FINAL

National Institute for Health and Care Excellence

Suspected acute respiratory infection in over 16s: assessment at first presentation and initial management

[D] Evidence summary for acute respiratory infection

NICE guideline NG237
Evidence reviews underpinning recommendations and recommendations for research in the NICE guideline

October 2023

Final

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1.1 Review questions

1. In people aged 16 years or over with suspected acute respiratory infection (ARI):
    a. What are the symptoms, signs, and early warning scores (EWS) that have been evaluated?
    b. What are the strategies for the triage of patients (for example, applying clinical prediction rules using symptoms, signs, EWS thresholds) to avoid serious illness?
2. What is the clinical effectiveness and cost-effectiveness of different near-patient, rapid microbiological or biomarker tests alone or in combination to guide initial assessment and management in people aged 16 and over with suspected ARI?
3. In people aged over 16, what is the diagnostic accuracy of near-patient, rapid tests to distinguish between bacterial and viral infection in suspected acute respiratory infection?

1.1.1 Introduction

Before the COVID-19 pandemic, people with suspected acute respiratory infections either presented to NHS111 or primary care for assessment and management, with more severe cases referred for hospital assessment, or they presented directly to A&E or to the ambulance service if their symptoms were more serious. Since the pandemic, the levels of acute respiratory infection (particularly pneumonia caused by COVID-19 infection) have increased.

In response to this the NHS has set up a number of acute respiratory infection (ARI) hubs and acute respiratory infection virtual wards to relieve pressure on other parts of the local healthcare system.

NICE has been asked to produce a number of related products to support and inform the expansion of virtual ward provision and other intermediate care areas. This guideline will aid healthcare professionals in deciding where to refer people aged 16 and over with suspected acute respiratory infections including referrals to Virtual Wards and ARI Hubs.

1.1.2 Summary of the protocols

These 3 tables are reproduced from the relevant evidence reviews. See below for details.

Table 1: RQ1: Symptoms, signs, and early warning scores

Population	People aged 16 years or over with suspected ARI (including bronchitis, common cold, glandular fever, influenza, laryngitis, sore throat (pharyngitis and tonsillitis), pneumonia and severe acute respiratory syndrome (SARS)). **Exclusion criteria:** People aged 16 or over with a confirmed COVID-19 diagnosis, who are hospital in-patients, who have a respiratory infection during end-of-life care, and those with aspiration pneumonia, bronchiectasis, cystic fibrosis, or known immunosuppression.

Phenomenon of interest	Symptoms, signs and externally validated EWS for the assessment of suspected ARI, including: cough, coughing up blood, purulent sputum, malaise, coryza, temperature/signs of fever, sore throat, hoarse voice, breathlessness and/or increased respiratory rate, wheeze/chest tightness, cyanosis, loss of appetite, lethargy, agitation, confusion, delirium, drowsiness, headache, rigors, chest pain, monitoring parameters based on digital technologies where available (e.g. pulse oximetry, peak flow), sudden deterioration in any of the above, EWS (including NEWS/NEWS2, CRB-65/CURB-65, CENTOR criteria), and any combination of the above.

Outcomes	Assessed within 4 weeks of consultation:
	• Hospital admission
	• Escalation of care to any setting including:
	  ○ Face to face consultation
	  ○ Re-consultation/appointment
	  ○ Virtual ward
	  ○ Referral to ARI hub
	  ○ A&E visit
	• Unplanned hospital admission
	• Hospital length of stay
	• Follow-up consultation/ongoing monitoring
	• Antibiotic/antiviral use
	• Time to clinical cure/resolution of symptoms
	• Mortality
	Secondary outcomes:
	• Patient acceptability
	• Patient preference
	• HRQoL (using a validated scale)

Study type	Systematic reviews.

For the full protocol see Evidence review A (Appendix A).

Table 2: RQ2: Different near-patient, rapid microbiological or biomarker tests

Population	**Inclusion criteria** People aged 16 years or over with suspected acute respiratory infection. **Exclusion criteria** People aged 16 years or over: • With a confirmed COVID-19 diagnosis (patients with known COVID will be triaged in a different way, suspected COVID would be treated as suspected ARI). • All inpatients in hospital. • Who have a respiratory infection during end-of-life care. • With aspiration pneumonia, bronchiectasis, cystic fibrosis or known immunosuppression.

	• Who are presenting with acute respiratory infections that rarely require or lead to escalation of care to hospital admission such as otitis media and sinusitis.
Intervention	Near patient, rapid tests (turnaround time ≤ 45mins, also known as point of care tests) which are currently licensed and available for use in the UK as follows: • Rapid antigen test • Rapid PCR tests • Urinary antigen tests • C-reactive protein • Procalcitonin • Serum sodium • Urea nitrogen • Partial pressure O_2 • Blood gases • Full blood count • White blood cell count • Myxovirus resistance protein A • TNF-related apoptosis-induced ligand (TRAIL) • Interferon-γ-induced protein-10 (IP-10)
Comparator	Current practice

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

Study type	Systematic reviews. Randomised controlled trials

For the full protocol see Evidence review B (Appendix 1).

Table 3: RQ3: Accuracy of near-patient, rapid tests to distinguish between bacterial and viral infection in suspected ARI

Population	People aged 16 years or over with suspected acute respiratory infection, including (but not limited to) the following symptoms:

	• Cough or shortness of breath • Sore throat • Rhinitis

Index tests	• Symptoms and signs of acute respiratory infection; either individual symptoms/signs, or in combination (as part of a clinical decision tool)
	• "Host-response" (or "biomarker") point of care tests (POCTs), including:
	  ○ CRP
	  ○ Procalcitonin
	  ○ CRP and MxA (FebriDx)
	  ○ TRAIL, IP-10 and CRP (ImmunoXpert/MeMed BV)
	  ○ White cell differential count
	• Multiplex or single POCTs (with a turnaround time of <45 minutes) for (or including) the following specific organisms:
	  ○ Influenza (A and B)
	  ○ Respiratory syncytial virus (RSV)

Comparator/Reference standard	Any reference standard
Outcomes	Diagnostic accuracy measures • Sensitivity • Specificity • Area under the curve (AUC)
Study type	Diagnostic test accuracy studies

For the full protocol see Evidence review C (Appendix A).

1.1.3 Methods and process

This evidence summary summarises the evidence from 3 rapid systematic reviews undertaken for NICE by 3 NIHR-funded Evidence Synthesis Groups. The summaries of evidence presented in this document are taken from those reviews, which contain full details.

The 3 evidence reviews were developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this individual review questions are described in the individual reviews.

Table 4: ESGs who undertook evidence syntheses

Review question	Review	Author details	Review title
1	[A]	York Evidence Synthesis	Evidence review for acute respiratory infection in adults over 16 years: initial assessment and management

		(YES) Group	
2	[B]	West Midlands Evidence Synthesis Group	Rapid tests to inform triage and antibiotic prescribing decisions for adults presenting with suspected acute respiratory infection: A rapid evidence synthesis of clinical effectiveness and cost-utility studies
3	[C]	Bristol Evidence Synthesis Group	Evidence reviews for diagnostic accuracy of point of care tests for viral vs bacterial infection

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4 Effectiveness and diagnostic evidence

1.1.4.1 Included studies

See individual reviews for details of the searches and the number of studies identified at each stage of sifting.

A study selection summary is presented as a PRISMA diagram in an appendix in each review.

Full references of the included studies can be found in each review.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in an appendix of each review.

1.1.5 Summary of studies included in the evidence

The summaries of studies tables are presented below for each of the evidence reviews. Fuller details are included in each evidence review.

Table 5: RQ1: Symptoms, signs, and early warning scores – included studies

Study details	Population	Setting	Prognostic factors/ Prognostic model(s)	Outcomes	Risk of bias
Individual signs/symptoms and Centor score for adults presenting with sore throat symptoms					
Aalbers (2011)[2] Systematic review including 21 studies	Adults (≥15 years of age) presenting with sore throat symptoms	Primary care and the emergency department (USA, Canada, Europe, New Zealand, Thailand, Israel)	Individual symptoms and signs (absence of cough, fever, anterior cervical adenopathy, tender anterior cervical adenopathy, any exudates) and Centor score	Usefulness of individual symptoms and signs in assessing the risk of streptococcal pharyngitis and diagnostic accuracy of the Centor score as a decision rule for antibiotic treatment	Low
Early warning scores (EWS) for patients with community acquired pneumonia (CAP)					
Akram (2011)[3] Systematic review including 13 studies	Outpatients with community acquired pneumonia (CAP)	Outpatients; either exclusively managed in the community or discharged from an emergency department <24 hours after admission (USA, Canada, Netherlands, Germany, Spain, France, UK)	CRB65, CURB65 and Pneumonia Severity Index (PSI)	Outpatient mortality and diagnostic accuracy	Low
Chalmers (2011)[4] Systematic review including 6 studies	Outpatients with CAP	Emergency department and walk-in medical centre (USA, Canada, Spain, France)	PSI and other criteria for assessing severity/requirement for in-patient care	Proportion of patients treated as outpatients, mortality, hospital re-admissions, health related quality of life, return to usual activities and patient satisfaction with care.	Low
Ebell (2019)[5] Systematic review including 29 studies; 15 were in emergency department or	Patients with CAP	The review included hospitalised patients, ambulatory patients and both; the 15 studies that included patients in emergency department or	CRB-65	Prediction of mortality	High

Study details	Population	Setting	Prognostic factors/ Prognostic model(s)	Outcomes	Risk of bias
primary care settings (update of McNally 2010)		primary care settings are relevant to this review (most studies from Europe)			
McNally (2010)[6] Systematic review including 14 studies; 4 included community-based patients	Adults (≥16 years of age) with a primary diagnosis of CAP	The review included hospitalised patients, primary care patients and patients treated as outpatients; the 4 studies that included primary care patients and patients treated as outpatients are relevant to this review (study location not reported)	CRB-65	30-day mortality	Low
Metlay (2019)[7] Systematic review including 7 studies relating to the question of interest	Adults diagnosed with CAP	Inpatient versus outpatient treatment location (study location not reported)	PSI and CURB-65	Initial site of treatment	High
Nannan Panday (2017)[8] Systematic review including 42 studies; 4 included patients with CAP or respiratory distress	Adults (≥16 years of age) at the emergency department or acute medical unit	Emergency department and acute medical unit (Denmark, Netherlands, Norway, Germany, Hong Kong, Ireland, Israel, Italy, Singapore, South Africa, South Korea, Sri Lanka, Sweden, Switzerland,	25 different types of early warning score (EWS). For the 4 studies relevant to our question, the scores assessed were Chronic Respiratory Early Warning Score (CREWS), CRB-65, CURB-65, National Early Warning Score (NEWS), PSI, Systemic Inflammatory Response Syndrome (SIRS), Standardised	Prediction of mortality and/or intensive care unit (ICU) admission	Low

Study details	Population	Setting	Prognostic factors/ Prognostic model(s)	Outcomes	Risk of bias
		Turkey, UK, USA and Vietnam)	Early Warning Score (SEWS) and Salford National Early Warning Score (S-NEWS)		
Smith (2021)[9] Systematic review including 38 studies relating to the question of interest	Adult emergency department patients diagnosed with CAP	Emergency department (USA, Spain, Switzerland, Australia, Canada, China, France, Japan, Korea, Turkey, UK and Europe, where reported)	PSI and CURB-65 for predicting mortality. 5 clinical decision aids for predicting the need for ICU admission: American Thoracic Society (ATS) 2001, Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) 2007, Severe CAP (SCAP/CURXO-80), SMART-COP, Risk of Early Admission to the ICU (REA-ICU)	Prediction of mortality (PSI and CURB-65) and prediction of need for ICU admission (ATS 2001, IDSA/ATS 2007, SCAP/CURXO-80, SMART-COP and REA-ICU)	Unclear
Early warning scores (EWS) for patients with nursing home acquired pneumonia (NHAP)					
Dosa (2005)[10] Systematic review including 3 studies relating to the question of interest	Nursing home residents with nursing home acquired pneumonia (NHAP)	Nursing homes (USA)	PSI, a 5-point scale developed by Naughton and Mylotte and an 8-variable model developed by Mehr et al.	Prediction of mortality	High

Abbreviations: ATS = American Thoracic Society; CAP = community acquired pneumonia; EWS = early warning scores; ICU = intensive care unit; IDSA/ATS = Infectious Diseases Society of America/American Thoracic Society; MEDS = Mortality in Emergency Department Sepsis score; MEWS = Modified Early Warning Score; NEWS = National Early Warning Score; NHAP = nursing home acquired pneumonia; PSI = Pneumonia Severity Index; REA-ICU = Risk of Early Admission to the ICU; REMS = Rapid Emergency Medicine Score; SCAP = Severe CAP.

Table 6: RQ2: Different near-patient, rapid microbiological or biomarker tests - Characteristics of included studies for C-reactive protein point of care tests

Study Details	Participants	Interventions	Outcomes	Comments[a]
Afinion CRP point-of-care testing				
Andreeva 2014 [29] Russia Open-label cluster RCT January to April 2010 **Follow-up**: 14 days	179 patients: CRP 101, usual care 78 Acute cough/lower RTI for < 28 days	Interventions: Single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 14 days • Hospital admission (not stated, assume within 14 days) • Number of re-consultations within 14 days • Number of participants fully or almost recovered within 14 days	Funding: Not reported. Test kits provided by manufacturer and CRP readers acquired at reduced prices. Overall risk of bias: High
Butler 2019 [24] **Francis 2020** [34] UK (England & Wales) Open-label RCT January 2015 to September 2017	649 patients: CRP 325, usual care 324 Acute exacerbation of COPD between 24 hours and 21 days duration	Interventions: Single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 28 days • Antibiotics prescribed within 4 weeks post-randomisation (patient-reported) • Mortality within 28 days • Hospital admissions within 6 months • Primary and/or secondary care consultations during 6 months follow-up • HRQoL (EQ-5D-5L index value) at 1, 2 and 4 weeks and at 6 months	Funding: Non-commercial Overall risk of bias: High

Study Details	Participants	Interventions	Outcomes	Comments[a]
Follow-up: 4 weeks and 6 months			• HRQoL (EQ-5D-5L health status) at 1, 2 and 4 weeks and at 6 months HRQoL (CRQ-SAS)	
Nycocard II CRP point-of-care testing *(Not currently available in the UK)*				
Althaus 2019 [30] Thailand and Myanmar Open-label RCT June 2016 to June 2017 **Follow-up:** Day 5 + 14	937 patients (adults subgroup) CRP 614, usual care 323 Documented fever or chief complaint of fever (< 14 days)	Interventions: Single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation	Funding: Non-commercial Overall risk of bias: High
Cals 2009 [26] **Cals 2013**[35] The Netherlands Open-label cluster-RCT Winter periods 2005-06 and 2006-07 **Follow-up:** 28 days	431 patients CRP 227, usual care 204 Suspected lower respiratory tract infection	Interventions: Single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 28 days • Mortality during 28 days • Hospital admissions during 28 days • Number of re-consultations within 28 days • Number of participants substantially improved within 28 days	Funding: Non-commercial Overall risk of bias: High

Study Details	Participants	Interventions	Outcomes	Comments[a]
Diederichsen 2000 [31] Denmark Open-label RCT January to April 1997 **Follow-up**: 1 week	673 patients CRP 342, usual care 331 All patients with index case of respiratory infection	Interventions: Single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation	Source of funding: Not reported Overall risk of bias: High
Do 2016 [33] Northern Vietnam Open-label RCT March 2014 to July 2015 **Follow-up:** 14 days	1008 patients CRP 507, usual care 501 Non-severe acute respiratory tract infection	Interventions: Single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 14 days (per protocol analysis) • Subsequent antibiotic use in those without an immediate antibiotic prescription • Antibiotic management change in those without an immediate antibiotic prescription • Time to resolution of symptoms • Mortality within 14 days	Funding: Non-commercial Overall risk of bias: High
Melbye 1995 [32] Norway Open-label RCT	239 patients CRP 108, usual care 131 Suspected lower RTI	Interventions: Single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 28 days • Number of participants substantially improved within 7 days • Number of participants substantially improved within 28 days	Funding: Nycomed Pharma Study terminated early due to parity at interim analysis and lack of interest in

Study Details	Participants	Interventions	Outcomes	Comments[a]
Study dates not reported **Follow-up**: 3 weeks				participating practices. Overall risk of bias: High
QuikRead CRP				
Boere 2021 [27] **Boere 2022** [36] The Netherlands Open-label cluster RCT September 2018 to March 2020 **Follow-up**: 3 weeks	241 patients CRP 162, usual care 79 Nursing home residents with suspected LRTI	Interventions: Single POC CRP Comparator: usual care	• Antibiotics prescribed at index consultation (including subgroup analysis for COPD) • Antibiotic treatment changes (start, cessation, switch, or prolongation) • Mortality within 3 weeks • Hospital admission within 3 weeks • Hospitalisation at initial consultation • Hospitalisation at 1 and 3 weeks • Number of participants substantially improved within 3 weeks • Number of participants fully recovered at 3 weeks	Funding: Non-commercial Overall risk of bias: High
Cals 2010 [28] The Netherlands Open-label RCT November 2007 to April 2008	258 patients CRP 129, usual care 129 Suspected acute LRTI or rhinosinusitis	Interventions: Single POC CRP Comparator: usual care	• Antibiotics use after index consultation (immediate prescription and/or delayed prescription and filled) • Antibiotics prescribed within 28 days • Mortality within 28 days • Hospital admissions within 28 days • Number of re-consultations within 28 days	Funding: Orion Diagnostica Espoo, Finland Overall risk of bias: High

Study Details	Participants	Interventions	Outcomes	Comments[a]
Follow-up: 28 days			• Number of participants substantially improved within 7 days • Patient reported time to full recovery	
Little 2013 [25] **Little 2019** [37] Belgium, UK, Poland, Spain, The Netherlands Open-label cluster-RCT February 2011 to May 2012 **Follow-up**: 12 months	1932 patients CRP 1062, usual care 870 Upper or lower respiratory tract infection	Interventions: Single POC CRP Comparator: usual care	• Hospital admissions within 4 weeks • Number of re-consultations within 28 days • Resolution of moderately bad symptoms, • Mortality	Funding: Non-commercial Overall risk of bias: High

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

Table 7: RQ2: Different near-patient, rapid microbiological or biomarker tests - Characteristics of included studies for procalcitonin tests

Study Details	Participants	Interventions	Outcomes and Results	Comments[a]
BRAHMS PCT Procalcitonin				
Lhopitallier 2021 [38] Switzerland Open-label cluster-RCT September 2018 to March 2020 **Follow-up:** 28 days	469 patients Procalcitonin 195, usual care 122 Lower RTI/acute cough	Interventions: POC procalcitonin Comparator: usual care	• Antibiotics prescribed at index consultation • Antibiotics prescribed within 7 days • Antibiotics prescribed within 28 days • Number of re-consultations within 28 days • Hospital admissions within 7 days • Mortality within 28 days • Duration of symptoms by day 28	Funding: Non-commercial. POC test kits were provided by the manufacturer Overall risk of bias: High
[a] Overall risk of bias: see Appendix 9 for details. Abbreviations: POC – point-of-care; RCT – randomised controlled trial; RTI – respiratory tract infection.				

Table 8: RQ2: Different near-patient, rapid microbiological or biomarker tests - Characteristics of included studies for Group A Streptococcus tests

Study Details	Participants	Interventions	Outcomes and Results	Comments[a]
RADT OSOM® Strep A				
Llor 2011 [39] Spain	557 patients RADT 285, usual care 272	Interventions: RADT OSOM® Strep A test	• Antibiotics prescribed at index consultation	Funding: Non-commercial

Study Details	Participants	Interventions	Outcomes and Results	Comments[a]
Open-label cluster-RCT January to May 2008 **Follow-up**: NR	Acute pharyngitis	Comparator: usual care		Includes patients aged ≥14 years, slight difference to current review criteria. Overall risk of bias: High
RADT Clearview® Exact Strep A				
Worrall 2007 [40] Canada Open-label cluster-RCT February to April 2005 **Follow-up:** NR	533 patients RADT 120, usual care 141 Acute sore throat as primary symptom	Interventions: RADT Clearview® Exact Strep A dipstick Comparator: usual care	• Antibiotics prescribed at index consultation	Funding: Not reported Overall risk of bias: High

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

Table 9: RQ2: Different near-patient, rapid microbiological or biomarker tests - Characteristics of included study for Influenza tests

Study Details	Participants	Interventions	Outcomes and Results	Comments[a]
BD Directigen™ Flu A + B rapid test *(Not currently available in the UK)*				
Berthod 2015 [41] **NCT00821626** [42] Switzerland Open-label RCT December 2008 to November 2012 **Follow-up**: NR	93 patients RADT 60, usual care 33 Fever or cough or sore throat within 4 days; illness within 14 days of a trip abroad	Interventions: BD Directigen A + B Comparator: usual care	• Antibiotics prescribed at index consultation Mortality	Funding: Not reported Trial finished early due to low sensitivity of the intervention. Overall risk of bias: High

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

Table 10: RQ3: Accuracy of near-patient, rapid tests to distinguish between bacterial and viral infection in suspected ARI – Systematic reviews

Study details	Population	Index test(s)	Reference standard(s)	Target condition(s)	Risk of bias (ROBIS)
Carlton 2021	Adults and children presenting with symptoms of acute respiratory tract infection.	• TRAIL, IP-10 and CRP (ImmunoXpert) • CRP and MxA (FebriDx) • CRP and neopterin	Any reference standard, including consensus of an expert panel, clinical algorithms and microbiology.	• Bacterial respiratory tract infection • Viral respiratory tract infection	Low risk of bias
Gentilotti 2022	Adults and children with symptoms of acute respiratory infection, presenting to primary/emergency care settings.	• Individual symptoms and signs • CRP • Procalcitonin • Various POC tests for influenza	Any reference standard, including chest X-ray, microbiological assessment, expert opinion.	• Bacterial pneumonia • Influenza	Low risk of bias
Minnaard 2017	Adults with suspected lower respiratory tract infection, presenting to primary/emergency care settings.	Clinical prediction models incorporating combinations of symptoms and signs plus CRP measurement	Chest X-ray	• Pneumonia	Low risk of bias
Onwuchekwa 2023	Adults and children. No information on clinical presentation.	Any tests for RSV	RT PCR	• RSV	Low risk of bias
Pazmany 2021	Adults with COPD, presenting with an acute exacerbation to primary care/emergency department or in hospital.	Presence of purulent sputum	Microbiological culture	• Bacterial exacerbation of COPD	Low risk of bias

Study details	Population	Index test(s)	Reference standard(s)	Target condition(s)	Risk of bias (ROBIS)
Schierenberg 2017	Adults with an acute or worsened cough or lower respiratory tract infection, present to primary or emergency care.	Combinations of symptoms and signs (clinical prediction models)	Chest X-ray, CT or MRI	• Pneumonia	Low risk of bias

COPD chronic obstructive pulmonary disease; CRP C reactive protein; CT computed tomography; IP-10 interferon-γ-induced protein-10; MRI magnetic resonance imaging; MxA myxovirus resistance protein A; POC point of care; RSV respiratory syncytial virus; RT PCR real time polymerase chain reaction; TRAIL TNF-related apoptosis-induced ligand

Table 11: RQ3: Accuracy of near-patient, rapid tests to distinguish between bacterial and viral infection in suspected ARI – Primary studies included in the diagnostic evidence for white cell differential count

Study details	Population	Index test(s)	Reference standard(s)	Target condition(s)	Risk of bias (QUADAS 2)
Castro-Guardiola 2000	Adults (n = 284) with suspected pneumonia in an emergency department	• White blood cell count	Chest X-ray, plus clinical symptoms and signs	• Pneumonia	*Risk of bias:* Patient selection: low risk Index test: low risk Reference standard: high risk Flow and timing: low risk *Applicability:* Patient selection: low concern Index tests: high concern Reference standard: low concern

Study details	Population	Index test(s)	Reference standard(s)	Target condition(s)	Risk of bias (QUADAS 2)
Gulich 1999	Adults (n = 179) with sore throat, presenting to primary care	• White blood cell count	Microbiological culture	• Bacterial pharyngitis	*Risk of bias:* Patient selection: low risk Index test: low risk Reference standard: low risk Flow and timing: low risk *Applicability:* Patient selection: low concern Index tests: high concern Reference standard: low concern
Holm 2007	Adults (n = 364) with symptoms of a lower respiratory tract infection, presenting to primary care	• White blood cell count	Chest X-ray	• Pneumonia	*Risk of bias:* Patient selection: high risk Index test: high risk Reference standard: low risk Flow and timing: high risk *Applicability:* Patient selection: low concern Index tests: high concern Reference standard: low concern
Liu 2013	Adults (n = 500) with a diagnosis of community acquired pneumonia in an outpatient clinic	• White blood cell count	Microbiological culture and PCR	• Bacterial pneumonia	*Risk of bias:* Patient selection: unclear risk Index test: unclear risk Reference standard: low risk Flow and timing: low risk *Applicability:*

Study details	Population	Index test(s)	Reference standard(s)	Target condition(s)	Risk of bias (QUADAS 2)
					Patient selection: low concern Index tests: high concern Reference standard: low concern

Table 12: RQ3: Accuracy of near-patient, rapid tests to distinguish between bacterial and viral infection in suspected ARI – Primary studies included in the diagnostic evidence for multiplex PCR tests

Study details	Population	Index test(s)	Reference standard(s)	Target condition(s)	Risk of bias
Boku 2013	Adults with acute respiratory infection or fever and contact with influence in a hospital outpatient setting	• Verigene system RV+	Viral culture plus laboratory PCR	• Flu A/B	*Risk of bias:* Patient selection: unclear risk Index test: low risk Reference standard: unclear risk Flow and timing: low risk *Applicability:* Patient selection: low concern Index tests: low concern Reference standard: low concern
Escarate 2022	Adults aged ≥65 years with symptoms of respiratory illness in a care home setting	• Xpert Xpress Flu/RSV	Laboratory PCR	• Flu A • Flu B • RSV	*Risk of bias:* Patient selection: unclear risk Index test: low risk Reference standard: low risk Flow and timing: high risk *Applicability:* Patient selection: high concern Index tests: low concern Reference standard: low concern
Farfour 2022	Adults with suspected viral respiratory infection in an emergency department	• Idylla SARS CoV/Flu/RSV	Laboratory PCR	• Flu A • RSV	*Risk of bias:* Patient selection: low risk Index test: unclear risk Reference standard: low risk Flow and timing: high risk *Applicability:*

Study details	Population	Index test(s)	Reference standard(s)	Target condition(s)	Risk of bias
					Patient selection: low concern Index tests: low concern Reference standard: low concern
Hansen 2018	Adults (80%) and children (20%) with at least one sign of influenza in an emergency department setting	• Cobas Liat Influenza A/B	Laboratory PCR	• Flu A/B	*Risk of bias:* Patient selection: high risk Index test: low risk Reference standard: low risk Flow and timing: low risk *Applicability:* Patient selection: low concern Index tests: low concern Reference standard: low concern
Maignan 2016	Adults with fever and at least one sign of a respiratory infection in an emergency department setting	• Cobas Liat Influenza A/B	Laboratory PCR	• Flu A • Flu B • Flu A/B	*Risk of bias:* Patient selection: low risk Index test: low risk Reference standard: low risk Flow and timing: low risk *Applicability:* Patient selection: low concern Index tests: low concern Reference standard: low concern
Morris 2021	Adults (and children – subgroup data for adults were used) with symptoms of acute respiratory infection,	• Xpert Xpress Flu/RSV	Laboratory PCR	• Flu A • RSV	*Risk of bias:* Patient selection: high risk Index test: low risk Reference standard: low risk Flow and timing: low risk

Study details	Population	Index test(s)	Reference standard(s)	Target condition(s)	Risk of bias
	presenting to the emergency department				*Applicability:* Patient selection: low concern Index tests: low concern Reference standard: low concern
Peretz 2020	Adults with suspected influenza in an emergency department	• Xpert Xpress Flu A/B • Simplex Flu A/B and RSV	Rapid antigen test	• Flu A/B	*Risk of bias:* Patient selection: unclear risk Index test: unclear risk Reference standard: high risk Flow and timing: low risk *Applicability:* Patient selection: low concern Index tests: high concern Reference standard: low concern
Tanei 2014	Adults with symptoms of acute respiratory infection and a fever ≥37°C	• Verigene RV+	Rapid antigen test	• Flu A/B	*Risk of bias:* Patient selection: low risk Index test: unclear risk Reference standard: high risk Flow and timing: low risk *Applicability:* Patient selection: low concern Index tests: high concern Reference standard: low concern
Valentin 2019	Adults with acute, febrile respiratory tract infection with at least one risk factor for	• Xpert Xpress Flu/RSV • Cobas Liat Flu A/B	Laboratory based PCR	• Flu A • Flu B • Flu A/B	*Risk of bias:* Patient selection: low risk Index test: low risk Reference standard: low risk

Study details	Population	Index test(s)	Reference standard(s)	Target condition(s)	Risk of bias
	complications of influenza.				Flow and timing: high risk *Applicability:* Patient selection: low concern Index tests: high concern Reference standard: low concern
Yin 2022	Adults (77%) and children (23%) with symptoms of acute respiratory infection in an emergency department.	• Cobas Liat Flu A/B	Rapid antigen test plus culture plus Cobas Liat test	• Flu A • Flu B • RSV	*Risk of bias:* Patient selection: unclear risk Index test: low risk Reference standard: high risk Flow and timing: low risk *Applicability:* Patient selection: low concern Index tests: high concern Reference standard: low concern
Youngs 2019	Adults with suspected influenza in an emergency department	• Cobas Liat Flu A/B	Laboratory PCR and alternative rapid multiplex test	• Flu A • Flu B • Flu A/B	*Risk of bias:* Patient selection: low risk Index test: low risk Reference standard: high risk Flow and timing: high risk *Applicability:* Patient selection: low concern Index tests: low concern Reference standard: low concern
Zuurbier 2022	Adults with symptoms of acute respiratory tract infection at home or	• Xpert Xpress Flu/RSV	Laboratory PCR	• RSV	*Risk of bias:* Patient selection: low risk Index test: low risk

Study details	Population	Index test(s)	Reference standard(s)	Target condition(s)	Risk of bias
	in a primary care setting				Reference standard: low risk Flow and timing: high risk *Applicability:* Patient selection: high concern Index tests: low concern Reference standard: low concern

1

See appendices of individual reviews for full evidence tables.

1.1.6 Summary of the evidence

1.1.6.1 RQ1: Symptoms, signs, and early warning scores – evidence statements

a) In people aged 16 years or over with suspected acute respiratory infection (ARI), what are the symptoms, signs and early warning scores (EWS) that have been evaluated?

Several EWS have been evaluated in people aged 16 years or over with suspected ARI: Centor, CRB-65, CURB-65, PSI, CREWS, NEWS, SIRS, SEWS, S-NEWS, ATS 2001, IDSA/ATS 2007, SCAP/CURXO-80, SMART-COP and REA-ICU. Nine systematic reviews addressed this research question; all assessed patients presenting in face-to-face settings (primary care, walk-in medical centre, emergency department, acute medical unit or nursing home) rather than remote settings. The most commonly assessed EWS were the PSI, CRB-65 and CURB-65.

b) In people aged 16 years or over with suspected acute respiratory infection (ARI), what are the strategies for the triage of patients (for example, applying clinical prediction rules using symptoms, signs, EWS thresholds) to avoid serious illness?

The evidence was insufficient to definitively answer this question.

Seven systematic reviews assessed EWS for predicting mortality and/or to determine the site of treatment for patients with community acquired pneumonia. There was a great deal of overlap in the primary studies included in the reviews and many of the primary studies were considered to have significant limitations.

Two reviews that assessed the CRB-65 (both good quality) concluded that further research is needed in community settings. One of these reviews also assessed the PSI; however, the PSI requires data from a large number of tests, some of which are not routinely conducted in community settings. One review (also good quality) concluded that NEWS appears to provide the most accurate score for predicting mortality and the need for ICU admission in patients with respiratory distress in an emergency department or acute medical unit setting.

One review (good quality) concluded that individual symptoms and signs (absence of cough, fever, anterior cervical adenopathy, tender anterior cervical adenopathy, any exudates) have only a modest ability to rule in or out a diagnosis of streptococcal pharyngitis in adults presenting to primary care or the emergency department with sore throat. The review concluded that the Centor score (cut-off ≥3) has reasonably good specificity and can enhance the appropriate prescribing of antibiotics for streptococcal pharyngitis, but that it should be used with caution in low prevalence settings, such as primary care.

Only one review (good quality) assessed the use of EWS (PSI and two other scores) for predicting mortality in nursing home residents with nursing home acquired pneumonia; the review concluded that there are numerous problems with using the scores in clinical practice.

The review of economic evidence identified a single study which indicated that clinical scores may be a cost-effective approach to triage patients compared with delayed prescribing. The study also offers insight into the cost-effectiveness of diagnostic testing in ARI scenarios. In this particular case, the findings indicated that there is no apparent advantage in incorporating diagnostic testing alongside clinical scores compared to using clinical scores alone. It is unclear whether the results obtained from managing a short-term condition (sore throat) are generalisable to the broader assessment of other ARI conditions.

1.1.6.2 RQ2: Different near-patient, rapid microbiological or biomarker tests –

What is the clinical effectiveness and cost effectiveness of different near-patient, rapid microbiological or biomarker tests alone or in combination to guide initial assessment and management in people aged 16 and over with suspected ARI?

GRADE summary table

Table 13: C-reactive POCT versus usual care in adults with suspected ARI

	Summary of findings			Quality[o]
	No of patients		Effect	
No of studies (design)	CRP	Usual care	Result (95%CI)	
Hospital admission immediately after triage				
NR				
Hospital admission at 3 weeks to 6 months				
1 cluster-RCT[a]	0/49	0/38	Not reported	VERY LOW
1 cluster-RCT[b]	2/33	1/18	RR 1.09 (95% CI 0.11, 11.22)	VERY LOW
1 cluster-RCT[c]	0/65	0/59	Not reported	VERY LOW
1 cluster-RCT[d]	5/583	1/478	RR 4.10 (95% CI 0.48, 34.97)	VERY LOW
1 RCT[e]	35/304	34/301	RR 1.02 (95% CI 0.65, 1.59)	VERY LOW
1 RCT[f]	0/129	0/129	Not reported	VERY LOW
Escalation of care: re-consultation/appointment				
3 cluster-RCTs/1 RCT[k]	180/695	103/738	RR 1.61 (95% CI 1.07, 2.41)	VERY LOW
Escalation of care: virtual ward				
NR				
Escalation of care: emergency department visit				
NR				
Escalation of care: unplanned hospital admission				
NR				
Mortality at 7 days				
NR				
Mortality at 28 days				
1 cluster-RCT[b]	1/33	0/19	RR 1.68 (95% CI 0.07, 39.16)	VERY LOW
1 cluster-RCT[c]	0/65	0/59	Not reported	VERY LOW
1 cluster-RCT[d]	0/583	0/478	Not reported	VERY LOW
1 RCT[e]	0/325	2/324	RR 0.20 (95% CI 0.01, 4.14)	VERY LOW
1 RCT[f]	0/129	0/129	Not reported	VERY LOW
1 RCT[n]	0/507	0/501	Not reported	VERY LOW

[a] Andreeva 2014.
[b] Boere 2021.
[b] Cals 2009.
[d] Little 2013.
[e] Butler 2019.
[f] Cals 2010.

[g] Very serious limitations due to uncertainties around selection bias and high risk of bias due to lack of blinding.
[h] Very serious limitations due to uncertainties around selection bias and high risk of bias due to lack of blinding and incomplete outcome data reporting.
[i] Very serious imprecision because the 95% CI for the RR crosses 0.8 and 1.25.
[j] Serious indirectness as test(s) not currently available in the UK.
[k] Andreeva 2014,[29] Cals 2009,[26] Little 2013[25] and Cals 2010.[28]
[l] Serious inconsistency due to moderate heterogeneity (I^2=56.6%).
[m] Serious imprecision because the 95% CI for the RR crosses 1.25.
[n] Do 2016.[33]
[o] The overall quality of evidence for each outcome was downgraded to low for any serious factors and to very low for any very serious factors in the quality of evidence.

Table 14: Procalcitonin POCT versus usual care in adults with suspected ARI

	Summary of findings			
	No of patients		Effect	Quality[e]
No of studies (design)	Procalcitonin	Usual care	Result (95%CI)	
Hospital admission immediately after triage				
NR				
Hospital admission at 28 days				
NR				
Escalation of care: re-consultation/appointment				
1 cluster-RCT[a]	53/195	33/122	RR 1.00 (95% CI 0.69, 1.46)	VERY LOW
Escalation of care: virtual ward				
NR				
Escalation of care: emergency department visit				
NR				
Escalation of care: unplanned hospital admission				
NR				
Mortality at 7 days				
1 cluster-RCT[a]	0/163	0/114	Not reported	VERY LOW
Mortality at 28 days				
1 cluster-RCT[a]	0/163	0/114	Not reported	VERY LOW
Abbreviations: CI – confidence interval; CRP – C-reactive protein; NR – not reported; RCT – randomised controlled trial; RR – relative risk.				

[a] Lhopitallier 2021
[b] Very serious limitations due to lack of blinding and unclear allocation concealment.
[c] Very serious limitations due to lack of blinding, unclear allocation concealment and incomplete outcome data.
[d] Very serious imprecision because the 95% CI for the RR crosses 0.8 and 1.25.
[e] The overall quality of evidence for each outcome was downgraded to low for any serious factors and to very low for any very serious factors in the quality of evidence.

1.1.6.3 RQ3: Accuracy of near-patient, rapid tests to distinguish between bacterial and viral infection in suspected ARI

What is the diagnostic accuracy of near-patient, rapid tests to distinguish between bacterial and viral infection in suspected acute respiratory infection?

Table 15: Symptoms and signs for the diagnosis of bacterial pneumonia

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Certainty of the body of evidence	Interpretation of effect
Individual symptoms and signs						
Cough	Gentilotti 2022	13 (8423)	Sensitivity	89.1% (66.4 to 97.1)	VERY LOW[1]	Cough may have adequate sensitivity, but the evidence was uncertain. Many people with bacterial pneumonia may have a cough.
			Specificity	13.4% (2.5 to 48.4)	MODERATE[2]	Cough probably has poor specificity. Among people with suspected acute respiratory infection, it is likely that many people who do not have bacterial pneumonia will also have a cough.
Sputum production	Gentilotti 2022	7 (6392)	Sensitivity	63.9% (40.5 to 82.1)	LOW[3]	Sputum production may have inadequate sensitivity. Many people with bacterial pneumonia may not have productive sputum.
			Specificity	45.3% (25.9 to 66.3)	MODERATE[2]	Sputum production probably has poor specificity. Among people with suspected acute respiratory infection, it is likely that many people who do not have bacterial pneumonia will still have productive sputum.
Discoloured sputum	Gentilotti 2022	9 (3014)	Sensitivity	54.0% (39.8 to 67.7)	MODERATE[2]	Discoloured sputum probably has inadequate sensitivity. It is likely that many

						people with bacterial pneumonia will not have discoloured sputum.
			Specificity	53.0% (39.0 to 66.5)	MODERATE[2]	Discoloured sputum probably has poor specificity. Among people with suspected acute respiratory infection, it is likely that many people who do not have bacterial pneumonia will have discoloured sputum.
Purulent sputum (to detect bacterial exacerbations in people with COPD)	Pazmany 2021	3 (259)	Sensitivity	71% (42 to 90)	VERY LOW[4]	Purulent sputum may have inadequate sensitivity to detect bacterial exacerbations of COPD, but the evidence was uncertain. Many people with bacterial exacerbations of COPD may not have purulent sputum.
			Specificity	51% (30 to 73)	MODERATE[5]	Purulent sputum probably has poor specificity to detect bacterial exacerbations of COPD. Among people with suspected acute respiratory infection, it is likely that many people who do not have bacterial exacerbations of COPD will still have productive sputum.
Chest pain	Gentilotti 2022	15 (8161)	Sensitivity	33.9% (21.5 to 49.0)	MODERATE[2]	Chest pain probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have chest pain.
			Specificity	73.0% (61.7 to 81.9)	LOW[3]	Chest pain may have inadequate specificity. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may still have chest pain.
Dyspnoea	Gentilotti 2022	14 (6215)	Sensitivity	62.6% (53.3 to 71.1)	MODERATE[2]	Dyspnoea probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have dyspnoea.
			Specificity	45.5% (32.1 to 59.5)	MODERATE[2]	Dyspnoea probably has inadequate specificity. Among people with suspected acute respiratory infection, it is likely that

						many people who do not have bacterial pneumonia will still have dyspnoea.
Sore throat	Gentilotti 2022	5 (1096)	Sensitivity	32.6% (20.2 to 48.0)	MODERATE[2]	Sore throat probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have a sore throat.
			Specificity	45.1% (33.1 to 57.6)	MODERATE[2]	Sore throat probably has inadequate specificity. Among people with suspected acute respiratory infection, it is likely that many people who do not have bacterial pneumonia will still have a sore throat.
Runny nose	Gentilotti 2022	7 (4630)	Sensitivity	45.3% (37.3 to 53.4)	MODERATE[2]	Runny nose probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have a runny nose.
			Specificity	41.8% (28.1 to 56.8)	MODERATE[2]	Runny nose probably has inadequate specificity. Among people with suspected acute respiratory infection, it is likely that many people who do not have bacterial pneumonia will still have a runny nose.
Myalgia	Gentilotti 2022	6 (1430)	Sensitivity	41.6% (19.0 to 68.5)	MODERATE[2]	Myalgia probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have myalgia.
			Specificity	61.2% (40.7 to 78.4)	LOW[3]	Myalgia may have inadequate specificity. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may still have myalgia.
Chill	Gentilotti 2022	8 (1933)	Sensitivity	45.7% (31.5 to 60.8)	MODERATE[2]	Chills probably have inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have a chill.
			Specificity	60.2% (48.5 to 70.8)	MODERATE[2]	Chills probably have inadequate specificity. Among people with suspected acute

						respiratory infection, it is likely that many people who do not have bacterial pneumonia will still have chills.
Diarrhoea	Gentilotti 2022	5 (4268)	Sensitivity	10.8% (6.3 to 17.7)	MODERATE[2]	Diarrhoea probably has inadequate sensitivity. It is likely that most people with bacterial pneumonia will not have diarrhoea.
			Specificity	89.5% (75.4 to 95.9)	LOW[3]	Diarrhoea may have adequate specificity. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may not have diarrhoea.
Impaired consciousness	Gentilotti 2022	4 (3208)	Sensitivity	11.7% (9.3 to 14.5)	MODERATE[2]	Impaired consciousness probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have impaired consciousness.
			Specificity	92.9% (90.5 to 94.7)	MODERATE[2]	Impaired consciousness probably has high specificity. Among people with suspected acute respiratory infection, it is likely that most people who do not have bacterial pneumonia will not have impaired consciousness.
$Sp0_2$	Gentilotti 2022	6 (2821)	Sensitivity	22.8% (12.4 to 38.2)	MODERATE[2]	Low oxygen saturations probably have inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have low oxygen saturations.
			Specificity	86.6% (80.7 to 90.9)	LOW[3]	Low oxygen saturations may have adequate specificity. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may not have low oxygen saturations.
Fever >37.8^{0}C	Gentilotti 2022	17 (11219)	Sensitivity	42.0% (26.7 to 58.9)	MODERATE[2]	Fever probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have a fever.

			Specificity	80.4% (59.8 to 91.9)	VERY LOW[1]	Fever may have adequate specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may also not have a fever.
Systolic BP	Gentilotti 2022	4 (3262)	Sensitivity	9.6% (2.8 to 28.3)	MODERATE[2]	Low systolic blood pressure probably has inadequate sensitivity. It is likely that most people with bacterial pneumonia will not have a low systolic blood pressure.
			Specificity	95.0% (80.7 to 98.8)	LOW[3]	Low systolic blood pressure may have high specificity. Among people with suspected acute respiratory infection, most people who do not have bacterial pneumonia may not have a low systolic blood pressure.
Tachycardia	Gentilotti 2022	11 (9474)	Sensitivity	27.2% (15.1 to 43.9)	MODERATE[2]	Tachycardia probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have tachycardia.
			Specificity	84.2% (71.5 to 91.9)	VERY LOW[1]	Tachycardia may have adequate specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may not have tachycardia.
Tachypnoea	Gentilotti 2022	12 (10351)	Sensitivity	27.9% (13.1 to 49.8)	MODERATE[2]	Tachypnoea probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have tachypnoea.
			Specificity	80.2% (58.2 to 92.2)	VERY LOW[1]	Tachypnoea may have adequate specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may not have tachypnoea.

Reduced breath sounds	Gentilotti 2022	4 (459)	Sensitivity	24.7% (8.3 to 54.4)	MODERATE[2]	Reduced breath sounds probably have inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have reduced breath sounds.
			Specificity	89.0% (75.0 to 95.6)	LOW[3]	Reduced breath sounds may have adequate specificity. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may not have reduced breath sounds.
Wheezing	Gentilotti 2022	6 (2403)	Sensitivity	17.3% (9.6 to 29.2)	MODERATE[2]	Wheezing probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have wheeze.
			Specificity	86.4% (70.5 to 94.4)	VERY LOW[1]	Wheezing may have adequate specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may not have wheeze.
Crackles	Gentilotti 2022	10 (6175)	Sensitivity	40.3% (23.6 to 59.7)	MODERATE[2]	Presence of crackles on auscultation probably have inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have crackles.
			Specificity	83.1% (58.5 to 94.5)	VERY LOW[1]	Presence of crackles on auscultation may have adequate specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may not have crackles.
Combinations of symptoms and signs						
Presence/absence of specific symptoms and signs	Schierenberg 2017	6 (not reported)	Area under the curve	Ranged from 53% to 79% depending on model used	VERY LOW[6]	Combinations of signs and symptoms may not have adequate diagnostic accuracy to identify bacterial pneumonia, although this will vary according to the model used.
Combinations of symptoms and signs plus CRP measurement						

Predicted risk threshold 2.5%	Minnaard 2017	8 (5308)	Sensitivity	97% (95 to 98)	MODERATE[7]	At a predicted risk threshold of 2.5%, clinical prediction models incorporating CRP probably have adequate sensitivity. It is likely that most people with bacterial pneumonia will have a predicted risk of >2.5%. .
			Specificity	36% (34 to 37)	MODERATE[7]	At a predicted risk threshold of 2.5%, clinical prediction models incorporating CRP probably have inadequate specificity. Among people with suspected acute respiratory infection, it is likely that many people who do not have bacterial pneumonia will also have a predicted risk >2.5%.
Predicted risk threshold 20%	Minnaard 2017	8 (5308)	Sensitivity	70% (66 to 73)	MODERATE[7]	At a predicted risk threshold of 20%, clinical prediction models incorporating CRP probably have inadequate sensitivity. It is likely that many people with bacterial pneumonia will have a predicted risk <20%.
			Specificity	90% (89 to 91)	LOW[8]	At a predicted risk threshold of 20%, clinical prediction models incorporating CRP may have high specificity. Among people with suspected acute respiratory infection, most people who do not have bacterial pneumonia may have a predicted risk <20%.

1 Downgraded by three levels due to a serious risk of bias and very serious imprecision. Note that inconsistency was not able to be assessed for this outcome.
2 Downgraded by one level for a serious risk of bias. Note that inconsistency was not able to be assessed for this outcome.
3 Downgraded by two levels due to a serious risk of bias and serious imprecision. Note that inconsistency was not able to be assessed for this outcome.
4 Downgraded by three levels for a serious risk of bias and very serious imprecision.
5 Downgraded by one level for a serious risk of bias.
6 Downgraded by one level for serious inconsistency, one level for serious imprecision and one level for publication bias, as authors were unable to access data from at least four publications for inclusion in their IPD meta-analysis.
7 Downgraded by one level for publication bias, as authors were unable to access data from at least four publications for inclusion in their IPD meta-analysis.
8 Downgraded by one level for publication bias (as authors were unable to access data from at least four publications for inclusion in their IPD meta-analysis) and downgraded by one level for serious imprecision.

Table 16: Host biomarkers to detect bacterial or viral respiratory tract infection

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Certainty of the body of evidence	Interpretation of effect
CRP						
CRP >10mg/L	Gentilotti 2022	4 (944)	Sensitivity	92% (56 to 99)	VERY LOW[1]	CRP (>10mg/L) may have high sensitivity, but the evidence was uncertain. Most people with bacterial pneumonia may have a CRP level >10mg/L.
			Specificity	43% (22 to 66)	MODERATE[2]	CRP (>10mg/L) probably has inadequate specificity. Among people with suspected acute respiratory infection, it is likely that many people who do not have bacterial pneumonia will have a CRP level >10mg/L.
CRP >20mg/L	Gentilotti 2022	5 (3531)	Sensitivity	83% (64 to 93)	VERY LOW[1]	CRP (>20mg/L) may have adequate sensitivity, but the evidence was uncertain. Many people with bacterial pneumonia may have a CRP level >20mg/L.
			Specificity	55% (37 to 73)	MODERATE[2]	CRP (>20mg/L) probably has inadequate specificity. Among people with suspected acute respiratory infection, it is likely that many people who do not have bacterial pneumonia will have a CRP level >20mg/L.
CRP >20mg/L (primary care only, adults and children)	Gentilotti 2022	4 (3362)	Sensitivity	78% (57 to 90)	VERY LOW[3]	CRP (>20mg/L) may have adequate sensitivity in a primary care setting, but the evidence was uncertain. Many people with bacterial pneumonia may have a CRP level >20mg/L.

			Specificity	58% (36 to 78)	VERY LOW[4]	CRP (>20mg/L) probably has inadequate specificity in a primary care setting. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may have a CRP level >20mg/L. .
CRP >50mg/L	Gentilotti 2022	5 (4219)	Sensitivity	77% (51 to 91)	VERY LOW[1]	CRP (>50mg/L) may have adequate sensitivity, but the evidence was uncertain. Many people with bacterial pneumonia may have a CRP level >50mg/L
			Specificity	74% (51 to 88)	LOW[5]	CRP (>50mg/L) may have inadequate specificity. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may have a CRP level >50mg/L.
CRP >100mg/L	Gentilotti 2022	6 (4418)	Sensitivity	52% (31 to 72)	MODERATE[2]	CRP (>100mg/L) probably has inadequate sensitivity. It is likely that many people with bacterial pneumonia will not have a CRP level >100mg/L
			Specificity	91% (79 to 97)	LOW[5]	CRP (>100mg/L) may have high specificity. Among people with suspected acute respiratory infection, most people who do not have bacterial pneumonia may have a CRP level ≤100mg/L.
Procalcitonin						
Procalcitonin >0.1 mcg/mL	Gentilotti 2022	4 (1092)	Sensitivity	74% (38 to 93)	VERY LOW[1]	Procalcitonin (>0.1mcg/mL) may have inadequate sensitivity, but the evidence was very uncertain. Many people with bacterial pneumonia may not have a procalcitonin level >0.1mcg/mL.

			Specificity	74% (36 to 94)	VERY LOW[1]	Procalcitonin (>0.1mcg/mL) may have inadequate specificity, but the evidence was very uncertain. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may have a procalcitonin level >0.1mcg/mL.
Procalcitonin >0.25 mcg/mL	Gentilotti 2022	5 (4019)	Sensitivity	44% (14 to 79)	LOW[5]	Procalcitonin (>0.25mcg/mL) may have inadequate sensitivity. Many people with bacterial pneumonia may not have a procalcitonin level >0.25mcg/mL.
			Specificity	89% (50 to 98)	VERY LOW[1]	Procalcitonin (>0.25mcg/mL) may have adequate specificity. Among people with suspected acute respiratory infection, most people who do not have bacterial pneumonia may have a procalcitonin level ≤0.25mcg/mL.
Procalcitonin >0.50 mcg/mL (adults and children)	Gentilotti 2022	4 (1195)	Sensitivity	44% (19 to 33)	LOW[6]	Procalcitonin (>0.50mcg/mL) may have inadequate sensitivity. Many people with bacterial pneumonia may not have a procalcitonin level >0.50mcg/mL.
			Specificity	93% (43 to 100)	VERY LOW[3]	Procalcitonin (>0.50mcg/mL) may have high specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, most people who do not have bacterial pneumonia may have a procalcitonin level ≤0.50mcg/mL.
TRAIL, IP-10 and CRP (ImmunoXpert)						
TRAIL, IP-10 and CRP to diagnose bacterial infection	Carlton 2021	4 (1291)	Sensitivity	85% (75 to 91)	VERY LOW[7]	ImmunoXpert may have adequate sensitivity, but the evidence was uncertain. Most people with bacterial pneumonia may have a positive (bacterial) result.

(adults and children)			Specificity	86% (73 to 93)	VERY LOW[8]	ImmunoXpert may have adequate specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia may have a negative (bacterial) result.
TRAIL, IP-10 and CRP to diagnose viral infection (adults and children)	Carlton 2021	3 (989)	Sensitivity	90% (79 to 96)	VERY LOW[9]	ImmunoXpert may have high sensitivity, but the evidence was uncertain. Most people with viral infection may have a positive (viral) result.
			Specificity	92% (83 to 96)	VERY LOW[7]	ImmunoXpert may have high specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, many people who do not have a viral infection may have a negative (viral) result.
CRP and MxA (FebriDx)						
CRP and MxA to diagnose bacterial infection (adults and children)	Carlton 2021	4 (598)	Sensitivity	84% (75 to 90)	LOW[10]	FebriDx may have adequate sensitivity. Many people with bacterial pneumonia may have a positive (bacterial) result.
			Specificity	93% (90 to 95)	MODERATE[11]	FebriDx probably has high specificity. Among people with suspected acute respiratory infection, it is likely that most people who do not have bacterial pneumonia will have a negative (bacterial) result.
CRP and MxA to diagnose viral infection (adults and children)	Carlton 2021	4 (583)	Sensitivity	87% (72 to 95)	VERY LOW[12]	FebriDx may have adequate sensitivity, but the evidence was uncertain. Many people with viral infection may have a positive (viral) result.
			Specificity	82% (66 to 86)	LOW[10]	FebriDx may have adequate specificity. Among people with suspected acute respiratory infection, many people who

						do not have a viral infection may have a negative (viral) result.
White cell differential count						
White cell count to diagnose pneumonia	Castro-Guardiola 2000, Holm 2007, Liu 2013	3 (1148)	2 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. 1 study reported an area under the curve of 0.65.		VERY LOW[13]	The evidence regarding the diagnostic accuracy of white cell counts to diagnose bacterial respiratory infection was very uncertain.
White cell count to diagnose bacterial pharyngitis	Gulich 1999	1 (179)	Area under the curve	0.68 (no confidence intervals)	LOW[14]	White cell count may have inadequate diagnostic accuracy to diagnose bacterial pharyngitis.
Other host biomarkers						
CRP and neopterin to diagnose bacterial infection	Carlton 2021	1 (198)	Sensitivity	80% (71 to 86)	VERY LOW[15]	CRP and neopterin may have adequate sensitivity, but the evidence was uncertain. Many people with bacterial pneumonia may have an elevated CRP/neopterin level.
			Specificity	82% (71 to 89)	VERY LOW[15]	CRP and neopterin may have adequate specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, many people who do not have bacterial pneumonia will not have an elevated CRP/neopterin level.

1 Downgraded by one level for serious risk of bias, and by two levels for very serious imprecision. Note that inconsistency was not able to be assessed for this outcome.
2 Downgraded by one level for serious risk of bias. Note that inconsistency was not able to be assessed for this outcome.
3 Downgraded by one level for serious risk of bias, one level for indirectness (as adults and children were included) and by two levels for very serious imprecision. Note that inconsistency was not able to be assessed for this outcome.
4 Downgraded by one level for serious risk of bias, one level for indirectness (as adults and children were included) and by one level for serious imprecision. Note that inconsistency was not able to be assessed for this outcome.
5 Downgraded by one level for serious risk of bias, and by one level for serious imprecision. Note that inconsistency was not able to be assessed for this outcome.
6 Downgraded by one level for serious risk of bias and one level for indirectness (as adults and children were included). Note that inconsistency was not able to be assessed for this outcome.
7 Downgraded by one level for serious risk of bias, one level for indirectness (as adults and children were included) and by one level for serious imprecision.
8 Downgraded by one level for serious risk of bias, one level for indirectness (as adults and children were included) and by two levels for very serious imprecision.

9 Downgraded by one level for serious risk of bias, one level for indirectness (as adults and children were included), one level for inconsistency and by one level for serious imprecision.
10 Downgraded by one level for serious indirectness (as adults and children were included) and one level for serious imprecision.
11 Downgraded by one level for serious indirectness (as adults and children were included).
12 Downgraded by one level for serious indirectness (as adults and children were included) and two levels for very serious imprecision.
13 Downgraded by one level for serious risk of bias, one level for indirectness (as all index tests were carried out in a laboratory setting, not actually at point of care), one level for inconsistency and by two levels for very serious imprecision (only a narrative synthesis was possible, and estimates from individual studies varied considerably).
14 Downgraded by one level for indirectness (as the index test was carried out in a laboratory setting, not actually at point of care) and by one level for serious imprecision (no confidence intervals were reported)
15 Downgraded by one level for serious risk of bias, one level for indirectness (as neopterin tests were carried out in a laboratory setting, not actually at point of care), and by one level for serious imprecision.

Table 17: Single pathogen tests for influenza and RSV

Index test	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Certainty of the body of evidence	Interpretation of effect
Single pathogen tests for influenza						
Immunochromatography	Gentiloti 2022	15 (2897)	Sensitivity	65% (47 to 79)	LOW[1]	Immunochromatography tests may have inadequate sensitivity. Many people with influenza may not have a positive test.
			Specificity	96% (92 to 98)	MODERATE[2]	Immunochromatography tests probably have high specificity. Among people with suspected acute respiratory infection, it is likely that most people without influenza will have a negative test.
Immunochromatography (adults and children, primary care only)	Gentiloti 2022	11 (3351)	Sensitivity	56% (36 to 74)	LOW[3]	Immunochromatography tests may have inadequate sensitivity in a primary care setting. Many people with influenza may not have a positive test.
			Specificity	95% (89 to 98)	VERY LOW[4]	Immunochromatography tests may have high specificity in a primary care setting, but the evidence was uncertain. Among people with suspected acute respiratory infection, most people without influenza may have a negative test.

Immunochromatography (adults and children, emergency department only)	Gentiloti 2022	25 (15021)	Sensitivity	71% (60 to 80)	LOW[5]	Immunochromatography tests may have inadequate sensitivity in an emergency department setting. Many people with influenza may not have a positive test.
			Specificity	98% (96 to 99)	MODERATE[6]	Immunochromatography tests probably have high specificity in an emergency department setting. Among people with suspected acute respiratory infection, it is likely that most people without influenza will have a negative test.
Immunochromatography (adults and children, outpatient department only)	Gentiloti 2022	17 (6110)	Sensitivity	66% (55 to 76)	LOW[5]	Immunochromatography tests may have inadequate sensitivity in an outpatient setting. Many people with influenza may not have a positive test.
			Specificity	97% (93 to 99)	MODERATE[6]	Immunochromatography tests probably have high specificity in an outpatient setting. Among people with suspected acute respiratory infection, it is likely that most people without influenza will have a negative test.
Direct immunofluorescence (adults and children)	Gentiloti 2022	19 (7635)	Sensitivity	78% (67 to 86)	VERY LOW[4]	Direct immunofluorescence may have adequate sensitivity, but the evidence was very uncertain. Many people with influenza may have a positive test.
			Specificity	95% (90 to 98)	LOW[3]	Direct immunofluorescence tests may have high specificity. Among people with suspected acute respiratory infection, most people without influenza may have a negative test.
Direct immunofluorescence (adults and children, emergency department only)	Gentiloti 2022	5 (1314)	Sensitivity	82% (72 to 89)	VERY LOW[4]	Direct immunofluorescence may have adequate sensitivity in an emergency department setting, but the evidence was very uncertain. Many people with influenza may have a positive test.
			Specificity	96% (93 to 97)	LOW[3]	Direct immunofluorescence tests may have high specificity in an emergency department setting. Among people with suspected acute respiratory infection, most people without influenza may have a negative test.

Optical immunoassay (adults and children)	Gentiloti 2022	9 (3910)	Sensitivity	68% (51 to 81)	VERY LOW[4]	Optical immunoassays may have inadequate sensitivity, but the evidence was very uncertain. Many people with influenza may not have a positive test.
			Specificity	88% (81 to 93)	VERY LOW[4]	Optical immunoassays may have adequate specificity, but the evidence was very uncertain. Among people with suspected acute respiratory infection, many people without influenza may have a negative test.
MariPOC test (adults and children)	Gentiloti 2022	5 (1231)	Sensitivity	78% (61 to 89)	VERY LOW[4]	MariPOC tests may have adequate sensitivity, but the evidence was very uncertain. Many people with influenza may have a positive test.
			Specificity	99% (97 to 99)	LOW[3]	MariPOC tests may have high specificity. Among people with suspected acute respiratory infection, most people without influenza may have a negative test.
Chemiluminescent neuraminidase assay (adults and children)	Gentiloti 2022	4 (787)	Sensitivity	81% (51 to 94)	VERY LOW[7]	Chemiluminescent neuraminidase assays may have adequate sensitivity, but the evidence was uncertain. Many people with influenza may have a positive test.
			Specificity	82% (65 to 91)	VERY LOW[7]	Chemiluminescent neuraminidase assays may have adequate specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, many people without influenza may have a negative test.
Nucleic acid amplification tests: standalone, single pathogen PCR (adults and children)	Gentiloti 2022	30 (25027)	Sensitivity	95.1% (89.3 to 97.8)	VERY LOW[4]	Single pathogen PCR tests may have high sensitivity, but the evidence was uncertain. Most people with influenza may have a positive test.
			Specificity	97.5% (95.5 to 98.7)	LOW[3]	Single pathogen PCR tests may have high specificity. Among people with suspected acute respiratory infection, most people without influenza may have a negative test.

Nucleic acid amplification tests: non-PCR based (adults and children)	Gentiloti 2022	23 (4863)	Sensitivity	92% (88 to 94)	VERY LOW[4]	Non-PCR based nucleic acid amplification tests may have high sensitivity, but the evidence was uncertain. Most people with influenza may have a positive test.
			Specificity	98% (95 to 99)	LOW[3]	Non-PCR based nucleic acid amplification tests may have high specificity. Among people with suspected acute respiratory infection, most people without influenza may have a negative test.
Nucleic acid amplification tests: non-PCR based (adults and children, emergency department only)	Gentiloti 2022	14 (3138)	Sensitivity	91% (87 to 94)	VERY LOW[4]	Non-PCR based nucleic acid amplification tests may have high sensitivity in an emergency department setting, but the evidence was uncertain. Most people with influenza may have a positive test.
			Specificity	98% (95 to 99)	LOW[3]	Non-PCR based nucleic acid amplification tests may have high specificity in an emergency department setting. Among people with suspected acute respiratory infection, most people without influenza may have a negative test.
Single pathogen tests for RSV						
Direct immunofluorescence	Onwuchekwa 2023	1 (49)	Sensitivity	56% (31 to 78)	VERY LOW[8]	Direct immunofluorescence may have inadequate sensitivity, but the evidence was uncertain. Many people who have RSV may not have a positive test.
			Specificity	100% (89 to 100)	VERY LOW[8]	Direct immunofluorescence may have high specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, most people without RSV may have a negative test.
Rapid antigen test	Onwuchekwa 2023	1 (281)	Sensitivity	18% (12 to 27)	LOW[9]	Rapid antigen tests may have inadequate sensitivity. Most people who have RSV may not have a positive test.
			Specificity	98% (86 to 100)	VERY LOW[10]	Rapid antigen tests may have high specificity, but the evidence was uncertain. Among people with suspected acute respiratory infection, most people without RSV may have a negative test.

1 Downgraded by one level for serious risk of bias and one level for serious imprecision. Note that inconsistency was not able to be assessed for this outcome.
2 Downgraded by one level for serious risk of bias. Note that inconsistency was not able to be assessed for this outcome.
3 Downgraded by one level for serious risk of bias and one level for indirectness (as adults and children were included). Note that inconsistency was not able to be assessed for this outcome.

4 Downgraded by one level for serious risk of bias, one level for indirectness (as adults and children were included), and one level for serious imprecision. Note that inconsistency was not able to be assessed for this outcome.
5 Downgraded by one level for serious indirectness and one level for serious imprecision.
6 Downgraded by one level for serious indirectness.
7 Downgraded by one level for serious risk of bias, one level for indirectness (as adults and children were included), and two levels for very serious imprecision. Note that inconsistency was not able to be assessed for this outcome.
8 Downgraded by two levels for imprecision due to wide confidence intervals and very small sample size, and one level for indirectness (as unclear whether this test was suitable for use at point of care).
9 Downgraded by one level for risk of bias and one level for indirectness (as this study included some retrospective [frozen] samples, and may have included hospitalised participants).
10 Downgraded by one level for risk of bias, one level for indirectness (as this study included some retrospective [frozen] samples, and may have included hospitalised participants) and one level for serious imprecision.

Table 18: Multiplex PCR for diagnosis of influenza and RSV

Index tests	Source of data	No. of included studies (participants)	Outcome	Result (95% CI)	Certainty of the body of evidence	Interpretation of effect
RSV						
All multiplex PCR tests for RSV	Farfour 2022, Morris 2021, Yin 2022, Youngs 2019, Zuurbier 2022	5 studies (2273)	Sensitivity	84.9% (73.5 to 91.9)	VERY LOW[1]	Multiplex PCR tests may have adequate sensitivity, but the evidence was uncertain. Most people with RSV may have a positive test.
			Specificity	99.5% (99.1 to 99.7)	MODERATE[2]	Multiplex PCR tests probably have high specificity. Among people with suspected acute respiratory infection, it is likely that most people without RSV will have a negative test.
Cobas Liat tests for RSV	Yin 2022, Youngs 2019	2 studies (965)	Sensitivity	86.7% (59.5 to 96.6)	VERY LOW[1]	Cobas Liat tests may have adequate sensitivity, but the evidence was uncertain. Most people with RSV may have a positive test.
			Specificity	99.3% (98.5 to 99.6)	MODERATE[2]	Cobas Liat tests probably have high specificity. Among people with suspected acute respiratory infection, it is likely that most people without RSV will have a negative test.

Xpert Xpress tests for RSV	Morris 2021, Zuurbier 2022	2 studies (1109)	Sensitivity	84.5% (69.4 to 92.9)	VERY LOW[1]	Xpert Xpress tests may have adequate sensitivity, but the evidence was uncertain. Most people with RSV may have a positive test.
			Specificity	99.6% (99.0 to 99.9)	MODERATE[2]	Xpert Xpress tests probably have high specificity. Among people with suspected acute respiratory infection, it is likely that most people without RSV will have a negative test.
Influenza A						
All multiplex PCR tests for influenza A	Escarate 2022, Farfour 2022, Morris 2021, Maignan 2016, Valentin 2019 (two tests included), Yin 2022, Youngs 2019.	8 studies (2212)	Sensitivity	98.2% (90.7 to 99.7)	LOW[3]	Multiplex PCR tests may have high sensitivity. Most people with influenza A may have a positive test.
			Specificity	98.6% (96.6 to 99.4)	LOW[3]	Multiplex PCR tests may have high specificity. Among people with suspected acute respiratory infection, most people without influenza A may have a negative test.
Cobas Liat tests for influenza A	Maignan 2016, Valentin 2019, Yin 2022, Youngs 2019.	4 studies (1259)	Sensitivity	99.8% (18.8 to 100)	VERY LOW[4]	Cobas Liat tests may have high sensitivity, but the evidence was uncertain. Most people with influenza A may have a positive test.
			Specificity	97.9 (94.0 to 99.3)	MODERATE[5]	Cobas Liat tests probably have high specificity. Among people with suspected acute respiratory infection, it is likely that most people without influenza A will have a negative test.

Xpert Xpress tests for influenza A	Escarate 2022, Morris 2021, Valentin 2019.	3 studies (754)	Sensitivity	97.0% (92.9 to 98.7)	MODERATE [2]	Xpert Xpress tests probably have adequate sensitivity. It is likely that most people with influenza A will have a positive test.
			Specificity	98.5% (96.2 to 99.4)	MODERATE [2]	Xpert Xpress tests probably have high specificity. Among people with suspected acute respiratory infection, it is likely that most people without influenza A will have a negative test.
Influenza B						
All multiplex PCR tests for influenza B	Escarate 2022, Maignan 2016, Valentin 2019 (two tests included), Yin 2022, Youngs 2019.	6 studies (1823)	Sensitivity	94.5% (88.6 to 97.5)	VERY LOW[6]	Multiplex PCR tests may have high sensitivity, but the evidence was uncertain. Most people with influenza B may have a positive test.
			Specificity	99.1 (98.1 to 99.6)	LOW[3]	Multiplex PCR tests may have high specificity. Among people with suspected acute respiratory infection, most people without influenza B may have a negative test.
Cobas Liat tests for influenza B	Maignan 2016, Valentin 2019, Yin 2022, Youngs 2019.	4 studies (1420)	Sensitivity	92.9% (84.3 to 96.9)	LOW[6]	Cobas Liat tests may have high sensitivity. Most people with influenza B may have a positive test.
			Specificity	99.0% (97.6 to 99.6)	MODERATE [5]	Cobas Liat tests probably have high specificity. Among people with suspected acute respiratory infection, it is likely that most people without influenza B will have a negative test.
Xpert Xpress tests for influenza B	Escarate 2022, Valentin 2019.	2 studies (403)	Sensitivity	96.4% (90.7 to 99.0)	MODERATE [2]	Xpert Xpress tests probably have high sensitivity. It is likely that most people with influenza B will have a positive test.
			Specificity	99.4% (97.4 to 99.8)	MODERATE [2]	Xpert Xpress tests probably have high specificity. Among people with suspected acute respiratory

						infection, it is likely that most people without influenza B will have a negative test.
Influenza A and/or B						
All multiplex PCR tests for influenza A/B	Boku 2013, Escarate 2022, Hansen 2018, Maignan 2016, Valentin 2019 (two tests included), Yin 2022, Youngs 2019.	8 studies (2162)	Sensitivity	97.4% (92.9 to 99.0)	LOW[3]	Multiplex PCR tests may have high sensitivity. Most people with influenza A/B may have a positive test.
			Specificity	97.0% (94.5 to 98.4)	LOW[3]	Multiplex PCR tests may have high specificity. Among people with suspected acute respiratory infection, most people without influenza A/B may have a negative test.
Cobas Liat tests for influenza A/B	Hansen 2018, Maignan 2016, Valentin 2019, Yin 2022, Youngs 2019.	5 studies (1712)	Sensitivity	97.1% (88.6 to 99.3)	LOW[6]	Cobas Liat tests may have high sensitivity. Most people with influenza A/B may have a positive test.
			Specificity	96.8% (93.2 to 98.5)	MODERATE[5]	Cobas Liat tests probably have high specificity. Among people with suspected acute respiratory infection, it is likely that most people without influenza A/B will have a negative test.
Xpert Xpress tests for influenza A/B	Escarate 2022,	2 studies (403)	Sensitivity	97.5% (93.6 to 99.1)	MODERATE[2]	Xpert Xpress tests probably have high sensitivity. It is likely that most people with influenza A/B will have a positive test.

	Valentin 2019		Specificity	97.5% (94.5 to 98.9)	MODERATE [2]	Xpert Xpress tests probably have high specificity. Among people with suspected acute respiratory infection, it is likely that most people without influenza A/B will have a negative test.

1 Downgraded by one level for serious risk of bias and by two levels for very serious imprecision.
2 Downgraded by one level for serious risk of bias.
3 Downgraded by one level for serious risk of bias and by one level for serious inconsistency (due to a wide prediction region and relatively large tau2).
4 Downgraded by one level for serious inconsistency (due to a wide prediction region and relatively large tau2) and by two levels for very serious imprecision.
5 Downgraded by one level for serious inconsistency (due to a wide prediction region and relatively large tau2).
6 Downgraded by one level for serious inconsistency (due to a wide prediction region and relatively large tau2) and by one level for serious imprecision.
7 Downgraded by one level for risk of bias, by one level for serious inconsistency (due to a wide prediction region and relatively large tau2) and by one level for serious imprecision.

See appendices of individual reviews for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

See individual reviews for details of the searches and the number of studies identified at each stage of sifting. 1 study was identified for review question 1, and 8 studies were identified for review question 2. A review of the economic evidence was not undertaken for review question 3, due to the overlap with review question 2.

A study selection summary is presented as a PRISMA diagram in an appendix in each review.

Full references of the included studies can be found in each review.

1.1.7.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in an appendix of each review.

1.1.8 Summary of included economic evidence

The summaries of studies tables are presented below for each of the evidence reviews. Fuller details are included in each evidence review.

Table 19: RQ1: Symptoms, signs, and early warning scores – included economic studies

Study details	Applicability and limitations	Other comments	Costs	Effects	ICER	Uncertainty
Little (2014)	Partially applicable Minor limitations. This study is only partially relevant to the review question, but highlights the possible impact of using symptoms to assess short term ARI conditions.	• UK NHS setting • Cost-utility analysis • Cost-effectiveness analysis • Population: Patients aged ≥ 3 years and had acute sore throat • Comparators: 1. Clinical scores (FeverPAIN) 2. Rapid antigen detection tests (RADTs) 3. Delayed antibiotic prescribing (DP)	Total costs at 14 and 28-days (95% CI): - DP: £49.70 (43.30 to 56.00) - FeverPAIN: £45.90 (41.50 to 50.20) - RADT: £48.50 (45.00 to 52.00)	QALYs in 14-day period (95% CI (CI)): - DP: 0.0057 (0.0044 to 0.007) - FeverPAIN: 0.0058 (0.0045 to 0.0071) - RADT: 0.00584 (0.0046 to 0.0071 QALYs in 28-day period (95% CI): - DP: 0.0171 (0.0131 to 0.0211) - FeverPAIN: 0.01741 (0.0135 to 0.0213) - RADT: 0.01752 (0.0138 to 0.0212 Symptom score - DP: 3.15 (2.93 to 3.37) - FeverPAIN: 2.83 (2.61 to 3.05) - RADT: 2.84 (2.62 to 3.07)	Cost-utility analysis: -DP is dominated (more costly and less clinically effective) by FeverPAIN and RADT. -Compared to FeverPain, RADT generates an ICER of £74,286 and £24,528 at 14 and 28 days respectively. Cost-effectiveness analysis: -DP is dominated (more costly and less clinically effective) by FeverPAIN and RADT. -RADT is dominated (more costly and less clinically effective) by FeverPAIN	Cost-effectiveness acceptability curves indicated considerable uncertainty, particularly around the QALY estimate. At a threshold of £30,000 per QALY, the probabilities that delayed prescribing, clinical score and RADT are the most cost-effective option were 25%, 40% and 35% respectively, for the 14-day period, and 28%, 38% and 35%, respectively, for the 28-day period.

Abbreviations: CI = confidence interval; DP = delayed antibiotic prescribing; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years; RADT = rapid antigen detection test.

Table 20: RQ2: Different near-patient, rapid microbiological or biomarker tests – included economic studies

Study details	Applicability	Other comments	Costs	Effects	ICER	Uncertainty
C-reactive protein tests						
Holmes (2018)	Directly applicable	Adult patients; symptoms of ARI for >12 hours Alere Afinion AS100 CRP POCT UK NHS perspective.	Costs per patient Pragmatic use of testing: Test £52.35 No test £40.41 Adhering to guidelines: Test £48.79 No test £39.48	QALYs per patient Pragmatic use of testing: Test 0.0615 No test 0.0609 Adhering to guidelines: Test 0.0577 No test 0.0556	Pragmatic use of testing: £19,705 Adhering to guidelines: £4,390	*Pragmatic use of testing* The probability that test is cost-effective at £20,000 per QALY threshold is 49.06%, and 62.82% at £30,000 per QALY threshold. *Adhering to guidelines* Probability test is cost-effective at £20,000/QALY threshold is 84.10%, and 86.33% at £30,000. If the test cost 18p more, or test use fell by 5%, the ICER exceeds £20,000. Test results in higher utility but at a higher cost in 75% of simulations.
Hunter (2015)	Directly applicable	Adult patients attending primary care with RTI symptoms Afinion Analyzer CRP POCT by GP; CRP	Cost per 100 patients GP+CRP: £18,039 Nurse+CRP: £17,401 GP+CRP+training: £18,431	QALYs per 100 patients GP+CRP: 255.764 Nurse+CRP: 255.761	GP+CRP and nurse+CRP are dominant over current practice.	GP+CRP is dominant compared to current practice in 50% of simulations, in 65% the nurse+CRP is dominant and in 19% the

		POCT by nurse; CRP POCT by GP+ communication training for GP UK NHS perspective, primary care	No test: £18,081	GP+CRP+training: 255.588 No test: 255.630		GP+CRP+training is dominant. Nurse+CRP has the highest NMB in CEAC. Changing most model parameters has little impact on conclusions.
Oppong (2013)	Partially applicable Conducted in Sweden and Norway but used a health service perspective	Patients aged ≥18 years; presenting to GP with acute or worsened cough as the main symptom for up to 28 days, or suspected LRTI CRP POCT UK NHS perspective, primary care	Test increases healthcare costs by €11.27 per patient	QALY gain of 0.0012 with test per patient	€9,391	At a WTP threshold of €30,000, the probability of POC CRP being cost-effective is approximately 70%.
Francis (2020)	Directly applicable	Bacterial exacerbation of COPD Alere Afinion CRP POCT UK NHS perspective	Costs per patient: Test: £759.35 No test: £629.72	QALYs per patient: Test: 0.3 No test: 0.2915	£15,251	Results remained reasonably robust when cost inputs were changed but were sensitive to changes in QALY inputs. The ICER would reduce to £1,054 if COPD-related costs only were included. Most results found CRP POCT to be more costly but more effective. The CUA (using imputation

						and an ITT approach) gave an ICER of £14,334.
Group A Streptococcus tests (including Group C/G)						
Fraser (2020)	Directly applicable	Adults and children who present with an acute sore throat Group A streptococcus (GAS) POCT (14 tests evaluated) in conjunction with clinical scoring tools e.g. Centor and FeverPAIN score for strep A UK NHS and Personal Social Services.	Costs per 1000 patients in primary care: NADAL Strep A–test (cheapest test): £54,394 Cobas Liat Strep A Assay (most expensive test): £71,277 No test: £49,147 Costs per 1000 patients in secondary care: NADAL Strep A–test (cheapest test): £49,318 Cobas Liat Strep A Assay (most expensive): £65,186 No test £49,147	QALYs per 1000 patients in primary care: Abbott Clearview Exact Strep A cassette or test strip (lowest QALYs): 859.821 Cepheid's Xpert Xpress Strep A test (highest QALYs): 895.829 No test: 859.825 QALYs per 1000 patients in secondary care: Abbott Clearview tests generated fewer QALYs than usual care; remaining tests all generated more QALYs than usual care	Usual care dominant over Abbott Clearview Exact Strep A cassette or test strip ICERs for remaining tests suggest testing is more costly but more effective than usual care (primary and secondary care)	*Primary care* Results were similar to the base-case results, with ICERs indicating that usual care dominated two (the Abbott Clearview Strep A tests) of the 14 tests. The probability for testing to be cost-effective was zero at a cost-effectiveness threshold of £20,000 per QALY in all scenarios, regardless of the test used. The base-case ICERs are highly sensitive to model assumptions and inputs. *Secondary care* Results mirrored the primary care model.
Little (2014)	Partially applicable	Patients aged ≥3y; acute sore throat	Costs per patient:	QALYs per patient:	£74,286 (14 day) £24,528 (28 day)	At threshold of £30,000/QALY, the

	Intervention includes FeverPAIN which is not relevant to review inclusion criteria; includes children; results may still be useful given UK-based study and NHS perspective	Lancefield group A/C/G streptococci Clinical scoring algorithm (FeverPAIN) +RADT if score high on algorithm UK NHS perspective.	RADT £48.50 Clinical algorithm: £45.90 Control: £49.70	RADT 0.018 Clinical algorithm: 0.017 Control 0.017		probabilities of cost-effectiveness are 25%, 40% and 35%, for the delayed control, clinical algorithm and RADT groups, respectively (14-day results). For the 28-day QALY gain, the same values are 28%, 38% and 35%.
Other tests						
Michaelidis (2014)	Partially applicable US-based but took a healthcare system perspective; results may be relevant	Adults with ARTI symptoms POC procalcitonin-guided antibiotic therapy US healthcare system, outpatient clinic.	Costs per patient Patients judged to require antibiotics: Test $51 No test $29 Prior to any antibiotic decision: Test: $49 No test $15	QALYs per patient Patients judged to require antibiotics: Test: 0.00746 No test: 0.00765 Prior to any antibiotic decision: Test: 0.00743 No test: 0.00749	Patients judged to require antibiotics: $118,828 Prior to any antibiotic decision: $575,249	None conducted for cost-utility analyses.
Nicholson (2014)	Directly applicable	Patients aged >65y, or >18y with chronic heart or lung disease; acute exacerbation of chronic cardio-pulmonary illness or influenza-like illness of <7 days	Cost per patient: PCR: £1,978 Traditional: £2,327 POCT: £2,159	QALYs per patient PCR: 0.007779 Traditional: 0.007588 POCT: 0.008035	Traditional laboratory culture dominated. POCT compared to PCR: £734,717	Price reduction of the tests has a relatively small impact on results. Ranking of the strategies remains the same as the base case.

		Influenza A and B, respiratory syncytial virus and pneumococcal infection Rapid near-patient diagnostic tests (Quidel for influenza, and BinaxNOW for the pneumococcal antigen) UK NHS perspective, hospital setting				Probabilities (of error) of being cost-effective at WTP thresholds of £20,000 and £30,000 respectively are 0.183 and 0.186 for the POCT; 0.783 and 0.781 for PCR and 0.034 and 0.033 for the traditional strategy.
Abbreviations: CI = confidence interval; DP = delayed antibiotic prescribing; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life years; RADT = rapid antigen detection test; POCT = point of care test; PCR = polymerase chain reaction; WTP = willingness to pay; POC = point of care; ARTI = acute respiratory tract infection; LRTI = lower respiratory tract infection; ICER = incremental cost effectiveness ratio; NMB = net monetary benefit; CEAC = cost effectiveness acceptability curve						

1.1.9 Economic model

Economic modelling was not undertaken for any of the review questions.

1.1.10 Unit costs

Near patient rapid tests

Unit costs of near-patient tests are presented in Table 21.

Unit costs for the different C-reactive protein tests are taken from publicly available sources. These include the cost of the test cartridges and the cost of the analyser. For tests to detect procalcitonin or strep A, unit costs were obtained from relevant NICE guidance. All costs are exclusive of VAT.

Unit costs of tests for pneumococcal and influenza antigens could not be located in publicly available sources, and therefore were taken from economic evaluations of these tests. The costs in Table 4 for these tests also include the staff time to perform the test together with the cost of the equipment and materials.

Table 21: Costs of rapid near-patient tests

Test	Cost	Source
C-reactive protein tests		
QuikRead	£1,050 for the analyser £215 for 50 single use tests	NICE Medtech Innovation Briefing [MIB78] https://www.nice.org.uk/advice/mib78
COBAS Liat	£22,396.78 for the analyser	NHS Supply chain (accessed 25/07/23) https://my.supplychain.nhs.uk/catalogue/product/hhh3461
LumiraDX	£5,400 for the analyser £3.80 per test strip	NHS Supply chain https://my.supplychain.nhs.uk/catalogue/product/hhh3868 https://my.supplychain.nhs.uk/catalogue/product/hhh3873
Alere Afinion	£1,200 for the analyser £3.50 per test cartridge	NICE Medtech Innovation Briefing [MIB81] https://www.nice.org.uk/advice/mib81

FebriDx	£12.75 per test	NICE Medtech Innovation Briefing [MIB224] Test for CRP and myxovirus resistance protein A (MxA) https://www.nice.org.uk/advice/mib224
Strep A tests		
Clearview Exact Strep A cassette (Abbott)	£2.72	NICE diagnostic guidance for rapid tests for group A streptococcal infections in people with a sore throat [DG38]
Clearview Exact Strep A dipstick (Abbott)	£1.92	NICE diagnostic guidance for rapid tests for group A streptococcal infections in people with a sore throat [DG38]
Strep A rapid test cassette (Biopanda Reagents)	£0.82	NICE diagnostic guidance for rapid tests for group A streptococcal infections in people with a sore throat [DG38]
Strep A rapid test dipstick (Biopanda Reagents)	£0.64	NICE diagnostic guidance for rapid tests for group A streptococcal infections in people with a sore throat [DG38]
QuikRead Go Strep A test kit (Orion Diagnostica)	£4.34	NICE diagnostic guidance for rapid tests for group A streptococcal infections in people with a sore throat [DG38]
Alere TestPack Plus Strep A cassette (Abbott)	£2.70	NICE diagnostic guidance for rapid tests for group A streptococcal infections in people with a sore throat [DG38]
Alere i Strep A 2 (Abbott)	£22.94	NICE diagnostic guidance for rapid tests for group A streptococcal infections in people with a sore throat [DG38]
Cobas Strep A assay on Liat system (Roche Diagnostics)	£35	NICE diagnostic guidance for rapid tests for group A streptococcal infections in people with a sore throat [DG38]

Xpert Xpress Strep A (Cepheid)	£4.25	NICE diagnostic guidance for rapid tests for group A streptococcal infections in people with a sore throat [DG38]
Other tests		
Pneumococcal antigen	£25.56 per test	Includes staffing and materials (BinaxNOW) *Source: Nicholson (2014)*
Influenza antigen	£15.83 per test	Includes staffing and materials (Quidel® QuickVue Influenza A + B) *Source: Nicholson (2014)*
Procalcitonin	£13.79 per test	From DG18: procalcitonin testing for diagnosing and monitoring sepsis

Antibiotics

Unit cost of courses of antimicrobials for treating community-acquired pneumonia for adults aged 18 and over, recommended in NICE Guideline [NG138], are provided in Table 22.

Table 22: Unit costs of antibiotics for community-acquired pneumonia

Severity of pneumonia	Treatment	Cost of treatment
Low severity	Amoxicillin (500mg 3 times a day for 5 days)	£1.77
Low severity (penicillin allergy)	Doxycycline (200 mg on first day, then 100 mg once a day for 4 days)	£1.10
	Clarithromycin (500 mg twice a day for 5 days)	£4.08
Medium severity	Amoxicillin (500mg 3 times a day for 5 days) Clarithromycin (500 mg twice a day for 5 days)	**£5.85**
Medium severity (if penicillin allergy)	Doxycycline (200 mg on first day, then 100 mg once a day for 4 days)	£1.10
	Clarithromycin (500 mg twice a day for 5 days)	£4.08

High severity	**Co-**amoxiclav (125mg/500mg 3 times a day for 5 days) Clarithromycin (500 mg twice a day for 5 days)	£6.10
High severity (if penicillin allergy)	Levofloxacin (500 mg twice a day for 5 days)	£18.90

Source: NHS Electronic drug tariff (accessed 12/07/2023)

Locations of care

The cost of hospital admission and ITU admission for people with pneumonia and lower respiratory tract infection are represented in Table 23 below, to aid consideration of cost effectiveness on the escalation of care for people judged to have severe illness.

Table 23: Unit costs of hospital admission

Parameter	Average unit cost
Cost of hospital admission for pneumonia	
Lobar, Atypical or Viral Pneumonia, with Multiple Interventions	£7,258
Lobar, Atypical or Viral Pneumonia, with Single Intervention	£4,534
Lobar, Atypical or Viral Pneumonia, without Interventions	£2,259
Cost of hospital admission for lower respiratory tract infection	
Unspecified Acute Lower Respiratory Infection with Interventions	£4,569
Unspecified Acute Lower Respiratory Infection without Interventions	£1,531
Cost of ITU	
Adult Critical Care, 6 or more Organs Supported	£2,985
Adult Critical Care, 5 Organs Supported	£2,892
Adult Critical Care, 4 Organs Supported	£2,861
Adult Critical Care, 3 Organs Supported	£2,587
Adult Critical Care, 2 Organs Supported	£2,278
Adult Critical Care, 1 Organ Supported	£1,587
Adult Critical Care, 0 Organs Supported	£1,640

Source: NHS cost collection 2021/22

1.1.11 The committee's discussion and interpretation of the evidence

The committee discussion below relates to all of the evidence analysed in reviews A, B and C and summarised in this document.

1.1.11.1. The outcomes that matter most

None of the included studies provided direct evidence about virtual wards or ARI hubs. This meant that the committee's consideration of these was entirely based on their expertise and

experience of them. They noted that some of the severity scores might lend themselves to consensus recommendations about using the acute respiratory infection pathway, but that the scores were not validated or tested in undifferentiated populations in primary care which added additional uncertainty.

The committee agreed that for review question 1 (see evidence review [A]) and review question 2 (see evidence review [B]) the key outcomes related to severe illness so they were most interested in whether signs symptoms and scores could predict mortality, hospitalisation (including ICU) or other kinds of escalation of care. They were also interested in quality-of-life outcomes, such as patient acceptability and preference. They agreed that signs and symptoms, and physiological parameters including early warning scores (EWS) that could accurately predict severe illness (for which hospitalisation or mortality may be used as proxies) would be most useful to healthcare practitioners who were making an initial assessment of people with suspected ARI because they would help them to decide which care pathway best matched their level of risk of severe illness. The committee saw evidence for outcomes of mortality and escalation of care, and also for antibiotic prescribing, however for most point of care tests (POCT) there were only data for mortality. Only C-reactive protein (CRP) had outcome data for hospital admissions.

For review question 3 (see evidence review [C]), the committee were interested in diagnostic outcomes such as sensitivity, specificity and receiver-operator characteristic curves and area under the curve calculations. The question related to the prescribing of antibiotics (both antimicrobial and antiviral), so whilst acknowledging the importance of test sensitivity, in the interests of good antimicrobial stewardship, the committee agreed that specificity was the most important outcome since more specific tests would mean that the people who received medication would be more likely to have an infection. They agreed that a specificity of 75% was a reasonable value to use for this purpose.

1.1.11.2 The quality of the evidence

The committee noted the paucity of the evidence generally that meant they were unable to make very specific, strong recommendations in most areas. They particularly noted that most of the evidence was in older populations, and that the evidence reviewers had been unable to perform any sub-group analyses. They noted that people from some groups were known to have higher risk for deterioration in ARI, for example people with learning disabilities and autism. Some groups responded differently to biological tests, for example if they were very elderly or during pregnancy and the post-partum period. The committee ensured that the research recommendations included sub group analyses for protected characteristics and for pregnancy (see appendix K).

The committee also noted concern from a stakeholder that whooping cough had been excluded from one of the reviews as a childhood illness, but that whooping cough was more common in adults than children. While the committee agreed this was the case, they noted that there are very few cases of whooping cough in England each year and that presentation in adults tends to be atypical. For these reasons they agreed it was not an important omission.

The committee considered the evidence for the usefulness of symptoms, signs and EWS for predicting mortality and escalation of care (including hospital admission). This included evidence for absence of cough, fever, anterior cervical adenopathy, tender anterior cervical adenopathy and any exudates in people with suspected pharyngitis, and for the following EWS in suspected ARI (including pneumonia):

Centor, CRB-65, CURB-65, PSI, CREWS, NEWS, SIRS, SEWS, S-NEWS, ATS 2001, IDSA/ATS 2007, SCAP/CURXO-80, SMART-COP and REA-ICU.

Since the review was a tertiary review (a review of systematic reviews), the quality of the included studies was assessed with the ROBIS tool. Using this tool, 5 included reviews were at low risk of bias, 1 was at unclear risk of bias and 3 were at high risk of bias.

The review of POCT did not find any evidence for several of the tests that were outlined in the review protocol:

- Rapid PCR tests
- Urinary antigen tests
- Serum sodium
- Urea nitrogen
- Partial pressure O^2
- Blood gases
- Full blood count
- White blood cell count
- Myxovirus resistance protein A
- TNF-related apoptosis-induced ligand (TRAIL)

However, there was evidence for CRP and procalcitonin. There was also evidence on rapid antigen tests for Group A Streptococcus and influenza. All of the outcomes reported by this review were assessed using GRADE as being of very low confidence, which means that further research is likely to change the estimated effectiveness of the tests. The main reason for downgrading was for methodological limitations, with very serious methodological concerns being noted for all of the included studies. This was mostly due to uncertainties around selection bias and high risk of bias due to lack of blinding and incomplete outcome data reporting. The committee noted that some of the studies were conducted in resource poor settings where the prescribing context was likely to be different. They acknowledged that there were some concerns with comparing outcomes from high income and middle income countries.

For the diagnostic question about identifying bacterial or viral infection, the committee were reassured that there was a range of evidence for symptoms and signs, CRP, procalcitonin and white cell differential count. There was also evidence for viral tests for influenza and for respiratory syncytial virus (RSV). The evidence showed that point of care microbiological tests for people with suspected ARIs were not accurate enough to determine whether an infection was bacterial or viral. The committee noted that the evidence showed that some tests for influenza virus and respiratory syncytial virus (RSV) were quite accurate, especially as rule in tests (i.e. they had high specificity), however the most accurate tests were ones that would not normally be available outside of hospital settings. The committee also noted that normally, decisions about prescribing for flu are made by the UKHSA and communicated locally via communicable disease control units. Therefore, they did not recommend testing for flu. The evidence for symptoms and signs was of very low to moderate quality assessed using GRADE. The main reasons for downgrading were risk of bias/methodological

limitations and imprecision. The evidence for biomarker tests and for flu/RSV tests was also assessed using GRADE as ranging from very low to moderate due to methodological limitations, imprecision and indirectness.

The authors also note that for some outcomes it was not possible to assess imprecision or inconsistency, so the committee noted that some of the GRADE assessments may be spuriously high.

Overall, the quality of the evidence was poor, with the majority of the evidence being assessed as low or very low confidence. This meant that the committee had to defer to clinical judgment in many recommendations, and to make a lower strength recommendation than they would have been able to make if the evidence had been more robust. None of the evidence came from studies that included remote consultations and therefore the committee had to use their expertise and experience to extrapolate from the evidence about face-to-face consultations to remote consultations.

1.1.11.3 Benefits and harms

The committee were asked to produce a guideline that covered the first encounter between an NHS service and a person with symptoms and signs that might indicate they had an ARI.

The purpose of the guideline is to support the decisions made in that initial encounter to get the person onto the best care pathway for them. The committee noted that the first contact could occur in a range of settings (both in-person and remotely), with a wide variety of healthcare practitioners and professionals with very different training and skills. The committee agreed that, in the majority of cases, ARI were self-limiting and people could be given self-care advice, and advice about what to do if things didn't improve, but they agreed it was very important to identify the cases that weren't self-limiting and could lead to serious illness and noted the overlaps between ARI symptoms and symptoms of other illnesses, for example some heart conditions. The committee agreed that once the initial assessment had been made, a range of NICE guidelines relating to respiratory infections came into play, for example NICE's guidelines on antimicrobial prescribing for acute sore throat and acute cough.

Remote consultations

The committee discussed the evidence from the review about the usefulness of signs symptoms and early warning scores. They noted that although the evidence came from a range of settings, including primary care, emergency departments and outpatients, and in one case nursing homes, none of the systematic reviews included in the evidence has assessed any of the tools in remote consultations. Therefore the committee extrapolated from the evidence based on their expertise and experience.

The committee discussed remote consultations. They noted that a remote consultation can vary from a text message or an email to a video-based call (such as Zoom or Skype). They noted that the nature of the assessment that could be undertaken would depend on the medium of the consultation. For example, a video call might be adequate for a healthcare practitioner to notice pallor or sweating or laboured breathing, whereas a telephone conversation would likely not allow this. They also agreed that not all people were conversant with using all of the different forms of communication, and that for some people a video consultation (for example) might prove anxiety provoking, or a person might lack the necessary equipment and skills to participate in the consultation at all. They noted that

healthcare practitioners had a duty to make reasonable adjustments for people who were not comfortable with the means of consultation, and that this might involve offering them a face to face meeting, or, if they were unable to travel, a home visit. They discussed the equipment that might be needed to assess some symptoms. They agreed that some people have a pulse-oximeter at home since the COVID-19 pandemic, and that some people have blood pressure machines and thermometers at home. They pointed out that while many of these machines are reliable, there were others, for example smart watches, where readings might be less accurate. They also require proper use, which the healthcare practitioner might not be sure of if the consultation does not have a video component, especially if the person was confused or not comfortable using technology.

Based their discussions, the committee agreed that the most important thing at the beginning of a remote consultation was to establish whether the person was competent to use the method of consultation, or whether another method or face-to-face appointment might be more appropriate.

The committee agreed it was also important to rule out red flags early in the consultation and to assess people for possible sepsis and for pneumonia. The committee included a recommendation about this and linked to NICE's sepsis: recognition, diagnosis and early management guideline.

Remote consultations are provided by a range of healthcare practitioners with different levels of clinical acumen and judgment. To support practitioners in deciding whether a person might have a serious ARI, the committee examined the evidence for the diagnostic accuracy of various signs and symptoms. The included systematic reviews reported the sensitivity and specificity of various tests, and from these the committee were able to calculate positive and negative likelihood ratios. 3 symptoms had positive likelihood rations slightly over 2, which might indicate they have some usefulness for diagnosing pneumonia (there was no evidence for broader ARI), however there was low or very low confidence in most of the evidence as assessed by GRADE, so following consultation with stakeholders, the committee agreed not to include a list of symptoms but agreed that in their experience some symptoms were often useful, so they added some examples. The committee were interested in the potential for early warning scores such as NEWS2 to be used in remote consultations (if the right equipment were available) and made a research recommendation to explore this (see appendix K).

The committee agreed that if the healthcare practitioner doing the assessment thought that the person might have a serious ARI, or if they thought the person had a respiratory infection that was exacerbating a co-existing condition (such as COPD) that they should be seen for a face-to face appointment for a more complete assessment and prescription of an antibiotic if necessary.

The committee discussed where the face-to-face appointment should take place and agreed that it would depend on the level of concern for the person, based on their symptoms and co-morbidities. They agreed that in many cases, if a person needed a face-to-face appointment, this could be in general practice or through referral to another part of the acute respiratory infection pathway, for example an acute respiratory infection hub if one was operating in the area. However, if a person was severely ill or was deteriorating quickly then an emergency department, or sometimes an emergency ambulance might be the proportionate response.

The committee agreed that antibiotics should not normally be prescribed for respiratory infections on the basis of a remote consultation alone, and that this not only represented poor antimicrobial stewardship, but in some circumstances could compromise patient safety.

They agreed that while remote consultations are a very useful tool for ruling out people without serious illness, there were advantages to seeing a person face to face. It meant that a full physical examination could take place, including physiological measures that are not possible in most remote consultations. For this reason, the committee also suggested that if a person were ill enough to need antimicrobials, then they should probably be seen face to face for safety reasons, although they were aware that this is not always possible due to capacity issues and other factors that might make it difficult for a person to get, or attend, an in-person appointment. There might also be cases where the clinician was confident enough in their diagnosis that a face to face assessment was not required.

In-person consultations

In addition to their discussions about symptoms and signs, the committee also considered the evidence for rapid point of care tests that could be used in face-to-face appointments (evidence review [B]). They noted that all of the evidence was of very low quality and that they could not have much confidence in the effect estimates. They were also aware that the NICE pneumonia guideline made recommendations about assessing lower respiratory tract infections and suspected pneumonia in primary care settings, and they were reassured that there was consistency with NICE's guideline on pneumonia in adults: diagnosis and management.

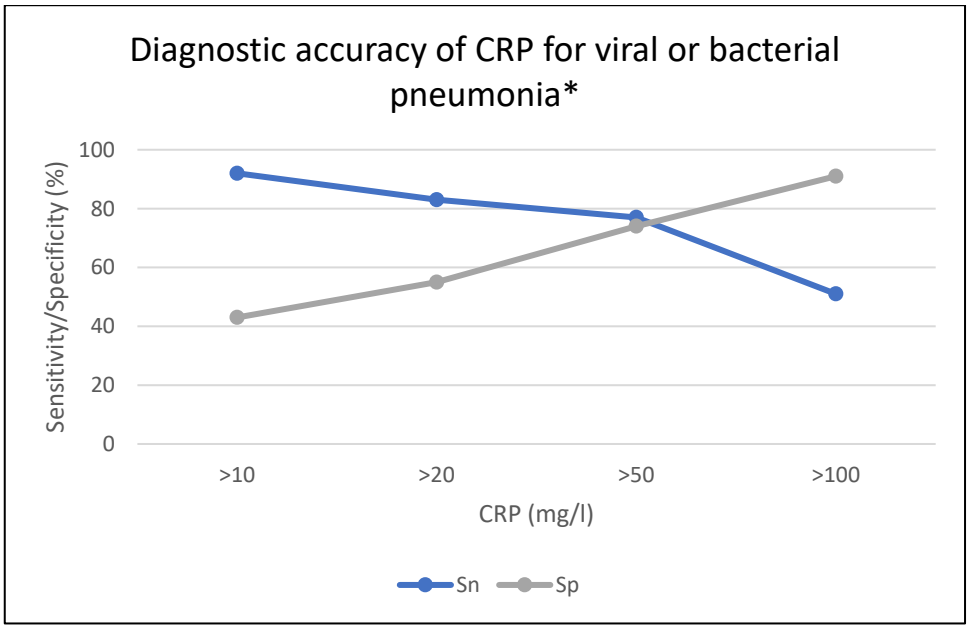
The committee discussed the evidence for microbiological and influenza tests for determining whether to prescribe antibiotics to people with a suspected ARI. They noted a range of point of care tests were available, but that in general they either required expensive equipment or required a lot of time to give a result, and none of them provided a clear advantage in terms making decisions about whether or not to prescribe an antimicrobial. The committee noted that there were very large seasonal swings in the number of consultations and admissions for respiratory infections, with much more illness seen in the winter months and that these seasonal surges were monitored by UKHSA. They agreed that in general the use of antivirals for influenza like illness is directed by the UKHSA when influenza season is officially announced and that this should drive antiviral prescribing in those circumstances. Based on those considerations, the committee agreed to align with the pneumonia guideline and recommended that clinicians do not use microbiological tests to help them decide whether or not to prescribe antibiotics. The evidence for POCT microbiological tests was of poor quality and there was low certainty in the evidence Therefore, the committee agreed that some of them may perform better in more robust trials, so they made a research recommendation to support this (see appendix K). They agreed that some influenza tests had very high sensitivity and specificity and therefore were very good at detecting influenza. While this gave no clear benefit over clinical judgment in terms of prescribing antivirals, the committee noted that influenza testing might be useful for surveillance or for infection control. The committee was also aware of some local schemes such as test and treat sore throat pilots in Wales that were being evaluated. They looked forward to considering that data in future updates.

The committee discussed the use of biomarkers, particularly C-reactive protein (CRP) as an aid to making a decision to prescribe antibiotics in ARI. Very low to moderate quality evidence assessed the sensitivity and specificity of CRP for detecting viral or bacterial ARI. They were interested that the evidence shows that CRP tests reduce the numbers of antibiotics prescribed both at index consultation and within 28 days of that consultation by a (statistically) significant amount, although the evidence was very uncertain. There was also some evidence (also very uncertain) that CRP testing might increase the likelihood of a further consultation within 28 days. They discussed the limitations of CRP testing because

there may be a time lag for onset of symptoms with infections (which corresponds to presence of CRPs), so a sample taken early in the course of infection could be falsely reassuring. They also noted that the CRP response can vary among different groups of people, for example in different ethnic groups, the very elderly, or during pregnancy and the post-partum period.

The committee noted that for CRP tests, the trend was as expected, with lower values having a high sensitivity and low specificity, and high values having a lower sensitivity and a higher specificity (see figure 1). The committee discussed antimicrobial stewardship alongside the risks to people of not prescribing antibiotics when they did have an ARI. The committee converted the sensitivity and specificity of the different thresholds for CRP reported in the evidence reviews to likelihood ratios to be able to better consider the evidence. The positive likelihood ratio for CRP> 100mg/l was slightly over 5, which represents a moderate increase in the probability of the disease given a positive test (approx 30%). Conversely, a CRP less than 20 mg/l gave a negative likelihood ratio of slightly less than 0.2, representing a moderate decrease of about 30% in the chances of having the disease given a negative test. They also noted that these data were for pneumonia specifically rather than other ARI. On the balance of all the factors, and acknowledging the uncertainty, they agreed that it was clinical judgment that should determine the management strategy for people with an ARI, paying close attention to the persons broader health and risk. The committee agreed, taking into account the low certainty in the evidence and based on their clinical experience, that CRP was a tool that could assist with making a decision about antibiotics, but that the decision should not be based on CRP alone. CRP testing should only be used when clinical assessment has not provided an adequate diagnosis and the clinician remains unsure about whether or not to prescribe antibiotics. Based on the likelihood ratios, the committee suggested cut offs for CRP levels in line with NICE's guideline on pneumonia whose recommendation was based on data from 3 European RCTs comparing CRP with usual care that covered LRTI and URTI, and on economic analysis. That guideline details how the threshold decisions were made by that guideline committee (table 16 in section 7.5 of the guideline).

Figure 1



*Based on data from evidence review [C]

The committee discussed early warning scores. They were surprised that there were so few studies researching the most commonly used scores, and that almost all of this evidence was in acute settings. They noted there were small amounts of evidence for a range of scores that are not in common use.

Evidence for EWS scores showed that patients in low-risk PSI and CRB-65 classes were found to be at low risk of death when managed as outpatients, but that they might over predict in primary care settings.

They noted that some of the EWS had requirements that meant they would not be useful in most primary care encounters, for example the Pneumonia Severity Index (PSI) for assessing people with suspected pneumonia included a range of measures that are usually only available as an inpatient in hospital (for example arterial pH, haematocrit). Similarly, CURB-65 requires a measurement of blood urea nitrogen so is not suitable for primary care settings.

They agreed that tools such as the NEWS2 and its associated tools (for example MEWS) were promising and generally had favourable results, especially for prediction of mortality in people with respiratory distress and prediction of ICU admission. However, all of the evaluations of NEWS2 were in emergency department or admissions unit populations, and it is unclear whether these can be extrapolated to the general population or to primary care. The committee were aware of the reservations about NEWS2 expressed by the Royal College of General Practitioners because they have often not been validated in primary care, and agreed their reservations were sensible. The committee were keen for research to be conducted about the effectiveness of NEWS2 for predicting severe illness in pneumonia in primary care and other non-hospital settings, and for all EWS in ARI hubs and made recommendations to research this (see appendix K).

Overall, the committee agreed that currently the most useful early warning score to use in people with a clinical diagnosis of pneumonia, in primary care and non-hospital settings was CRB-65. This is because the test does not require extensive testing or access to tests that are not likely to be available in non-hospital settings, and because people in low CRB-65 categories were shown in the evidence to be at low risk of mortality. The CRB-65 test assesses 4 attributes and assigns a score of 0 or 1 to each attribute to generate a score of 0 – 4 for the risk of the pneumonia leading to all-cause death at 30 days. Mortality is very low in people with a score of 0 (<1%), with a score of 1 or 2 it is 1-10%, and mortality rises to over 10% with a score of 3 or 4[a].

The committee agreed that this was a useful supplement to clinical judgment, but that decisions about a person's care should not be based on the CRB-65 alone. They noted that this was consistent with recommendations in the NICE pneumonia guideline.

The committee urged some caution in using CRB65 because in the experience and based on their expertise, it could be a 'blunt tool' that was in no way a replacement for clinical judgment. Many factors other than pneumonia could cause people to score artificially high or low so decisions about a person's care should not be based on the CRB-65 alone. They noted that this was consistent with recommendations in the NICE pneumonia guideline..

[a] Lim WS, van der Eerden MM, Laing R, et al. (2003) Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 58: 377–82

However, in spite of the reservations outlined above, they agreed it could be a useful adjunct to clinical judgment and help inform decision making.

The committee agreed that people with a CRB-65 score of 0 could be managed in an outpatient setting, unless there were specific concerns about them. They made a consensus recommendation that, for people who scored 1 or 2 on CRB-65, a shared decision should be made with the person about whether they could be adequately cared for at home, or whether they should be referred to a virtual ward or some other form of intermediate care. This decision would need to consider the person's frailty and any co-morbidities alongside their social circumstances and their preferences. For people with a score of 3 or 4 the committee agreed that clinicians would want to consider a hospital assessment since risk of mortality in those people was over 10%.

The committee also agreed that for people with ARIs that are not pneumonia, frailty and co-morbidities should be take into account when deciding on their treatment. ARIs can cause exacerbations of underlying conditions and may make people more vulnerable to severe outcomes. The committee agreed that for these people diagnostic thresholds and therefore likelihood of antibiotic prescription would be lower than for the general population in terms of providing antimicrobials or escalating care, for example to a virtual ward.

The committee discussed the general epidemiology of ARIs, pointing out that they were transmissible diseases that usually followed a seasonal pattern. As a result of this cyclical pattern, the prevalence of ARIs varies throughout the year, normally peaking in winter. Information from UKHSA about the national pattern of these diseases is important in deciding on diagnosis and treatment and clinicians should follow updates from UKHSA and advice from them about diagnosis and prescribing during seasons of high ARI prevalence.

1.1.11.4 Cost effectiveness and resource use

The committee reviewed economic evidence from the existing literature on the cost effectiveness of strategies on the initial assessment and management of suspected ARIs.

Using symptoms, signs and early warning scores to assess and manage people with suspected ARI

The evidence from the literature on the cost effectiveness of the use of different symptoms, signs and early warning scores came from one cost-effectiveness analysis (Little et al. 2014), which evaluated the assessment and management of people in primary care with acute sore throat symptoms. The analysis found that the use of a clinical symptom score (FeverPAIN) to guide antibiotic prescribing is a cost-effective approach compared with a delayed antibiotic prescribing strategy (standard care): although they result in similar numbers of QALYs, the use of a clinical symptom score provides lower costs over a 28-day period.

The committee noted that the sole economic evidence in this area was for a short-term upper respiratory tract infection. They considered that this evidence was consistent with that used to support the sore throat guideline and decided to cross refer to that guideline, along with guidelines on management on other ARI symptoms. The main focus of this guideline was decided to be on the management of lower respiratory tract infections and pneumonia, which have greater consequences to the patient and to the healthcare system if not managed appropriately.

There were no studies that evaluated the cost effectiveness of initial assessment or triaging strategies in people with ARIs that are more likely to require intensive care, such as

pneumonia. Identifying the symptoms associated with pneumonia that could be assessed remotely and recommending that people presenting with these should receive a face-to-face assessment in order to receive a more thorough assessment will help the healthcare practitioner assess possible red flags that may require urgent action. By recommending that these people receive further care means that healthcare resources such as general practice visits and ED assessment are used by those who need it most, and will support a more efficient healthcare system at times of pressure.

The committee agreed that antibiotics should not be prescribed based on a remote assessment alone. Recommending a face-to-face assessment for these people will save costs if it reduces unnecessary prescriptions, by not giving them to those unlikely to benefit from them. It also improves antimicrobial stewardship, which has long-term patient and economic benefits.

Rapid tests to inform triage and antibiotic prescribing decisions

Results from four cost-effectiveness studies suggest that rapid tests for C-reactive protein (CRP) given in primary care to people with symptoms of an ARI or a COPD exacerbation may be cost-effective when identifying whether their symptoms are due to a bacterial or viral infection and in guiding use of antibiotics.

In all cost effectiveness studies, people experienced a higher number of mean QALYs with the usage of CRP point of care tests (POCTs). The committee questioned the validity of this finding, and discussed whether avoiding unnecessary antibiotics would have an impact on those who do not need them. Some studies indicated that the favourable outcomes were due to a reduction in the duration of ARIs (although the studies and the committee were unclear on the reason for this) and the avoidance of antibiotic-related adverse events in a small proportion of people. They concluded that the QALY gains were very small in reality and may not be clinically significant, but that using CRP POCT to inform an antibiotic reduction strategy was not detrimental to patient outcomes.

The committee then questioned whether the use of CRP POCTs can be considered cost neutral or cost saving. The committee were also presented with a range of unit costs for different POCTs and courses of antibiotics (see Table 21 and Table 22) and noted the relatively small cost of antibiotics (ranging from approximately £1 to £6), depending on severity of pneumonia) compared to the cost of CRP testing. The cost of CRP testing is variable depending on the system that is used, but an economic evaluation in the review estimated that the total cost of a CRP test in primary care was £9.58 (2016/17 cost), once all relevant costs including staff costs, all consumables and materials, quality control and the need to re-test a proportion of people were taken into account. These cost findings are generally supported by the economic evaluations in the review, which found testing to be more expensive. However, while most studies only considered costs and outcomes in the short-term, there was one economic evaluation that modelled outcomes over a much longer time horizon and found that CRP POCTs provided cost savings overall due to favourable re-consultation and reinfection rates.

The committee also discussed the resource implications of providing CRP tests to people who present with ARI symptoms, and noted that there would be challenges in managing tests throughput in a primary care setting. One study (Holmes, 2018) demonstrated that CRP POCT is more likely to be cost effective if it was used strategically, and conducted a scenario in line with the recommendations in the current NICE pneumonia guideline (CG191). In this scenario, CRP tests are provided only when clinical assessment is not conclusive, and antibiotics are not routinely offered if CRP is <20mg/L or a delayed prescription is given if

CRP is between 20-100mg/L. Considering both the higher likelihood of being cost effective and the mitigation of the resource impact, the committee made recommendations in line with this scenario for the use of CRP POCT.

Other economic evaluations considered by the committee evaluated rapid tests for procalcitonin, streptococci, influenza and the pneumococcal antigen. They found that the evidence is too limited to draw conclusions or did not indicate good value for money for other rapid tests that were evaluated. Therefore, the committee recommended that these should not be used to assess patients in primary care.

Antimicrobial resistance

The committee agreed that a key motivation for optimising the use of antibiotics in ARIs is to reduce future antimicrobial resistance associated with unnecessary antibiotic prescribing. Strategies to minimise AMR can reduce long-term costs, and improve patient outcomes or avoid patient harm. However, there is no standardised methodology for estimating the costs and consequences associated with AMR in an economic evaluation. Two studies did make some attempt to incorporate an estimated cost associated with AMR into their sensitivity analyses, but the validity of their calculations was unclear. Therefore, the committee made a research recommendation on the best methods to incorporate this into economic evaluations (see Appendix K– Research recommendations – full details).

Location of care

Severity assessment tools may be used by clinicians to guide hospital admission or ITU assessment according to the severity of illness. As there were no economic evaluations on the use of CRB-65 scores in primary care to assess and manage people with pneumonia, the committee were provided with the cost of hospital admission and ITU admission are represented in Table 23 to aid consideration of cost effectiveness. The committee considered that CRB-65 is a reasonable measure for assessing the risk of pneumonia patients, and therefore it will also be cost effective to use it to inform their management, as they will ensure the most appropriate care is provided to patients and the resources are therefore used appropriately.

The committee agreed that people with a CRB-65 score of zero can be safely managed at home, and that people with a CRB-65 score of three should be managed more closely in hospital, due to the higher mortality risk in this group. Supported home-based care such as virtual wards were discussed as appropriate locations of care for people with CRB-65 score of 1 or 2, when used alongside clinical judgement following a face-to-face assessment. At the time of this guideline, NHS England has started to roll out more virtual wards for two pathways, including ARI, with a target to provide above 10,000 beds by the next influenza season. As an alternative solution to inpatient hospital care, admission to virtual wards can help reduce pressure on the healthcare system, particularly at times when the demand for urgent and emergency care is increased. The economic benefits of virtual wards in people with ARI and other conditions are being evaluated in other ongoing workstreams at NICE. An early value assessment of the technologies that support virtual wards is also being undertaken, and NICE is accessing and reviewing real-world economic data from NHS sites that have implemented virtual wards to provide general advice to support economic business case development. A review of the existing economic literature for virtual wards recently conducted by the Health Technology Assessment Innovation Laboratory (HTA Lab) at NICE has found that they are usually reported as cost saving, but uncertainties remain in this evidence.

1.1.12 Recommendations supported by this evidence review

This evidence summary and the three evidence reviews support the recommendations and the research recommendation on acute respiratory infection.

1.1.13 References – included studies

1.1.13.1 Effectiveness and diagnostic

See individual reviews for full references of included studies.

1.1.13.2 Economic

RQ1: Signs and symptoms

Little P, Hobbs FD, Moore M, Mant D, Williamson I, McNulty C, et al. PRImary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive randomised controlled trial with nested qualitative study and cost-effectiveness study. Health Technol Assess. 2014;18(6): 1-101. http://dx.doi.org/10.3310/hta18060

RQ2: rapid, near-patient tests

Francis NA, Gillespie D, White P, Bates J, Lowe R, Sewell B*, et al.* C-reactive protein point-of-care testing for safely reducing antibiotics for acute exacerbations of chronic obstructive pulmonary disease: the PACE RCT. *Health Technol Assess* 2020;**24**(15):1-108. http://dx.doi.org/10.3310/hta24150

Fraser H, Gallacher D, Achana F, Court R, Taylor-Phillips S, Nduka C*, et al.* Rapid antigen detection and molecular tests for group A streptococcal infections for acute sore throat: systematic reviews and economic evaluation. *Health Technol Assess* 2020;**24**(31):1-232.

Holmes EAF, Harris SD, Hughes A, Craine N, Hughes DA. Cost-Effectiveness Analysis of the Use of Point-of-Care C-Reactive Protein Testing to Reduce Antibiotic Prescribing in Primary Care. *Antibiotics* 2018;**7**(4):07. http://dx.doi.org/10.3390/antibiotics7040106

Hunter R. Cost-effectiveness of point-of-care C-reactive protein tests for respiratory tract infection in primary care in England. *Adv Ther* 2015;**32**(1):69-85. http://dx.doi.org/10.1007/s12325-015-0180-x

Little P, Hobbs FD, Moore M, Mant D, Williamson I, McNulty C, et al. PRImary care Streptococcal Management (PRISM) study: in vitro study, diagnostic cohorts and a pragmatic adaptive randomised controlled trial with nested qualitative study and cost-effectiveness study. Health Technol Assess. 2014;18(6): 1-101. http://dx.doi.org/10.3310/hta18060

Michaelidis CI, Zimmerman RK, Nowalk MP, Fine MJ, Smith KJ. Cost-effectiveness of procalcitonin-guided antibiotic therapy for outpatient management of acute respiratory tract infections in adults. *J Gen Intern Med* 2014;**29**(4):579-86. http://dx.doi.org/10.1007/s11606-013-2679-7

Nicholson KG, Abrams KR, Batham S, Medina MJ, Warren FC, Barer M*, et al.* Randomised controlled trial and health economic evaluation of the impact of diagnostic testing for influenza, respiratory syncytial virus and Streptococcus pneumoniae infection on the

management of acute admissions in the elderly and high-risk 18- to 64-year-olds. *Health Technol Assess* 2014;**18**(36):1-274, vii-viii. http://dx.doi.org/10.3310/hta18360

Oppong R, Jit M, Smith RD, Butler CC, Melbye H, Molstad S*, et al.* Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions. *Br J Gen Pract* 2013;**63**(612):e465-71. http://dx.doi.org/10.3399/bjgp13X669185

Appendices

Appendix A – Review protocols

See individual reviews for details of review protocols.

Appendix B – Literature search strategies

See individual reviews for details of searches undertaken and search strategies.

Appendix C – Effectiveness and diagnostic evidence study selection

See individual reviews for study selection details and PRISMA flow diagrams.

Appendix D – Effectiveness and diagnostic evidence

See individual reviews for evidence tables.

Appendix E – Forest plots

See individual reviews for forest plots.

Appendix F – GRADE tables

See individual reviews for GRADE tables.

Appendix G – Economic evidence study selection

See individual reviews for study selection details and PRISMA flow diagrams.

Appendix H – Economic evidence tables

See individual reviews for evidence tables.

Appendix I – Health economic model

No health economic modelling was undertaken for this guideline.

Appendix J – Excluded studies

See individual reviews for details of studies considered at full text and then excluded.

Appendix K– Research recommendations – full details

K1.1 Research recommendation

How accurate are early warning scores such as NEWS2 and CRB-65, when applied in face-to-face and remote consultations in:

- 111 and 999 call centres
- primary care and other non-hospital, low-prevalence settings?
- ARI hubs?

And how can the scores/thresholds inform clinical decisions about care pathways, for example, sending people home, to virtual ARI wards, or to same day emergency care

K1.1.1 Why this is important

Early warning scores are widely used in secondary care and have been shown to be very effective in those settings for predicting mortality or severe illness. Although the tools are being used outside of secondary care, they have not been validated for this use and therefore the guideline committee could not recommend them as confidently as they would have liked. It is also unclear how the different scores on these tools can inform clinical decisions about the best care pathway and what levels of risk are appropriate markers for virtual ARI ward admission, or hospital admission.

K1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	EWS may be useful tools to predict risk of severe illness or death in people with severe respiratory infections. Identifying this risk early means that people can be directed to the right services for their level of risk and avoid serious outcomes developing. For example to a respiratory virtual ward or to hospital.
Relevance to NICE guidance	EWS were considered as part of this update, but most of the data came from emergency departments and medical admissions. It may enable future recommendations to be made on this in any future updates of the NICE guidance
Relevance to the NHS	An accurate EWS will mean that people are cared for in the best place based on their risk of severe illness and death and will reduce the burden on secondary care of inappropriate referrals. There is also a potential cost saving element by reducing potential downstream cost through improved initial assessments and subsequent management of ARI.
National priorities	High. The role of virtual wards in managing acute respiratory infection is a priority.

Current evidence base	Reasonable data, but from different settings.
Equality considerations	EWS may need to have their thresholds modified to assess people with co-morbidities and frailty.

K1.1.3 Modified PICO table

Population	People aged over 16 with symptoms of an acute respiratory infection who are assessed by: • remote services (e.g. NHS 111) • primary care and other non-hospital, low-prevalence settings • ARI hubs
Prognostic tool	Early warning scores for predicting mortality or severe illness in people with acute respiratory infection (including pneumonia) used to determine care pathway
Outcome	• Severe illness (for example requiring unplanned hospital admission) • Mortality • Escalation of care • Antibiotic/antiviral use • Time to clinical cure/resolution of symptoms
Sub-group analysis	Sub-group analysis by • protected characteristics • pregnancy and post-partum
Study design	Cohort study
Timeframe	Long term
Additional information	None

K2.1 Research recommendation

What is the role of point of care microbiological testing for guiding management of people with signs and symptoms of an acute respiratory tract infection, taking into account good antimicrobial stewardship, cost and cost-effectiveness of the tests, and time taken to do the test and get a result?

K2.1.1 Why this is important

Currently the evidence does not support rapid, near patient microbiological testing to determine the initial management of acute respiratory infections, for example to guide

antimicrobial prescribing. However, faster and better tests are becoming available and these need to be assessed for their usefulness in non-hospital settings, paying due regard to their cost, how long they take and how much expertise is required to do the test as well as their diagnostic accuracy.

K2.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Swift and accurate diagnosis of the cause of a respiratory infection means that people can be given the best treatment for their condition.
Relevance to NICE guidance	The uncertainties about the value of microbiological testing outside of hospital, especially given the time taken to undertake tests and get results has an impact on their usefulness to guide initial management and means that currently people are managed on the basis of a clinical diagnosis.
Relevance to the NHS	Accurate identification of pathogens would lead to better prescribing of antimicrobials, improved antimicrobial stewardship, less resource waste through unnecessary antimicrobial prescription and less inappropriate referral to secondary care.
National priorities	Medium.
Current evidence base	Some data, see evidence reviews [B] and [C] and the committee discussion in this document.
Equality considerations	None known

K2.1.3 Modified PICO table

Population	People aged over 16 with symptoms of an acute respiratory infection who are assessed by: • primary care and other non-hospital, low-prevalence settings • ARI hubs
Intervention	Muliplex or single near patient, rapid tests (turnaround time ≤ 45mins, also known as point of care tests) which are currently licensed and available for use in the UK to identify specific respiratory viral and bacterial infections, including influenza (A and B) and respiratory syncytial virus (RSV).
Comparator	Usual care
Outcome	• Cost-utility • HRQoL

	• Severe illness (for example requiring unplanned hospital admission) • Mortality • Escalation of care • Antibiotic/antiviral use • Time to clinical cure/resolution of symptoms
Sub-group analysis	Sub-group analysis by • protected characteristics • pregnancy and post-partum
Study design	RCT with economic analysis
Timeframe	Short term
Additional information	None

K3.1 Research recommendation

How can we quantify the impact on antimicrobial resistance of interventions that safely reduce antibiotic prescribing, in terms of future healthcare costs and health-related quality of life?

K3.1.1 Why this is important

A key motivation for rapid testing is to optimise or prioritise antibiotic prescribing and subsequently reduce future antimicrobial resistance associated with unnecessary antibiotic prescribing. Frequently, areas across the country with high prescribing of antimicrobials also have high resistance to these treatments. Antimicrobial resistance means that standard treatments no longer work, infections are harder to control, the risk of the spread of infection to the rest of the population is increased, illness and hospital stays are prolonged, and the risk of death is greater.

However, there is no standardised, recommended methodology for estimating the costs and consequences associated with AMR in an economic evaluation. This is a key potential benefit of interventions which safely reduce antimicrobial prescribing, both in terms of reducing long-term costs and improving patient outcomes (or avoiding patient harm).

Incorporating the future costs and health consequences associated with AMR into economic evaluations of interventions that safely reduce antibiotic prescribing is likely to increase the likelihood of the intervention being cost-effectiveness. In some instances, where the cost effectiveness of a strategy is borderline, factoring in the impact of AMR can change the outcome of an economic analysis.

K3.1.2 Rationale for research recommendation

Importance to ‘patients’ or the population	People with infections caused by resistant bacteria experience worse outcomes than those

	who can be managed with antimicrobials. Being able to capture the impact of antimicrobial resistance will allow the more effective management strategies to be identified for these people. Treating individuals appropriately will also have consequences for the population health, with reduced risk of the spread of the infection.
Relevance to NICE guidance	Adequate methods of assessing the impact of improving antimicrobial resistance will allow us to fully capture the impact of interventions that improve this outcome, and allow us to recommend the most appropriate means of managing people with ARI.
Relevance to the NHS	Being able to quantify the impact of antimicrobial resistance to inform decisions about care means that infections will be easier to control if better management strategies are implemented. Capacity in hospitals will be reduced as inpatient stays will be longer in those who are resistant to antimicrobials.
National priorities	Medium
Current evidence base	Some methods exist to quantify the cost of antimicrobial resistance, but these have not been standardised or validated
Equality considerations	None known

K3.1.3 Modified PICO table

Population	People aged over 16 with symptoms of an acute respiratory infection
Intervention	Reduced or targeted or optimised antibiotics prescribing for acute respiratory infection
Comparator	Standard antibiotic prescribing
Outcome	• Cost-utility • HRQoL • Healthcare costs • Severe illness (for example requiring unplanned hospital admission) • Mortality • Escalation of care • Time to clinical cure/resolution of symptoms
Study design	Analysis of (longitudinal) observational data with economic analysis
Timeframe	Long term
Additional information	None

Appendix L – Methods

See descriptions of methods in the individual reviews.