The authors declare no conflicts of interest.	No summary data are reported. Superseded by Gentilotti 2022[33]

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Falk 2008[67]	'Population – participants in each study were to be recruited from a community, primary care setting or ambulatory setting, for example emergency departments, and have symptoms suggestive of acute respiratory infection suggestive of LRTI'	PubMed, EMBASE, Google Scholar, the Cochrane database and the MEDION database (July 2008)	QUADAS	8	CRP	Pneumonia	5–6 depending on threshold used	Adults (over 14 years)	ARI	Community and emergency care	Funded by Irish College of General Practitioners and Health Research Board Authors declare no conflicts of interest	Superseded by Gentilotti 2022[33]
Gentilotti 2022[33]	' … all the diagnostic test accuracy (DTA) studies [. . .] on patients of any age were eligible for inclusion.'	PubMed, Web of Science, the Cochrane Library, EMBASE and Open Gray (May 2021)	QUADAS-2	421	Symptoms and signs	Bacterial pneumonia	Between 4 and 26 studies, depending on symptoms/ sign	Adults	Suspected LRTI	Community/ emergency care settings	Funded by Innovative Medicines Initiative-2 Joint Undertaking	Included
					CRP	Pneumonia or bacterial pneumonia	4–6 (depending on threshold used)	Adults	Suspected LRTI	Community/ emergency care settings		
					Procalcitonin	Pneumonia or bacterial pneumonia	2–4 (depending on threshold used)	Adults	Suspected LRTI	Community/ emergency care settings	The joint undertaking receives support from various pharmaceutical companies	
	Supplementary information: 'A community-care setting was defined as the first point of contact with health services, including PC [primary care],				Immunochromatographic assay	Influenza A and/or B	15	Adults	Suspected LRTI	Community/ emergency care settings		
					Direct immunofluorescence	Influenza A and/or B	19	Mixed adults and children	Suspected LRTI	Community/ emergency care settings	The authors note that the commercial companies had no part in the design, analysis, writing or decision to publish the results.	
					Optical immunoassay	Influenza A and/or B	9	Mixed adults and children	Suspected LRTI	Community/ emergency care settings		
					Chemiluminescent neuraminidase assay	Influenza A and/or B	4	Mixed adults and children	Suspected LRTI	Community/ emergency care settings		

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TABLE 2 Systematic reviews meeting inclusion criteria for the overview of reviews (*continued*)

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
	LTCF [long term care facilities], OC [outpatient clinic], and ER [emergency room].				PCR-based NAAT	Influenza A and/or B	6	Adults	Suspected LRTI	Community/ emergency care settings	The authors declare no conflicts of interest	
					Non-PCR- based NAAT	Influenza A and/or B	2	Mixed adults and children	Suspected LRTI	Community/ emergency care settings		
					Rapid antigen detection test	RSV	35	Mixed adults and children	Suspected LRTI	Community/ emergency care settings		
					PCR-based NAAT	RSV	38	Mixed adults and children	Suspected LRTI	Community/ emergency care settings		
	POCT was defined as a test to support clinical decision-making (signs and symptoms or imaging or host biomarkers or pathogen-based tests), which is performed on any part of the patient's body or clinical samples, during or close to the time of consultation'				Non-PCR- based NAAT	RSV	5	Mixed adults and children	Suspected LRTI	Community/ emergency care settings		

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Hill 2019[68]	Adult outpatients with acute cough due to suspected pneumonia	PubMed, Scopus and the Cochrane Library (March 2017)	QUADAS and DART	Not stated	CRP	Pneumonia	Narrative synthesis of 6 articles	Adults	Suspected pneumonia	Not stated	No funding was received for the study. One author (RSI) reports they are Editor in Chief of the publishing journal. Remaining authors declare no conflicts of interest	Superseded by Gentilotti 2022[33]
					Procalcitonin	Pneumonia	Narrative synthesis of 6 articles	Adults	Suspected pneumonia	Not stated		
					Symptoms and signs	Pneumonia	Narrative synthesis of 2 articles	Adults	Suspected pneumonia	Not stated		
Han 2020[69]	Diagnostic test accuracy studies of lateral flow assays for influenza with at least 40 participants	PubMed, EMBASE, Web of Science and the Cochrane Library (November 2019)	QUADAS-2	13	Any lateral flow assay	Influenza A and/or B	13	Mixed adults and children	Not stated	Any	Funding information not reported. Authors declare no conflicts of interest	Superseded by Gentilotti 2022[33]
Hoult 2022[70]	'Cross-sectional, cohort and randomised controlled studies that describe associations between serum or sputum molecular or cellular biomarkers and evidence of bacterial infection in people with acute exacerbation of COPD were eligible for inclusion'	EMBASE and MEDLINE (March 2018)	QUADAS-2	39	CRP	Bacterial exacerbation of COPD	Narrative synthesis of 8 articles	Adults with COPD	Not stated	Outpatient, hospitalised inpatients and ICU	No funding received for the study. Several authors report financial support from pharmaceutical companies, for work outside the study	Excluded as setting not sufficiently similar in scope to this review, and unable to extract relevant data. Procalcitonin studies do not relate to people attending primary/emergency care
					Procalcitonin	Bacterial exacerbation of COPD	Narrative synthesis of 5 articles	Adults with COPD	People with acute exacerbations of COPD	Hospitalised inpatients and ICU		

continued

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TABLE 2 Systematic reviews meeting inclusion criteria for the overview of reviews (*continued*)

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Htun 2019[71]	'… published studies that assessed clinical predictors of community-acquired pneumonia [. . .]. Studies were included if participants aged ≥ 18 years without serious illness (e.g. mechanical ventilation) and pre-existing immune suppression (HIV, malnutrition, and immunosuppressant medication)'	PubMed, EMBASE, Cochrane Library (March 2018)	QUADAS-2	13	Symptoms and signs	Pneumonia	Between four and seven studies, depending on symptoms/ sign	Adults	Acute respiratory symptoms	Outpatient, primary or emergency care settings	Supported by Centre of Infectious Disease Epidemiology and Research (funded by Singapore Ministry of Defence). The authors declare no conflicts of interest	Superseded by Gentilotti 2022[33]
					CRP	Pneumonia	9	Adults	Acute respiratory symptoms	Outpatient, primary or emergency care settings		
					Procalcitonin	Pneumonia	4	Adults	Acute respiratory symptoms	Outpatient, primary or emergency care settings		
Huang 2018[72]	'Studies that evaluated the performance of FDA-approved mPCR systems for the detection of viral respiratory infection were included, as follow: (a) they assessed the accuracy of one or more the following systems: FilmArray, Nanosphere Verigene RV+ and Hologic Gen-Probe Prodesse assays [. . .] against reference standards'	PubMed, EMBASE (July 2017)	QUADAS-2	20	Multiplex PCR	Multiple single pathogens	22 (influenza A) 13 (influenza B) 13 (RSV) 8 (adenovirus) 8 (hMPV)	Adults and children	Mixture of symptomatic people and stored samples	Not stated	Supported in part by a National Taiwan University Hospital Research Grant The authors declare no conflicts of interest	Scope too narrow for inclusion. Review limited to two rapid multiplex tests (and one laboratory-based multiplex test)

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Lee 2021[73]	'… studies that evaluated the performance of the Quidel Sofia rapid influenza FIA, compared to a reference standard [. . .] studies that included patients with influenza-like illness.'	MEDLINE, EMBASE and the Cochrane Central Register (July 2020)	QUADAS-2	17	Quidel Sofia rapid influenza fluorescent immunoassay	Influenza A and B	2 (influenza A) 1 (influenza B)	Adults	People with influenza-like illness	Not stated	Supported by research grant from the Jeju National University Hospital The authors declare no conflicts of interest	Scope too narrow. Superseded by Gentilotti 2022[33]
Merckx 2017[74]	'. . . studies [. . .] on the diagnostic accuracy of rapid influenza tests against an RT-PCR reference standard. Eligible participants were children and adults with clinically suspected influenza during periods of influenza activity'	PubMed, EMBASE, BIOSIS Previews, Scopus, Web of Science and the Cochrane Central Register (May 2017)	QUADAS-2	162	Traditional RIDT	Influenza A and B	23 (influenza A) 5 (influenza B)	Adults	Clinically suspected influenza	Mixed primary, emergency and hospital settings	Supported in part by the Quebec Health Research Fund and by an investigator-initiated study grant from BD Diagnostic Systems. Several authors report personal fees from funders and other pharmaceutical companies	Superseded by Gentilotti 2022[33]
					DIA	Influenza A and B	8 (influenza A) 7 (influenza B)	Adults	Clinically suspected influenza	Mixed primary, emergency and hospital settings		
					Rapid NAAT	Influenza A and B	4 (influenza A) 4 (influenza B)	Adults	Clinically suspected influenza	Mixed primary, emergency and hospital settings		

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TABLE 2 Systematic reviews meeting inclusion criteria for the overview of reviews (*continued*)

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Minnaard 2017[34]	'All studies on diagnostic accuracy of CRP for pneumonia (e.g. infiltrate on chest radiography as the reference standard) were eligible. Study participants had to be adults (≥ 18 years) suspected by their physician of having a lower respiratory tract infection presenting in a primary health care setting'	MEDLINE, EMBASE, the Cochrane Library (Not stated. Most recent included study published in 2013)	QUADAS-2	8	CRP and signs and symptoms	Pneumonia	8	Adults	Suspected LRTI	Primary and emergency care	Funding information not reported. Several authors report grants received from various sources, including pharmaceutical companies	Included
Nicholson 2014[75]	'. . . publications on influenza POCT diagnostic accuracy studies between 1991 and 2011 (inclusive) that met the following five criteria:1. Articles written in English.2. Commercially available test kits.3. Testing done in human seasonal and pandemic influenza... '	MEDLINE, BIOSIS and the Cochrane Library (May 2011)	QUADAS and STARD	70	Any POCT for influenza	Influenza	43	Mixed adults and children	Not stated	Not stated	Funded by the NIHR Health Technology Assessment programme. Lead author previously consultant to GSK and Novartis. Various authors report paid work from pharmaceutical companies	Superseded by Gentilotti 2022[33]

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Onwuchekwa 2023[35]	'… primary studies were eligible if they reported on the diagnostic test performance or compared RSV detection rates using different specimens. We excluded [. . .] studies in children, and in vitro studies'	EMBASE, MEDLINE, Web of Science (December 2021)	QUADAS-2	156	DFA	RSV	1	Adults	Acute exacerbation of asthma	Any setting	Funded by Pfizer. Open access fees paid by Pfizer. Authors employees of Pfizer or P95 (the company contracted by Pfizer to conduct this work)	Included data on DFA and RADT. Excluded data on multiplex tests, as new review of multiplex tests was conducted
					RADT	RSV	1	Adults	LRTI and URTI	Any setting		
					Multiplex PCR	RSV	1	Adults	LRTI and URTI	Any setting		
Pazmany 2021[36]	'(a) adult patients with bacterial and non-bacterial AECOPD; (b) results of microbiology tests (as the reference standard) with samples taken from sputum, tracheal aspirates or blood; and (c) at least one other on-admission diagnostic test performed from serum or sputum(-index tests), were considered eligible'	MEDLINE, EMBASE, CENTRAL, Scopus and Web of Science (October 2019)	QUADAS-2	21	Symptoms and signs (sputum colour only)	Bacterial acute exacerbation of COPD	3	Adults	Acute exacerbation of COPD	Any setting	Funded by EU within the framework Programme Széchenyi 2020 and Human Resources Development Operational Programme. The authors declare no conflicts of interest	Data on sputum included, as predominantly primary care setting. Other data relates to hospitalised participants. Not sufficiently close in scope to this review question (no data relating to outpatient/ primary/emergency settings)
					CRP	Bacterial acute exacerbation of COPD	9	Adults	Acute exacerbation of COPD	Any setting		
					Procalcitonin	Bacterial acute exacerbation of COPD	8	Adults	Acute exacerbation of COPD	Any setting		
					Neutrophil/lymphocyte ratio	Bacterial acute exacerbation of COPD	1	Adults	Acute exacerbation of COPD	Any setting		
					Eosinophil %	Bacterial acute exacerbation of COPD	1	Adults	Acute exacerbation of COPD	Any setting		

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TABLE 2 Systematic reviews meeting inclusion criteria for the overview of reviews (*continued*)

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Petrozzino 2010[76]	'Articles reporting RFT and clinical diagnostic performance, and effects on decision-making and diagnostic outcomes.' Adults and children with influenza-like illness	PubMed/ MEDLINE; the Cochrane Library; British Medical Journal Clinical Evidence; Surveillance, Epidemiology and End Results; the World Health Organization website, the Agency for Healthcare Research and Quality website (2009)	US Preventive Services Task Force (USPSTF) evidence-based guidelines for internal validity of diagnostic accuracy studies	16	QuickVue RFT	Influenza A and B	5	Adults (≥ 15 years)	People presenting with influenza-like illness	Any setting	Supported by the Quidel Corporation, through the Aequitas Group. Several authors report being a consultant/ employee of Aequitas during project	Superseded by Gentilotti 2022[33] Data on symptoms and signs are outside the scope of the protocol: clinical symptoms and signs for a specific pathogen, rather than bacterial/ viral infection
					Symptoms and signs (clinical assessment)	Influenza A and B	11	Adults (≥ 15 years)	People presenting with influenza-like illness	Any setting		
Schierenberg 2016[37]	'Models eligible for inclusion were logistic regression models including S&S [signs and symptoms] for predicting the probability of pneumonia in primary care patients with acute cough or suspected LRTI'	PubMed, EMBASE and the Cochrane Library (August 2012)	QUADAS-2	8	Any clinical prediction rule for pneumonia (signs and symptoms)	Pneumonia	8	Adults	Acute or worsened cough or LRTI symptoms	Primary or emergency care	No direct funding received for the study. The authors declare no conflicts of interest	No summary estimates provided. Included

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Van der Meer 2005[77]	'We aimed to include studies that compared C reactive protein with a chest radiograph [. . .] or microbiological work-up [. . .]. We excluded articles concerning immunocompromised patients, patients treated in intensive care units, or patients with hospital acquired pneumonia'	MEDLINE and EMBASE (April 2004)	Lijmer criteria	17	CRP	Pneumonia	5	Adults	ARI	Primary/ emergency care	No funding received. The authors declare no conflicts of interest	Superseded by Gentilotti 2022[33]
Vos 2019[78]	Supplementary material: 'We included peer-reviewed studies in English or Dutch providing original data on the diagnostic accuracy or clinical impact of a molecular rapid test for respiratory viruses, among which at least influenza virus and/or RSV, as compared to (non-rapid) molecular techniques. [. . .] The domain included patients of all ages with suspected (viral) RTI presenting in a hospital setting'	MEDLINE, EMBASE, Cochrane Library (August 2017)	QUADAS-2	56	Any molecular rapid test	Influenza A and/or B and/or RSV (pooled estimate)	7	Adults	Mixed (some studies with symptoms of ARI, some not reported)	Not stated	Funding information not reported The authors declare no conflicts of interest	Superseded by Gentilotti 2022[33]

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TABLE 2 Systematic reviews meeting inclusion criteria for the overview of reviews (*continued*)

Reference	Eligibility criteria	Databases searched (search date)	Tool used to assess the validity of primary studies	Total number of studies included in the review	Index test	Target condition	Number of studies included in most relevant analysis	Population	Clinical features	Setting	Funding/ conflicts of interest	Notes
Wu, 2013[79]	'… articles [that provided an] evaluation of procalcitonin alone or compared with other laboratory markers, such as CRP, to diagnose bacterial pneumonia in patients with H1N1 influenza infection'	MEDLINE, EMBASE and the Cochrane Library (November 2011)	QUADAS	6	Procalcitonin	Bacterial pneumonia	6	Adults	All diagnosed with H1N1 flu	Predominantly ICU or inpatient	Funding information not reported. The authors declare no conflicts of interest	Two studies in emergency department or outpatient Superseded by Gentilotti 2022[33]

DART, Documentation and Appraisal Review Tool; DFA, direct fluorescence antigen; DIA, digital immunoassay; EU, European Union; FDA, Food and Drug Administration; hMPV, human metapneumovirus; ICU, intensive care unit; LRTI, lower respiratory tract infection; NAAT, nucleic acid amplification test; POCT, point-of-care test; RADT, rapid antigen detection tests; RFT, rapid flu test; RIDT, rapid influenza diagnostic test; RTI, respiratory tract infection; STARD, Standards for Reporting of Diagnostic Accuracy; URTI, upper respiratory tract infection.

Appendix 3

TABLE 3 Results and GRADE assessments for symptoms and signs to diagnose bacterial infection

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
Signs and symptoms										
Cough	Gentilotti 2022[33]	13 (8423)	Sensitivity	89.1% (66.4 to 97.1)	Serious[a]	Not serious[b]	Unable to assess[c]	Very serious[d]	Undetected	Very low
			Specificity	13.4% (2.5 to 48.4)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
Sputum production	Gentilotti 2022[33]	7 (6392)	Sensitivity	63.9% (40.5 to 82.1)	Serious[a]	Not serious[b]	Unable to assess[c]	Serious[e]	Undetected	Low
			Specificity	45.3% (25.9 to 66.3)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
Discoloured sputum	Gentilotti 2022[33]	9 (3014)	Sensitivity	54.0% (39.8 to 67.7)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	53.0% (39.0 to 66.5)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
Purulent sputum (to detect bacterial exacerbations in people with COPD)	Pazmany 2021[36]	3 (259)	Sensitivity	71% (42 to 90)	Serious[f]	No serious	Not serious	Very serious[d]	Undetected	Very low
			Specificity	51% (30 to 73)	Serious[f]	No serious	Not serious	Not serious	Undetected	Moderate
Chest pain	Gentilotti 2022[33]	15 (8161)	Sensitivity	33.9% (21.5 to 49.0)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	73.0% (61.7 to 81.9)	Serious[a]	Not serious[b]	Unable to assess[c]	Serious[e]	Undetected	Low
Dyspnoea	Gentilotti 2022[33]	14 (6215)	Sensitivity	62.6% (53.3 to 71.1)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	45.5% (32.1 to 59.5)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
Sore throat	Gentilotti 2022[33]	5 (1096)	Sensitivity	32.6% (20.2 to 48.0)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	45.1% (33.1 to 57.6)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
Runny nose	Gentilotti 2022[33]	7 (4630)	Sensitivity	45.3% (37.3 to 53.4)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	41.8% (28.1 to 56.8)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
Myalgia	Gentilotti 2022[33]	6 (1430)	Sensitivity	41.6% (19.0 to 68.5)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	61.2% (40.7 to 78.4)	Serious[a]	Not serious[b]	Unable to assess[c]	Serious[e]	Undetected	Low

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TABLE 3 Results and GRADE assessments for symptoms and signs to diagnose bacterial infection (*continued*)

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
Chill	Gentilotti 2022[33]	8 (1933)	Sensitivity	45.7% (31.5 to 60.8)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	60.2% (48.5 to 70.8)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
Diarrhoea	Gentilotti 2022[33]	5 (4268)	Sensitivity	10.8% (6.3 to 17.7)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	89.5% (75.4 to 95.9)	Serious[a]	Not serious[b]	Unable to assess[c]	Serious[e]	Undetected	Low
Impaired consciousness	Gentilotti 2022[33]	4 (3208)	Sensitivity	11.7% (9.3 to 14.5)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	92.9% (90.5 to 94.7)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
SpO_2	Gentilotti 2022[33]	6 (2821)	Sensitivity	22.8% (12.4 to 38.2)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	86.6% (80.7 to 90.9)	Serious[a]	Not serious[b]	Unable to assess[c]	Serious[e]	Undetected	Low
Fever > 37.8 °C	Gentilotti 2022[33]	17 (11,219)	Sensitivity	42.0% (26.7 to 58.9)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	80.4% (59.8 to 91.9)	Serious[a]	Not serious[b]	Unable to assess[c]	Very serious[d]	Undetected	Very low
Systolic BP	Gentilotti 2022[33]	4 (3262)	Sensitivity	9.6% (2.8 to 28.3)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	95.0% (80.7 to 98.8)	Serious[a]	Not serious[b]	Unable to assess[c]	Serious[e]	Undetected	Low
Tachycardia	Gentilotti 2022[33]	11 (9474)	Sensitivity	27.2% (15.1 to 43.9)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	84.2% (71.5 to 91.9)	Serious[a]	Not serious[b]	Unable to assess[c]	Very serious[d]	Undetected	Very low
Tachypnoea	Gentilotti 2022[33]	12 (10,351)	Sensitivity	27.9% (13.1 to 49.8)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	80.2% (58.2 to 92.2)	Serious[a]	Not serious[b]	Unable to assess[c]	Very serious[d]	Undetected	Very low

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
Reduced breath sounds	Gentilotti 2022[33]	4 (459)	Sensitivity	24.7% (8.3 to 54.4)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	89.0% (75.0 to 95.6)	Serious[a]	Not serious[b]	Unable to assess[c]	Serious[e]	Undetected	Low
Wheezing	Gentilotti 2022[33]	6 (2403)	Sensitivity	17.3% (9.6 to 29.2)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	86.4% (70.5 to 94.4)	Serious[a]	Not serious[b]	Unable to assess[c]	Very serious[d]	Undetected	Very low
Crackles	Gentilotti 2022[33]	10 (6175)	Sensitivity	40.3% (23.6 to 59.7)	Serious[a]	Not serious[b]	Unable to assess[c]	Not serious	Undetected	Moderate
			Specificity	83.1% (58.5 to 94.5)	Serious[a]	Not serious[b]	Unable to assess[c]	Very serious[d]	Undetected	Very low
Combinations of signs and symptoms										
Presence/absence of specific symptoms and signs	Schierenberg 2017[37]	6 (not reported)	Area under the curve	Ranged from 53% to 79% depending on model used	Not serious	Not serious	Serious[g]	Serious[e]	Serious[h]	Very low
Symptoms, signs and CRP										
Predicted risk threshold 2.5%	Minnaard 2017[34]	8 (5308)	Sensitivity	97% (95 to 98)	Not serious	Not serious	Unable to assess[c]	Not serious	Serious[h]	Moderate
			Specificity	36% (34 to 37)	Not serious	Not serious	Unable to assess[c]	Not serious	Serious[h]	Moderate
Predicted risk threshold 20%	Minnaard 2017[34]	8 (5308)	Sensitivity	70% (66 to 73)	Not serious	Not serious	Unable to assess[c]	Not serious	Serious[h]	Moderate
			Specificity	90% (89 to 91)	Not serious	Not serious	Unable to assess[c]	Serious[e]	Serious[h]	Low

a Serious risk of bias as majority of studies included had a high or unclear risk of bias in at least one QUADAS-2 domain.
b Rated as no serious risk of indirectness, as adult patients, attending primary, ambulatory or emergency care with symptoms of ARI were included. However, note that chest X-ray was used as the reference standard in many studies, which may not adequately distinguish between bacterial and viral pneumonia.
c No information on heterogeneity is provided, and no forest plots are available to assess inconsistency.
d Confidence interval crosses two decision thresholds (taken to be 90% and 75%).
e Confidence interval crosses one decision threshold (taken to be 90% and 75%).
f Two included studies at unclear risk of bias in patient selection, one included study at high risk and another at unclear risk of bias for patient flow and timing.
g Confidence intervals for individual studies do not overlap.
h Studies were only included if the authors were able to provide original individual participant data. Four studies were excluded, as the authors were unable to provide this, or did not reply to the request.

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TABLE 4 Results and GRADE assessments for host biomarkers

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
CRP										
CRP > 10 mg/l	Gentilotti 2022[33]	4 (944)	Sensitivity	92% (56 to 99)	Serious[a]	Not serious	Unable to assess[b]	Very Serious[c]	Undetected	Very low
			Specificity	43% (22 to 66)	Serious[a]	Not serious	Unable to assess[b]	Not serious	Undetected	Moderate
CRP > 20 mg/l	Gentilotti 2022[33]	5 (3531)	Sensitivity	83% (64 to 93)	Serious[a]	Not serious	Unable to assess[b]	Very Serious[c]	Undetected	Very low
			Specificity	55% (37 to 73)	Serious[a]	Not serious	Unable to assess[b]	Not serious	Undetected	Moderate
CRP > 20 mg/l (primary care only, adults and children)	Gentilotti 2022[33]	4 (3362)	Sensitivity	78% (57 to 90)	Serious[a]	Serious[d]	Unable to assess[b]	Very Serious[c]	Undetected	Very low
			Specificity	58% (36 to 78)	Serious[a]	Serious[d]	Unable to assess[b]	Serious[e]	Undetected	Very low
CRP > 50 mg/l	Gentilotti 2022[33]	5 (4219)	Sensitivity	77% (51 to 91)	Serious[a]	Not serious	Unable to assess[b]	Very Serious[c]	Undetected	Very low
			Specificity	74% (51 to 88)	Serious[a]	Not serious	Unable to assess[b]	Serious[e]	Undetected	Low
CRP > 100 mg/l	Gentilotti 2022[33]	6 (4418)	Sensitivity	52% (31 to 72)	Serious[a]	Not serious	Unable to assess[b]	Not serious	Undetected	Moderate
			Specificity	91% (79 to 97)	Serious[a]	Not serious	Unable to assess[b]	Serious[e]	Undetected	Low
Procalcitonin										
Procalcitonin > 0.1 mcg/ml	Gentilotti 2022[33]	4 (1092)	Sensitivity	74% (38 to 93)	Serious[a]	Not serious	Unable to assess[b]	Very serious[c]	Undetected	Very low
			Specificity	74% (36 to 94)	Serious[a]	Not serious	Unable to assess[b]	Very serious[c]	Undetected	Very low
Procalcitonin > 0.25 mcg/ml	Gentilotti 2022[33]	5 (4019)	Sensitivity	44% (14 to 79)	Serious[a]	Not serious	Unable to assess[b]	Serious[e]	Undetected	Low
			Specificity	89% (50 to 98)	Serious[a]	Not serious	Unable to assess[b]	Very serious[c]	Undetected	Very low
Procalcitonin > 0.50 mcg/ml (adults and children)	Gentilotti 2022[33]	4 (1195)	Sensitivity	44% (19 to 73)	Serious[a]	Serious[d]	Unable to assess[b]	Not serious	Undetected	Low
			Specificity	93% (43 to 100)	Serious[a]	Serious[d]	Unable to assess[b]	Very serious[c]	Undetected	Very low
TRAIL, IP-10 and CRP (ImmunoXpert)										
TRAIL, IP-10 and CRP to diagnose bacterial infection (adults and children)	Carlton 2021[32]	4 (1291)	Sensitivity	85% (75 to 91)	Serious[f]	Serious[g]	Not serious	Serious[e]	Undetected	Very low
			Specificity	86% (73 to 93)	Serious[f]	Serious[g]	Not serious	Very serious[c]	Undetected	Very low

TABLE 4 Results and GRADE assessments for host biomarkers (*continued*)

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
TRAIL, IP-10 and CRP to diagnose viral infection (adults and children)	Carlton 2021[32]	3 (989)	Sensitivity	90% (79 to 96)	Serious[f]	Serious[g]	Serious[h]	Serious[e]	Undetected	Very low
			Specificity	92% (83 to 96)	Serious[f]	Serious[g]	Not serious	Serious[e]	Undetected	Very low
CRP and MxA (FebriDx)										
CRP and MxA to diagnose bacterial infection (adults and children)	Carlton 2021[32]	4 (598)	Sensitivity	84% (75 to 90)	No serious	Serious[g]	No serious	Serious[e]	Undetected	Low
			Specificity	93% (90 to 95)	No serious	Serious[g]	No serious	Not serious	Undetected	Moderate
CRP and MxA to diagnose viral infection (adults and children)	Carlton 2021[32]	4 (583)	Sensitivity	87% (72 to 95)	No serious	Serious[g]	No serious	Very serious[c]	Undetected	Very low
			Specificity	82% (66 to 86)	No serious	Serious[g]	No serious	Serious[e]	Undetected	Low
Other host biomarkers										
CRP and neopterin to diagnose bacterial infection	Carlton 2021[32]	1 (198)	Sensitivity	80% (71 to 86)	Serious[i]	Serious[j]	Not serious	Serious[e]	Undetected	Very low
			Specificity	82% (71 to 89)	Serious[i]	Serious[j]	Not serious	Serious[e]	Undetected	Very low

a Serious risk of bias as majority of studies included had an unclear risk of bias in at least one QUADAS-2 domain.
b No information on heterogeneity is provided, and no forest plots are available to assess inconsistency.
c Confidence interval crosses two decision thresholds (taken to be 90% and 75%).
d Serious indirectness, as this analysis included adults and children.
e Confidence interval crosses one decision threshold (taken to be 90% and 75%).
f High or unclear risk of bias in at least one domain of every study. Majority of studies considered high risk of bias for at least one domain overall.
g Adults and children included in analysis. May include some participants who were hospitalised.
h Confidence intervals for individual studies do not overlap.
i Serious risk of bias in two QUADAS-2 domains.
j Serious indirectness, as samples were stored before analysis, and unclear whether neopterin can be measured at point of care.

This article should be referenced as follows: Webster KE, Parkhouse T, Dawson S, Jones HE, Brown EL, Hay AD, *et al*. Diagnostic accuracy of point-of-care tests for acute respiratory infection: a systematic review of reviews [published online ahead of print October 2 2024]. *Health Technol Assess* 2024. https://doi.org/10.3310/JLCP4570

DOI: 10.3310/JLCP4570

TABLE 5 Results and GRADE assessments for single pathogen tests for influenza and RSV

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
Single pathogen tests for influenza										
Immunochromatography	Gentilotti 2022[33]	15 (2897)	Sensitivity	65% (47 to 79)	Serious[a]	Not serious	Unable to assess[b]	Serious[c]	Undetected	Low
			Specificity	96% (92 to 98)	Serious[a]	Not serious	Unable to assess[b]	Not serious	Undetected	Moderate
Immunochromatography (adults and children, primary care only)	Gentilotti 2022[33]	11 (3351)	Sensitivity	56% (36 to 74)	Serious[a]	Serious[d]	Unable to assess[b]	Not serious	Undetected	Low
			Specificity	95% (89 to 98)	Serious[a]	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Very low
Immunochromatography (adults and children, emergency department only)	Gentilotti 2022[33]	25 (15,021)	Sensitivity	71% (60 to 80)	Not serious	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Low
			Specificity	98% (96 to 99)	Not serious	Serious[d]	Unable to assess[b]	Not serious	Undetected	Moderate
Immunochromatography (adults and children, outpatient department only)	Gentilotti 2022[33]	17 (6110)	Sensitivity	66% (55 to 76)	Not serious	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Low
			Specificity	97% (93 to 99)	Not serious	Serious[d]	Unable to assess[b]	Not serious	Undetected	Moderate
Direct immunofluorescence (adults and children)	Gentilotti 2022[33]	19 (7635)	Sensitivity	78% (67 to 86)	Serious[a]	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Very low
			Specificity	95% (90 to 98)	Serious[a]	Serious[d]	Unable to assess[b]	Not serious	Undetected	Low
Direct immunofluorescence (adults and children, emergency department only)	Gentilotti 2022[33]	5 (1314)	Sensitivity	82% (72 to 89)	Serious[a]	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Very low
			Specificity	96% (93 to 97)	Serious[a]	Serious[d]	Unable to assess[b]	Not serious	Undetected	Low
Optical immunoassay (adults and children)	Gentilotti 2022[33]	9 (3910)	Sensitivity	68% (51 to 81)	Serious[a]	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Very low
			Specificity	88% (81 to 93)	Serious[a]	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Very low
MariPOC test (adults and children)	Gentilotti 2022[33]	5 (1231)	Sensitivity	78% (61 to 89)	Serious[a]	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Very low
			Specificity	99% (97 to 99)	Serious[a]	Serious[d]	Unable to assess[b]	Not serious	Undetected	Low
Chemiluminescent neuraminidase assay (adults and children)	Gentilotti 2022[33]	4 (787)	Sensitivity	81% (51 to 94)	Serious[a]	Serious[d]	Unable to assess[b]	Very serious[e]	Undetected	Very low
			Specificity	82% (65 to 91)	Serious[a]	Serious[d]	Unable to assess[b]	Very serious[e]	Undetected	Very low

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
Nucleic acid amplification tests: standalone, single pathogen PCR (adults and children)	Gentilotti 2022[33]	30 (25,027)	Sensitivity	95.1% (89.3 to 97.8)	Serious[f]	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Very low
			Specificity	97.5% (95.5 to 98.7)	Serious[f]	Serious[d]	Unable to assess[b]	Not serious	Undetected	Low
Nucleic acid amplification tests: non-PCR-based (adults and children)	Gentilotti 2022[33]	23 (4863)	Sensitivity	92% (88 to 94)	Serious[f]	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Very low
			Specificity	98% (95 to 99)	Serious[f]	Serious[d]	Unable to assess[b]	Not serious	Undetected	Low
Nucleic acid amplification tests: non-PCR-based (adults and children, emergency department only)	Gentilotti 2022[33]	14 (3138)	Sensitivity	91% (87 to 94)	Serious[f]	Serious[d]	Unable to assess[b]	Serious[c]	Undetected	Very low
			Specificity	98% (95 to 99)	Serious[f]	Serious[d]	Unable to assess[b]	Not serious	Undetected	Low
Single pathogen tests for RSV										
Direct immunofluorescence	Onwuchekwa 2023[35]	1 (49)	Sensitivity	56% (31 to 78)	Not serious	Serious[g]	Not serious	Very serious[h]	Undetected	Very low
			Specificity	100% (89 to 100)	Not serious	Serious[g]	Not serious	Very serious[h]	Undetected	Very low
Rapid antigen test	Onwuchekwa 2023[35]	1 (281)	Sensitivity	18% (12 to 27)	Serious[i]	Serious[j]	Not serious	Not serious	Undetected	Low
			Specificity	98% (86 to 100)	Serious[i]	Serious[j]	Not serious	Serious[c]	Undetected	Very low

a Serious risk of bias as majority of studies included had a high or unclear risk of bias in at least one QUADAS-2 domain.
b No information on heterogeneity is provided, and no forest plots are available to assess inconsistency.
c Confidence interval crosses one decision threshold (taken to be 90% and 75%).
d Serious indirectness, as this analysis included adults and children.
e Confidence interval crosses two decision thresholds (taken to be 90% and 75%).
f Serious risk of bias as majority of studies included had a high or unclear risk of bias in at least one QUADAS-2 domain. Note that this assessment was based on all nucleic acid amplification tests, not the specific studies included in this analysis.
g Specific tests used in this study unlikely to be suitable for a point-of-care setting.
h Confidence interval crosses one decision threshold, and number of participants included was extremely small.
i Three QUADAS-2 domains were rated as unclear risk of bias.
j Study included some retrospective (frozen) samples, and may have included hospitalised participants.

This article should be referenced as follows: Webster KE, Parkhouse T, Dawson S, Jones HE, Brown EL, Hay AD, *et al*. Diagnostic accuracy of point-of-care tests for acute respiratory infection: a systematic review of reviews [published online ahead of print October 2 2024]. *Health Technol Assess* 2024. https://doi.org/10.3310/JLCP4570

Appendix 4

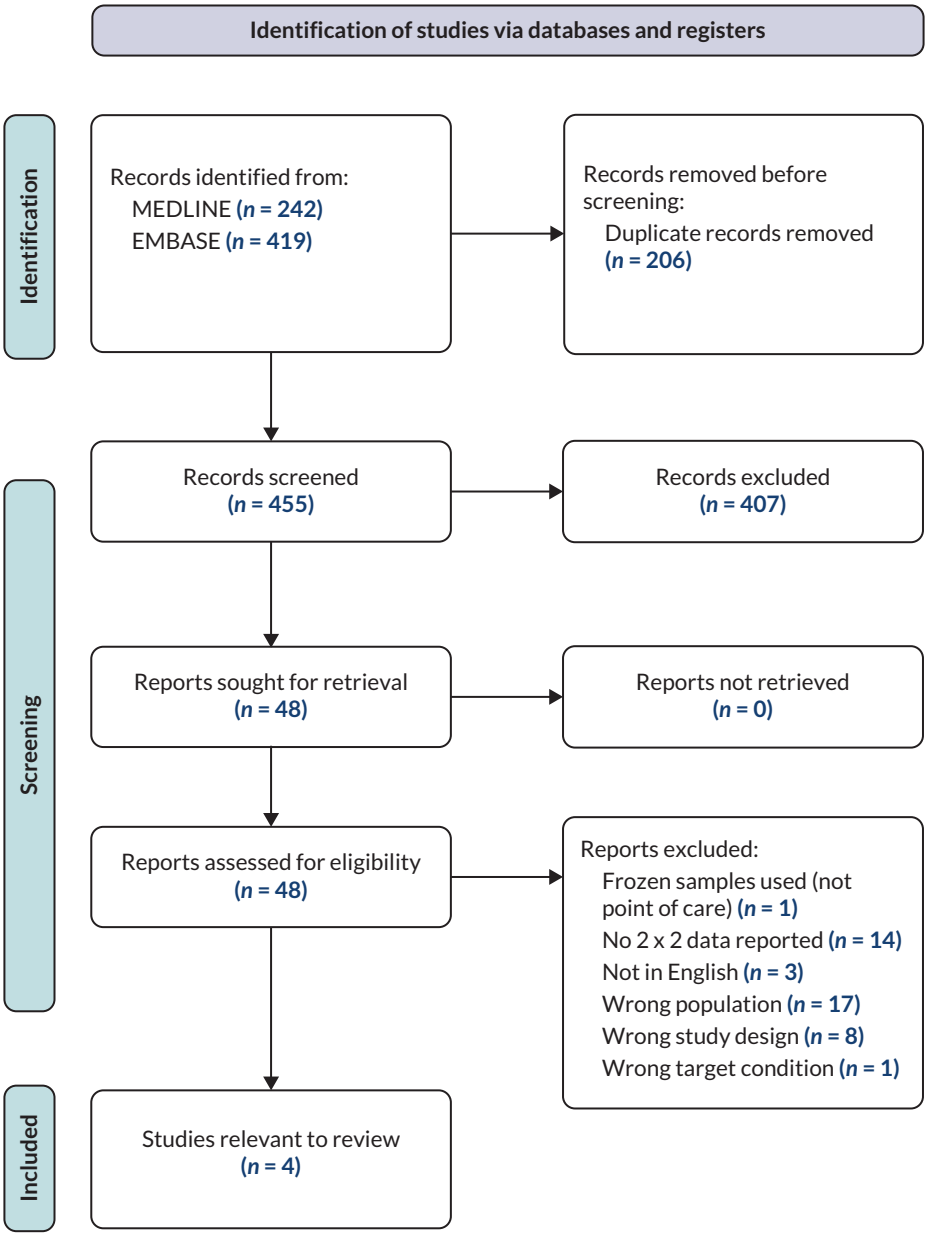

FIGURE 4 PRISMA flow diagram for white cell differential count.

TABLE 6 Included primary studies for white cell differential count

Reference	Population	Clinical features	Setting	Target condition assessed	Index tests	Reference standard	Outcomes reported	Funding/conflicts of interest
Castro-Guardiola 2000[40]	Adults (*n* = 284) 62% male. Mean age 57.2 years [standard deviation (SD) 20]	People who have been assessed by a clinician as having suspected pneumonia	Emergency department, Spain	Pneumonia	White blood cell count	Typical findings on a chest X-ray, plus at least two of the following features: • Respiratory symptoms • Fever > 38 °C • White cell count > 12 million/ml • Microbiological confirmation	Area under the curve 0.65	Not reported
Gulich 1999[43]	Adults (*n* = 179) 46.4% male. Mean age 34.3 years (SD 13.4)	People presenting with a sore throat	Primary care, Germany	Bacterial pharyngitis	White blood cell count	Culture of group A or C beta-haemolytic streptococci, or *Haemophilus influenzae*	Area under the curve 0.68	The study was supported by Bundesverband der Betriebskrankenkassen and by Nycomed GmbH, Munich
Holm 2007[41]	Adults (*n* = 364) 47% male. Median age 50 years	People with symptoms of a lower respiratory tract infection	Primary care, Denmark	Pneumonia	White cell count ≥ 10 million/ml	Chest X-ray	Sensitivity 46% and specificity 80% (no confidence intervals reported)	Financial support received from the various contributors, including The Danish Lung Association, The Danish Medical Research Association and the Institute of Clinical Research. The authors declare no conflicts of interest
Liu 2013[42]	Adults (*n* = 500) 58% male. Mean age 42.7 years (range 18–94)	People with a diagnosis of community-acquired pneumonia, based on findings from a chest X-ray and symptoms	Outpatient, China	Bacterial pneumonia	White cell count < 4 million/ml, 4–10 million/ml or > 10 million/ml	Microbiological culture and PCR	2×2 data, sufficient to calculate sensitivity and specificity to diagnose bacterial infection at different thresholds of white cell count	Supported by grants from Beijing Science and Technology Key Projects Foundation. The authors declare no conflicts of interest

continued

This article should be referenced as follows: Webster KE, Parkhouse T, Dawson S, Jones HE, Brown EL, Hay AD, *et al*. Diagnostic accuracy of point-of-care tests for acute respiratory infection: a systematic review of reviews [published online ahead of print October 2 2024]. *Health Technol Assess* 2024. https://doi.org/10.3310/JLCP4570

DOI: 10.3310/JLCP4570

TABLE 6 Included primary studies for white cell differential count (*continued*)

Reference	Population	Clinical features	Setting	Target condition assessed	Index tests	Reference standard	Outcomes reported	Funding/conflicts of interest
							< 4 million/ml Sensitivity 10.07 (95% CI 5.74 to 16.06) Specificity 94.59 (95% CI 91.68 to 96.71) **4–10 million/ml** Sensitivity 71.14 (95% CI 63.16 to 78.26) Specificity 31.34 (95% CI 26.52 to 36.48) **> 10 million/ml** Sensitivity 18.79 (95% CI 12.87 to 26) Specificity 74.07 (95% CI 69.16 to 78.58)	

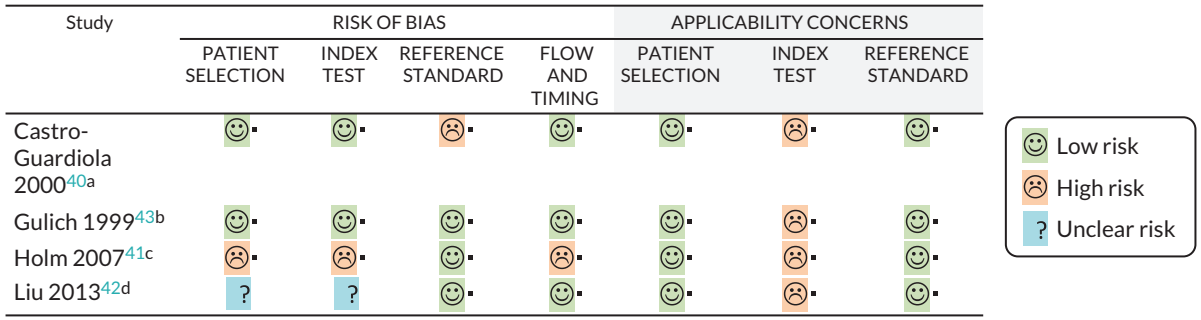

FIGURE 5 QUADAS-2 assessments: white cell differential count. [a]Index test was incorporated as part of the reference standard, and was also not conducted in a point-of-care setting (central laboratory analysis of white cell count). [b]Index test was not conducted in a point-of-care setting (central laboratory analysis of white cell count). [c]People with more severe illness (requiring hospital admission) were excluded from participation. Index test was not conducted in a point-of-care setting (central laboratory analysis of white cell count). Participants with possible malignancy were excluded from analysis. [d]Unclear whether sampling was consecutive/random. Unclear how white cell count was assessed, but not conducted in a point-of-care setting.

Appendix 5

TABLE 7 Results and GRADE assessments for white cell differential count

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
White cell differential count										
White cell count to diagnose pneumonia	Castro-Guardiola 2000,[40] Holm 2007,[41] Liu 2013[42]	3 (1148)	Two studies reported sensitivity estimates ranging from 10.1% to 71.1%, and specificity estimates ranging from 31.3% to 94.6%, depending on the threshold used (see *Appendix 4*, *Table 6* for full details). One study reported an area under the curve of 0.65		Serious[a]	Serious[b]	Serious[c]	Very serious[d]	Undetected	Very low
White cell count to diagnose bacterial pharyngitis	Gulich 1999[43]	1 (179)	Area under the curve	0.68 (no confidence intervals)	Not serious	Serious[b]	Not serious	Serious[e]	Undetected	Low

a High or unclear risk of bias in at least one domain of every study. Majority of studies considered high risk of bias for at least one domain overall.
b All index tests were conducted in a laboratory setting, not using a point-of-care device.
c Confidence intervals for individual studies do not overlap.
d Considerable variation in estimates from individual studies. Unable to provide a pooled estimate across studies, due to variety of results presented.
e Unable to assess imprecision as no confidence intervals were presented.

This article should be referenced as follows: Webster KE, Parkhouse T, Dawson S, Jones HE, Brown EL, Hay AD, *et al.* Diagnostic accuracy of point-of-care tests for acute respiratory infection: a systematic review of reviews [published online ahead of print October 2 2024]. *Health Technol Assess* 2024. https://doi.org/10.3310/JLCP4570

Appendix 6

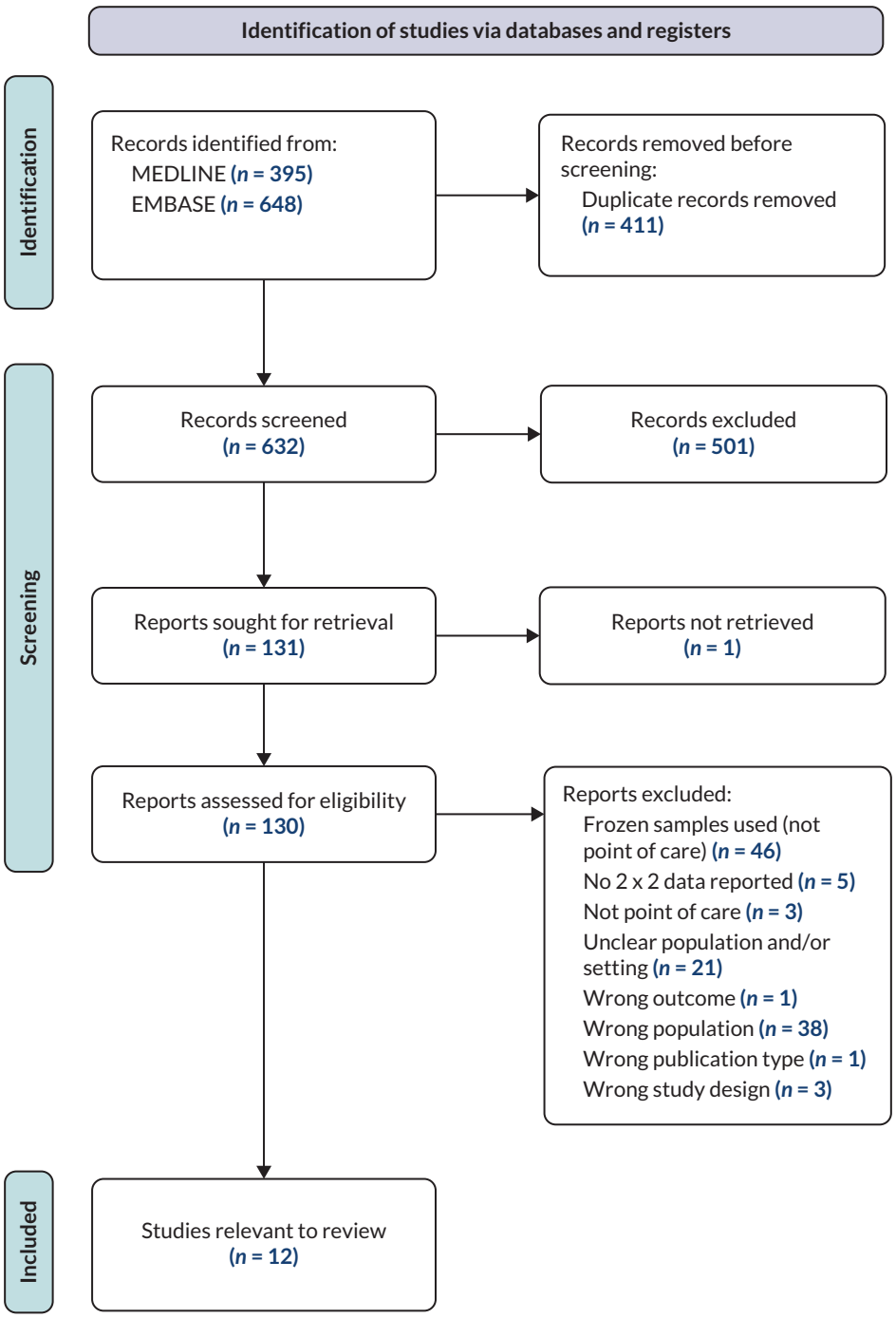

FIGURE 6 PRISMA flow diagram for multiplex PCR tests.

TABLE 8 Included primary studies for multiplex tests

Reference	Population	Clinical features	Setting	Target condition assessed	Index tests	Reference standard	Notes	Funding/conflicts of interest
Boku 2013[51]	Adults. Mean age 34.4 years (range 20–63) 53.1% male	Symptoms of acute respiratory infection, or presence of fever and known contact with influenza	Hospital outpatient setting, Japan	Flu A/B	Verigene system RV + on naso-pharyngeal swabs	Viral culture plus laboratory PCR		Not reported
Escarate 2022[44]	Adults. Aged ≥ 65 years. Sex not reported	Tested due to an outbreak of a respiratory illness. Symptoms of acute respiratory infection	Outpatient/ primary care (long-term care facilities), Australia	Flu A, Flu B and RSV	Xpert Xpress Flu/RSV on naso-pharyngeal swabs or combined nose and throat swabs	Primary reference standard: PCR from central laboratory Secondary reference standard: included expert opinion assessment of discordant specimens	Note that data are not included in the meta-analysis, as the authors only report specificity (not sensitivity) and the bivariate model requires both parameters	The authors declare no conflicts of interest
Farfour 2022[45]	Adults. Age not reported. Sex not reported	Suspected viral respiratory infection	Emergency department, France	Flu A, RSV	Idylla SARS CoV/ Flu/RSV on nasopharyngeal swabs	Laboratory-based multiplex PCR		No external funding received
Hansen 2018[52]	Adults and children (children comprised 20% of total population) Age not reported. Sex not reported	Presenting with at least one sign of influenza	Emergency department, USA	Flu A/B	Cobas Liat Influenza A/B assay on nasopharyngeal swabs	Primary reference standard: PCR from central laboratory. Secondary reference standard: included analysis of discordant specimens with a second multiplex rapid test		Partial funding for this study was provided by an unrestricted educational grant from Roche molecular to GTH and from the Minneapolis Medical Research
Maignan 2016[46]	Adults. Median 70 years (IQR 44–84). 51% male	Presenting with fever and at least one sign of a respiratory tract infection	Emergency department, France	Flu A, Flu B, Flu A/B	Cobas Liat Influenza A/B assay on nasopharyngeal swabs	Primary reference standard: PCR from central laboratory, with analysis of discordant results with Xpert Xpress Flu/RSV assay and results from the national influenza virus reference centre		Partially funded by Roche Diagnostics. Roche Diagnostics had no access to the data and were not involved in the interpretation of the data or the writing of the manuscript

continued

This article should be referenced as follows: Webster KE, Parkhouse T, Dawson S, Jones HE, Brown EL, Hay AD, *et al.* Diagnostic accuracy of point-of-care tests for acute respiratory infection: a systematic review of reviews [published online ahead of print October 2 2024]. *Health Technol Assess* 2024. https://doi.org/10.3310/JLCP4570

DOI: 10.3310/JLCP4570

TABLE 8 Included primary studies for multiplex tests (*continued*)

Reference	Population	Clinical features	Setting	Target condition assessed	Index tests	Reference standard	Notes	Funding/conflicts of interest
Morris 2021[47]	Adults and children included in the study. Data were extracted which relate to adults only. Median 55 years (IQR 29–73). 44.7% male	Symptoms of acute respiratory infection	Emergency department, respiratory admissions unit and bone marrow transplant unit were included in the study, UK. Extracted data relate to adults in an emergency department setting only	Flu A, RSV	Xpert Xpress Flu/RSV. Sample type unclear	Primary reference standard: laboratory-based PCR		No funding required. The authors declare no conflicts of interest
Peretz 2020[53]	Adults. Aged 18 to 97. 57% male	People with suspected influenza	Emergency department, Israel	Flu A/B	Xpert Xpress Flu A/B and Simplexa Flu A/B and RSV on nasopharyngeal swabs	Comparator: rapid antigen test	Note that this study provides data on concordance between multiplex PCR and a rapid antigen test. However, as the rapid antigen test is not regarded as a reference standard by the authors, these data were not included in the analysis **Comparison of Xpert Xpress Flu with Influ A+B K-SeT rapid antigen test:** Percentage positive agreement: 96.3% (87.3 to 99.6) Percentage negative agreement: 95.7% (90.2 to 98.6) **Comparison of Simplexa Flu A/B and** RSV **with Influ A+B K-SeT rapid antigen test:** Percentage positive agreement: 96.3% (87.3 to 99.6) Percentage negative agreement: 97.4% (92.5 to 99.5)	No funding required. The authors declare no conflicts of interest

Reference	Population	Clinical features	Setting	Target condition assessed	Index tests	Reference standard	Notes	Funding/conflicts of interest
Tanei 2014[54]	Adults. Median 30.5 years, range 20–63. 42.7% male	Symptoms of acute respiratory infection plus a fever of ≥ 37 °C	Outpatients in a hospital general medical department, Japan	Flu A/B	Verigene RV+	Primary reference standard: rapid antigen test	Note that this study provides data on concordance between multiplex PCR and a rapid antigen test. However, as the rapid antigen test is not regarded as a reference standard by the authors, these data were not included in the analysis **Comparison of Verigene RV+ with RapidTesta FLU II rapid antigen test:** Percentage positive agreement: 95.6% (84.9 to 99.5) Percentage negative agreement:56.8% (39.5 to 72.9)	This study was supported in part by a Grant-in-Aid from the MEXT Strategic Research Foundation Project for Private Universities. The authors declare no conflicts of interest
Valentin 2019[48]	Adults. Age not reported. Sex not reported	Adult patients suffering from acute febrile respiratory tract infection with at least one risk factor for complications of seasonal influenza	Emergency department, Austria	Flu A, Flu B, Flu A/B	Xpert Xpress Flu/RSV and Cobas Liat Influenza A/B assay on nasopharyngeal swabs	Primary reference standard: laboratory-based PCR		Reagents used for the tests were partly supplied by Roche and Cepheid. No other funding was received. The authors declare no conflicts of interest
Yin 2022[49]	Adults and children (23% of participants were children). Age not reported. 58% male	Symptoms of acute respiratory infection	Emergency department, Belgium	Flu A, Flu B, RSV	Cobas Liat Influenza A/B assay on nasopharyngeal swabs	Primary reference standard: composite of rapid antigen tests plus culture. Samples were considered positive if they were positive on at least two of the three tests used (including the index test)		Roche Diagnostics supplied instruments and reagents needed for this study. No personal grants or funding was received by the authors for this study. The authors declare no conflicts of interest
Youngs 2019[50]	Adults. Age not reported. Sex not reported	Suspected influenza	Emergency department, UK	Flu A, Flu B, Flu A/B	Cobas Liat Influenza A/B assay on throat swabs	Primary reference standard: composite of laboratory-based PCR method and an alternative multiplex test (Xpert Xpress Flu/RSV). Secondary reference standard: as above, but including expert opinion		The authors declare no conflicts of interest

continued

This article should be referenced as follows: Webster KE, Parkhouse T, Dawson S, Jones HE, Brown EL, Hay AD, *et al*. Diagnostic accuracy of point-of-care tests for acute respiratory infection: a systematic review of reviews [published online ahead of print October 2 2024]. *Health Technol Assess* 2024. https://doi.org/10.3310/JLCP4570

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DOI: 10.3310/JLCP4570

TABLE 8 Included primary studies for multiplex tests (*continued*)

Reference	Population	Clinical features	Setting	Target condition assessed	Index tests	Reference standard	Notes	Funding/conflicts of interest
Zuurbier 2022[55]	Adults. 45.9% male. Median age 75 years (IQR 67–80)	Symptoms of acute respiratory tract infection	Home setting/ primary care, Belgium, Netherlands, and UK	RSV	Xpert Xpress Flu/RSV on nasopharyngeal swabs	Primary reference standard: laboratory-based PCR		RESCEU has received funding from the Innovative Medicines Initiative 2 Joint Undertaking. Several authors declare they received personal fees from Roche, GSK and other pharmaceutical companies, outside the submitted work. Additionally, University Medical Centre Utrecht received funding from various pharmaceutical companies

IQR, interquartile range; MEXT, Ministry of Education, Culture, Sports, Science and Technology.

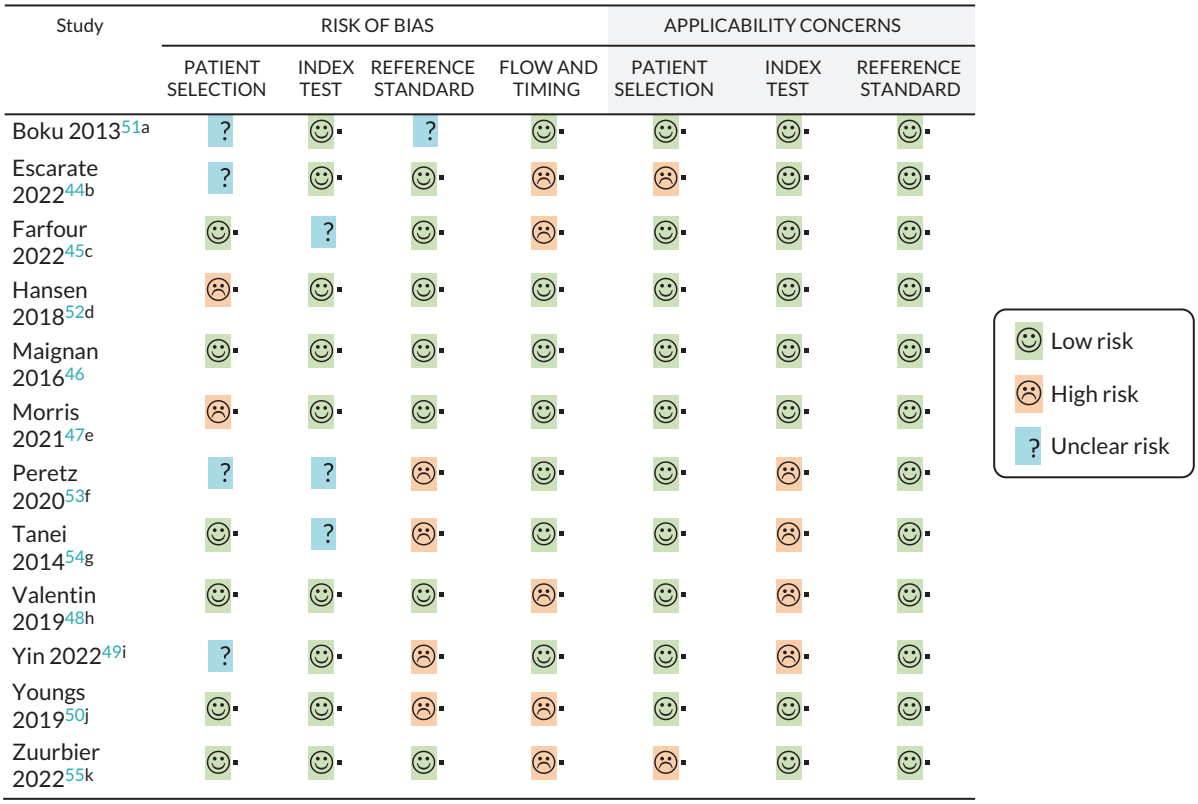

FIGURE 7 QUADAS-2 assessments: multiplex PCR tests. [a]Unclear if a consecutive/random sample of participants was enrolled. Unclear if reference standard results were interpreted without knowledge of the index test. [b]Unclear if a consecutive/random sample of participants was enrolled. Unclear if all participants would have attended for assessment by a healthcare provider if they were not enrolled in the study (care home residents). Some participants did not receive a reference standard and were excluded from the analysis. [c]Unclear whether the index test was carried out at point of care. Some participants were excluded from analysis. [d]Unclear if a consecutive/random sample of participants was enrolled. Participants with multiple conditions were excluded from this study. [e]Unclear if a consecutive/random sample of participants was enrolled. Staff were asked to collect samples 'as per usual practice'. No guidance on specific inclusion/exclusion criteria for sampling. [f]Unclear if a consecutive/random sample of participants was enrolled. Rapid antigen test was used as the reference standard. Unclear if the index test was interpreted without knowledge of the reference standard. Index test not actually conducted in a point-of-care setting. [g]Unclear if the index test was interpreted without knowledge of the reference standard. Rapid antigen test was used as the reference standard. Index test not actually conducted in a point-of-care setting. [h]Not all participants were included in the analysis. Index test not analysed at point of care. [i]Unclear if a consecutive/random sample of participants was enrolled. Index tests were a component of the reference standard. Not all samples analysed in point-of-care setting. [j]Reference standard results were interpreted with knowledge of the index test results. High number of exclusions. [k]Participants were undergoing home assessment for respiratory illness as part of a larger study. Many would not have sought medical care had it not been that they were participating in this study. High number of exclusions from analysis.

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Appendix 7

TABLE 9 Results and GRADE assessments for multiplex tests for influenza A

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
Multiplex tests										
All multiplex tests for influenza A	Escarate 2022,[44] Farfour 2022,[45] Morris 2021,[47] Maignan 2016,[46] Valentin 2019[48] (two tests included), Yin 2022,[49] Youngs 2019[50]	Eight studies (2212)	Sensitivity	98.2% (90.7 to 99.7)	Serious[a]	Not serious	Serious[b]	Not serious	Undetected	Low
			Specificity	98.6% (96.6 to 99.4)	Serious[a]	Not serious	Serious[b]	Not serious	Undetected	Low
Cobas Liat tests for influenza A	Maignan 2016,[46] Valentin 2019,[48] Yin 2022,[49] Youngs 2019[50]	Four studies (1259)	Sensitivity	99.8% (18.8 to 100)	Not serious	Not serious	Serious[b]	Very serious[c]	Undetected	Very low
			Specificity	97.9 (94.0 to 99.3)	Not serious	Not serious	Serious[b]	Not serious	Undetected	Moderate
Xpert Xpress tests for influenza A	Escarate 2022,[44] Morris 2021,[47] Valentin 2019[48]	Three studies (754)	Sensitivity	97.0% (92.9 to 98.7)	Serious[a]	Not serious	Not serious	Not serious	Undetected	Moderate
			Specificity	98.5% (96.2 to 99.4)	Serious[a]	Not serious	Not serious	Not serious	Undetected	Moderate

a High or unclear risk of bias in at least one domain of every study. Majority of studies considered high risk of bias for at least one domain overall.
b Prediction region wide, with relatively large tau^2.
c Confidence interval crosses two decision thresholds (taken to be 90% and 75%).

Test	Study	TP	FN	TN	FP	Sens (95% CI)	Spec (95% CI)
Cobas Liat flu A/B & RSV	Youngs 2019[49]	44	9	452	6	0.83 (0.71 to 0.91)	0.99 (0.97 to 0.99)
	Yin 2022[48]	49	0	221	23	1.00 (0.93 to 1.00)	0.91 (0.86 to 0.94)
Cobas Liat flu A/B	Maignan 2016[45]	27	0	159	1	1.00 (0.88 to 1.00)	0.99 (0.97 to 1.00)
	Valentin 2019[47]	42	0	223	3	1.00 (0.92 to 1.00)	0.99 (0.96 to 1.00)
	Pooled					**1.00 (0.19 to 1.00)**	**0.98 (0.94 to 0.99)**
Idylla SARS CoV/flu/RSV	Farfour 2022[44]	9	1	189	0	0.90 (0.60 to 0.99)	1.00 (0.98 to 1.00)
Xpert Xpress Flu/RSV	Morris 2021[46]	93	4	249	5	0.96 (0.90 to 0.98)	0.98 (0.95 to 0.99)
	Escarate 2022[43]	25	0	70	3	1.00 (0.87 to 1.00)	0.96 (0.89 to 0.99)
	Valentin 2019[47]	42	1	261	1	0.98 (0.88 to 1.00)	1.00 (0.98 to 1.00)
Pooled						**0.98 (0.91 to 1.00)**	**0.99 (0.97 to 0.99)**
						$\tau^2 = 2.44$	$\tau^2 = 1.05$

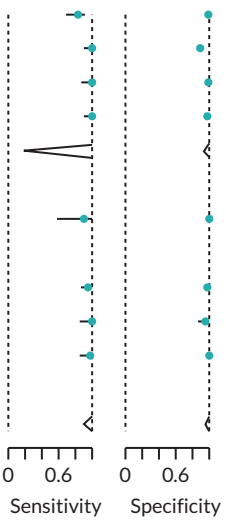

FIGURE 8 Meta-analysis for influenza A.

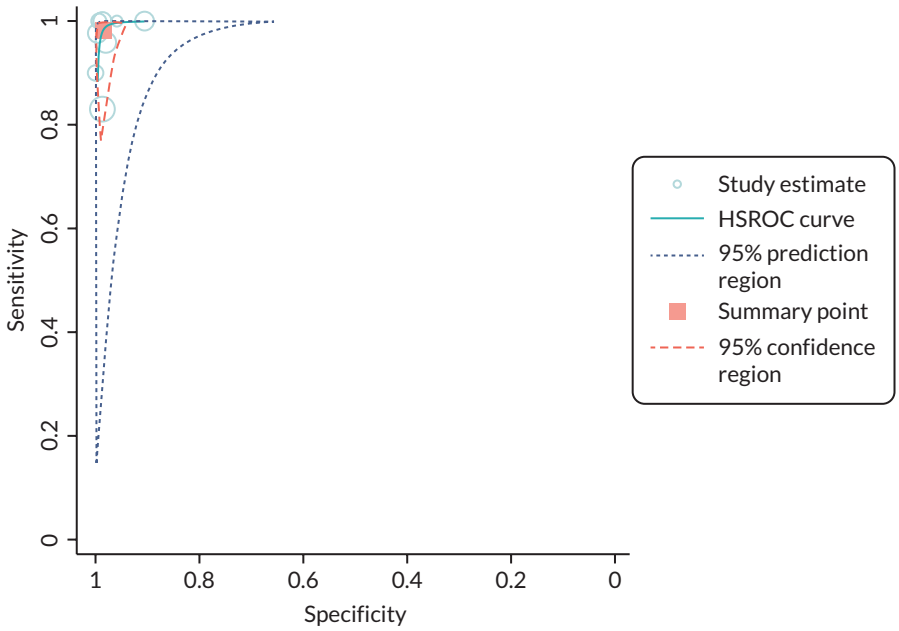

FIGURE 9 Influenza A data and meta-analysis results in ROC space.

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Appendix 8

TABLE 10 Results and GRADE assessments for multiplex tests for influenza B

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
Multiplex tests										
All multiple × tests for influenza B	Escarate 2022,[44] Maignan 2016,[46] Valentin 2019[48] (two tests included), Yin 2022,[49] Youngs 2019[50]	Six studies (1823)	Sensitivity	94.5% (88.6 to 97.5)	Serious[a]	Not serious	Serious[b]	Serious[c]	Undetected	Very low
			Specificity	99.1 (98.1 to 99.6)	Serious[a]	Not serious	Serious[b]	Not serious	Undetected	Low
Cobas Liat tests for influenza B	Maignan 2016,[46] Valentin 2019,[48] Yin 2022,[49] Youngs 2019[50]	Four studies (1420)	Sensitivity	92.9% (84.3 to 96.9)	Not serious	Not serious	Serious[b]	Serious[c]	Undetected	Low
			Specificity	99.0% (97.6 to 99.6)	Not serious	Not serious	Serious[b]	Not serious	Undetected	Moderate
Xpert Xpress tests for influenza B	Escarate 2022,[44] Valentin 2019[48]	Two studies (403)	Sensitivity	96.4% (90.7 to 99.0)	Serious[a]	Not serious	Not serious	Not serious	Undetected	Moderate
			Specificity	99.4% (97.4 to 99.8)	Serious[a]	Not serious	Not serious	Not serious	Undetected	Moderate

a High or unclear risk of bias in at least one domain of every study. Majority of studies considered high risk of bias for at least one domain overall.
b Prediction region wide, with relatively large tau^2.
c Confidence interval crosses one decision threshold (taken to be 90% and 75%).

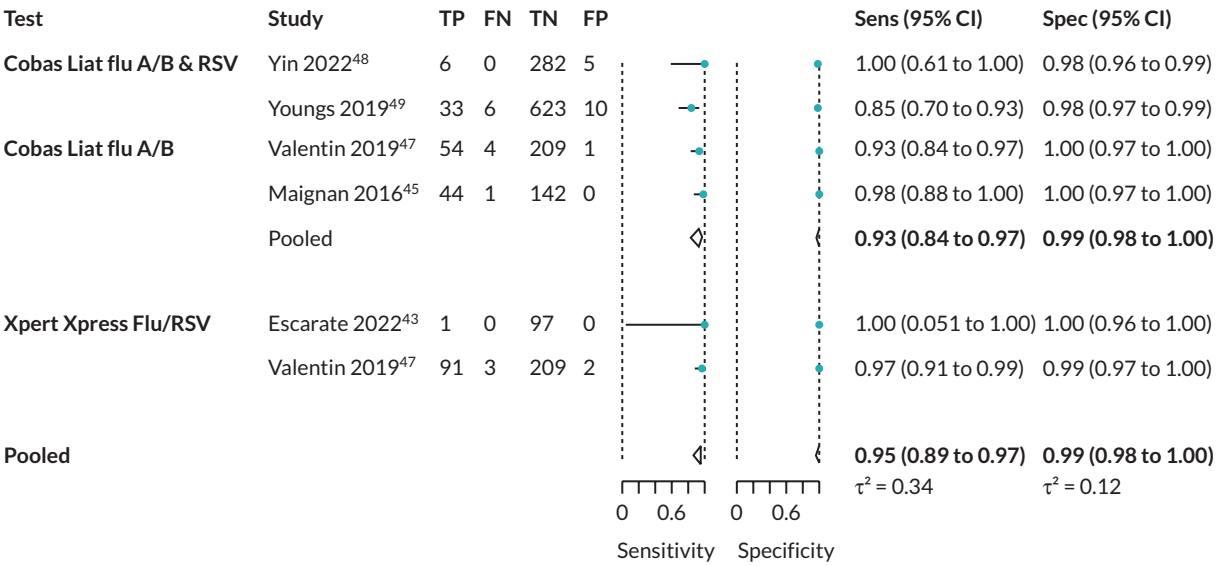

FIGURE 10 Meta-analysis for influenza B.

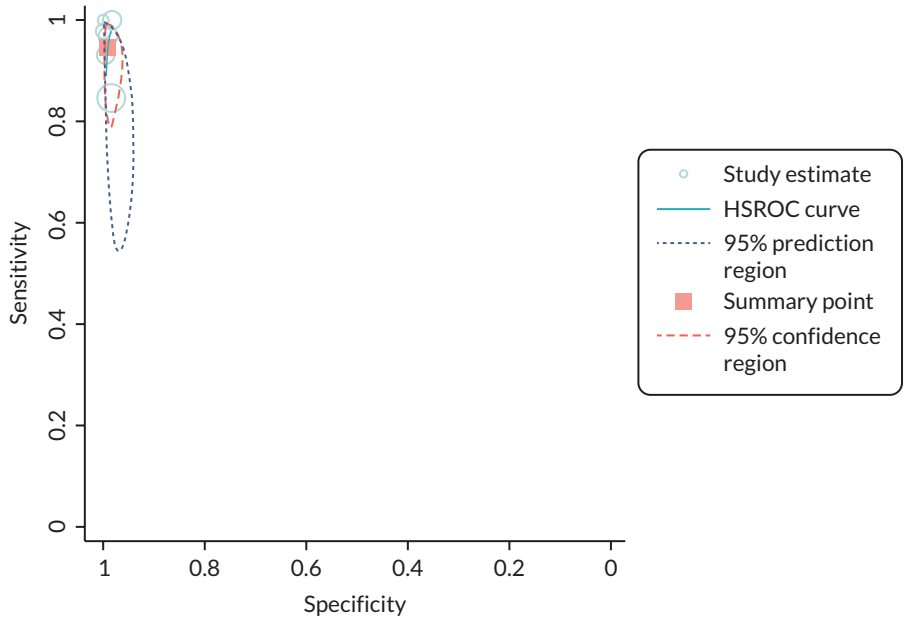

FIGURE 11 Influenza B data and meta-analysis results in ROC space.

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Appendix 9

TABLE 11 Results and GRADE assessments for multiplex tests for influenza A or B

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
Multiplex tests										
All multiple × tests for influenza A/B	Boku 2013,[51] Escarate 2022,[44] Hansen 2018,[52] Maignan 2016,[46] Valentin 2019[48] (two tests included), Yin 2022,[49] Youngs 2019[50]	Eight studies (2162)	Sensitivity	97.4% (92.9 to 99.0)	Serious[a]	Not serious	Serious[b]	Not serious	Undetected	Low
			Specificity	97.0% (94.5 to 98.4)	Serious[a]	Not serious	Serious[b]	Not serious	Undetected	Low
Cobas Liat tests for influenza A/B	Hansen 2018,[52] Maignan 2016,[46] Valentin 2019,[48] Yin 2022,[49] Youngs 2019[50]	Five studies (1712)	Sensitivity	97.1% (88.6 to 99.3)	Not serious	Not serious	Serious[b]	Serious[c]	Undetected	Low
			Specificity	96.8% (93.2 to 98.5)	Not serious	Not serious	Serious[b]	Not serious	Undetected	Moderate
Xpert Xpress tests for influenza A/B	Escarate 2022,[44] Valentin 2019[48]	Two studies (403)	Sensitivity	97.5% (93.6 to 99.1)	Serious[a]	Not serious	Not serious	Not serious	Undetected	Moderate
			Specificity	97.5% (94.5 to 98.9)	Serious[a]	Not serious	Not serious	Not serious	Undetected	Moderate

a High or unclear risk of bias in at least one domain of every study. Majority of studies considered high risk of bias for at least one domain overall.
b Prediction region wide, with relatively large tau^2.
c Confidence interval crosses one decision threshold (taken to be 90% and 75%).

Test	Study	TP	FN	TN	FP	Sens (95% CI)	Spec (95% CI)
Cobas Liat flu A/B & RSV	Yin 2022[48]	55	0	210	28	1.00 (0.93 to 1.00)	0.88 (0.84 to 0.92)
	Youngs 2019[49]	76	15	565	16	0.84 (0.75 to 0.90)	0.97 (0.96 to 0.98)
Cobas Liat flu A/B	Maignan 2016[45]	71	1	114	1	0.99 (0.93 to 1.00)	0.99 (0.95 to 1.00)
	Valentin 2019[47]	96	4	164	4	0.96 (0.90 to 0.98)	0.98 (0.94 to 0.99)
	Hansen 2018[51]	81	3	204	4	0.96 (0.90 to 0.99)	0.98 (0.95 to 0.99)
	Pooled					**0.97 (0.89 to 0.99)**	**0.97 (0.93 to 0.99)**
Verigene system RV+	Boku 2013[50]	35	1	11	0	0.97 (0.86 to 1.00)	1.00 (0.74 to 1.00)
Xpert Xpress Flu/RSV	Escarate 2022[43]	26	0	69	3	1.00 (0.87 to 1.00)	0.96 (0.88 to 0.99)
	Valentin 2019[47]	133	4	165	3	0.97 (0.93 to 0.99)	0.98 (0.95 to 0.99)
Pooled						**0.97 (0.93 to 0.99)** $\tau^2 = 1.11$	**0.97 (0.95 to 0.98)** $\tau^2 = 0.45$

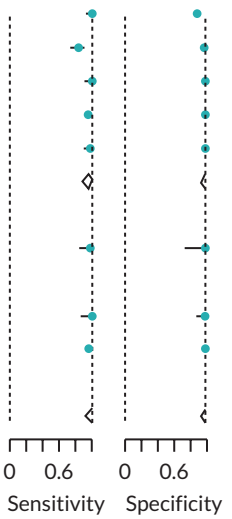

FIGURE 12 Meta-analysis for influenza A or B.

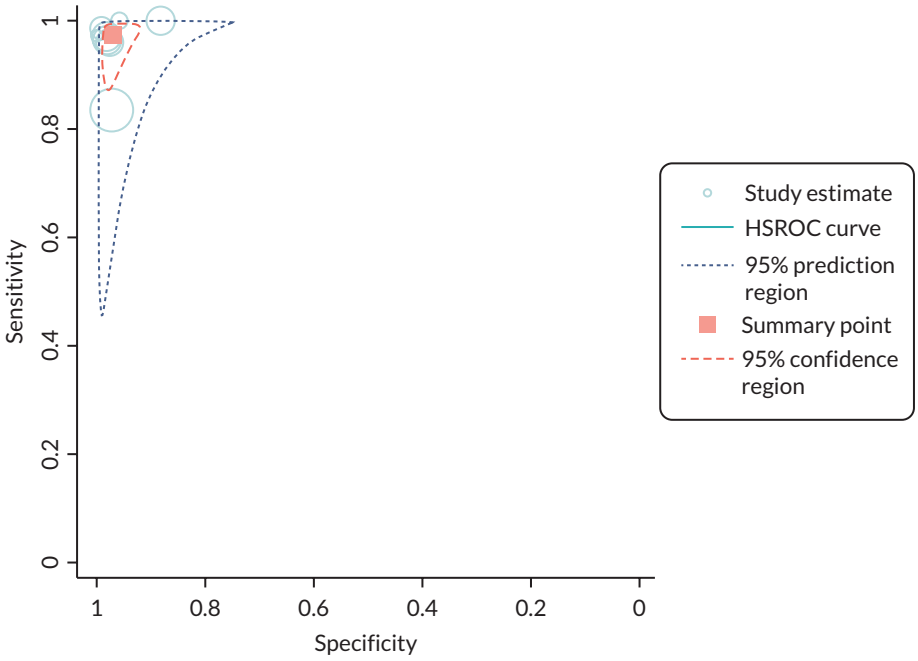

FIGURE 13 Influenza A/B data and meta-analysis results in ROC space.

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Appendix 10

TABLE 12 Results and GRADE assessments for multiplex tests for RSV

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Certainty of the body of evidence
Multiplex tests										
All multiplex tests for RSV	Farfour 2022,[45] Morris 2021,[47] Yin 2022,[49] Youngs 2019,[50] Zuurbier 2022[55]	Five studies (2273)	Sensitivity	84.9% (73.5 to 91.9)	Serious[a]	Not serious	Not serious	Very serious[b]	Undetected	Very low
			Specificity	99.5% (99.1 to 99.7)	Serious[a]	Not serious	Not serious	Not serious	Undetected	Moderate
Cobas Liat tests for RSV	Yin 2022,[49] Youngs 2019[50]	Two studies (965)	Sensitivity	86.7% (59.5 to 96.6)	Serious[a]	Not serious	Not serious	Very serious[b]	Undetected	Very low
			Specificity	99.3% (98.5 to 99.6)	Serious[a]	Not serious	Not serious	Not serious	Undetected	Moderate
Xpert Xpress tests for RSV	Morris 2021,[47] Zuurbier 2022[55]	Two studies (1109)	Sensitivity	84.5% (69.4 to 92.9)	Serious[a]	Not serious	Not serious	Very serious[b]	Undetected	Very low
			Specificity	99.6% (99.0 to 99.9)	Serious[a]	Not serious	Not serious	Not serious	Undetected	Moderate

a High or unclear risk of bias in at least one domain of every study. Majority of studies considered high risk of bias for at least one domain overall.
b Confidence interval crosses two decision thresholds (taken to be 90% and 75%).

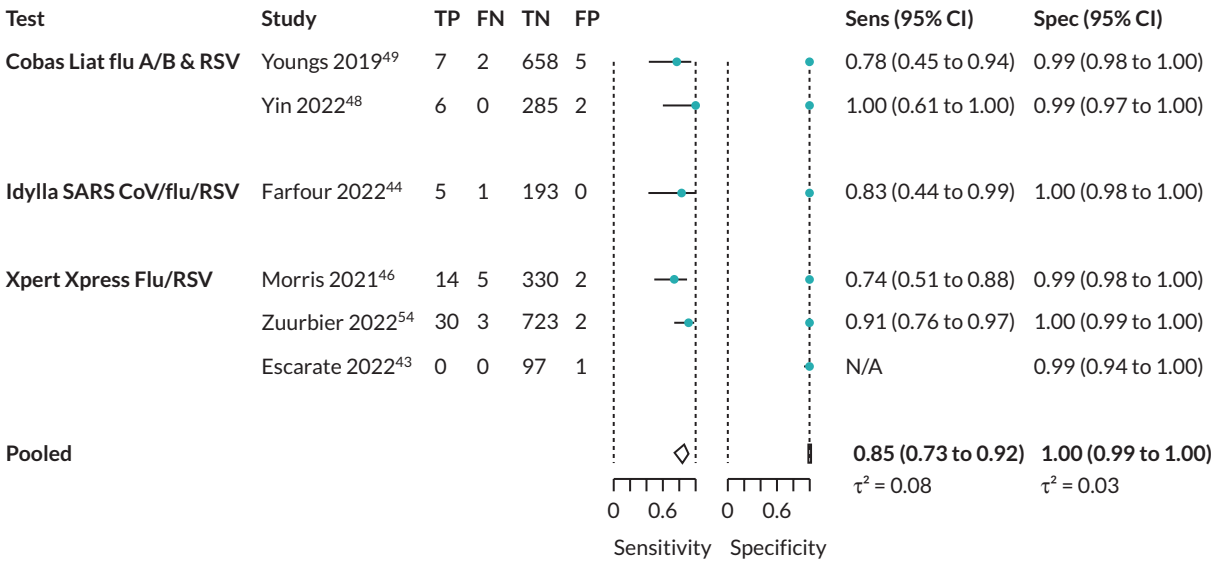

FIGURE 14 Meta-analysis for RSV.

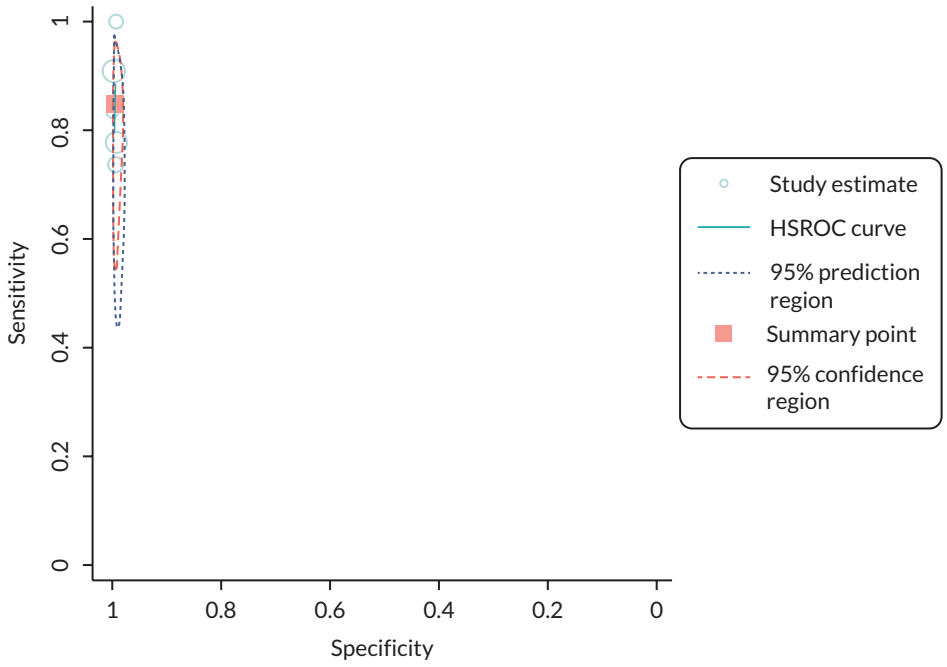

FIGURE 15 RSV data and meta-analysis results in ROC space.