National Institute for Health and Care Excellence

Final

Chapter 7 GP access to laboratory investigations

Emergency and acute medical care in over 16s: service delivery and organisation

NICE guideline 94

March 2018

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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ISBN: 978-1-4731-2741-8
Chapter 7 GP access to laboratory investigations

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7 Primary care access to laboratory investigations

7.1 Introduction

General practitioners working within the NHS will refer patients to secondary care (AMU/ED) urgently when following clinical assessment and the patient is deemed at risk of an acute medical emergency. A proportion of these patients will be discharged and reassured following an initial screen, either within an AMU or ED, following initial laboratory investigations. This review question seeks to further explore whether the provision of additional "point of care", or rapid biochemical/ haematological testing by the general practitioner at the first point of contact can have a positive impact upon clinical outcomes, and reduce the burden on the AME pathway, whilst improving patient and/or carer satisfaction.

The guideline committee discussed the generic issue of point-of-care testing for acute illness in primary care, and chose to focus on 2 acute conditions prioritised as important by family doctors in 3 European countries, including the UK: respiratory infection and inflammatory illnesses and heart failure.[30] For the former group, respiratory illness was taken as representing a common and important issue for general practice; the committee decided to focus the review on tests for C-Reactive Protein (CRP) as this test is available and gives rapid results.

7.2 Review question: Does primary care access to laboratory investigations with same day results improve outcomes?

For full details see review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults and young people (16 years and over) with a suspected or confirmed AME, or at risk of, an AME

Intervention	Stratification of interventions:
	• GP access to laboratory investigations within practice hours.
	• GP access to phlebotomy and blood tests with same day results including:
	  ○ Cardiac biomarkers including BNP (B-type natriuretic peptide).
	  ○ CRP (C reactive protein), renal function, full blood count, liver function tests (LFT).
	• GP access to laboratory investigations out of practice hours.
	• GP access to phlebotomy and blood tests with same day results including:
	  ○ Cardiac biomarkers including BNP (B-type natriuretic peptide).
	  ○ CRP (C reactive protein), renal function, full blood count, LFT.

Comparison	Standard services.
Outcomes	• Antibiotic usage (IMPORTANT) • Avoidable adverse events CRITICAL • Quality of life (CRITICAL) • Patient satisfaction (CRITICAL) • Lab/ Diagnostic turn around for result to GP (IMPORTANT) • ED attendance (CRITICAL)
Study design	Systematic reviews (SRs) of RCTs, RCTs, observational studies only to be included if no relevant SRs or RCTs are identified.

7.3 Clinical evidence

We searched for randomised trials comparing GP access to laboratory investigations with same day results to usual care.

Nine studies were included in the review;[3,6,10,14,17,21,22,38,44] these are summarised in Table 2 below. We have updated 1 Cochrane review[3] that initially included 6 RCTs[6,14,17,22,38,44] with 2 additional RCTs.[10,21] All included studies used C-reactive protein (CRP) testing as an intervention except for 1 study[10] which used B-type natriuretic peptide (BNP) testing.

Evidence from these studies is summarised in the GRADE clinical evidence profile/clinical evidence summary below (Table 3, Table 4). See also the study selection flow chart in Appendix B, study evidence tables in Appendix D, forest plots in Appendix C, GRADE tables in Appendix F and excluded studies list in Appendix G.

Table 2: Summary of studies included in the review

Study, study design and setting	Intervention and comparison	Population	Outcomes	Comments
CRP compared to standard care				
Aabenhus 2014 [3] Cochrane review	Point-of-care biomarkers (C-reactive protein). Versus Standard care to guide antibiotic treatment.	Patients with acute respiratory infections (ARIs) in primary care settings.	Primary outcomes: • Number of patients given an antibiotic prescription at the index consultation and at 28 days follow-up. • Number of patients with substantial improvement (including full recovery) at day 7. Secondary outcomes: • Number of patients in need of a hospital admission at 28 days follow-up. • Number of satisfied patients. • Number of patients with substantial improvement (including full recovery) at 28 days follow-up.	Six RCTs were included in the review. Three trials were cluster RCTs (Andreeva 2014, Cals 2009B, Little 2013) and 3 were patient randomised RCTs (Cals 2010A, Diederichsen 2000, Melbye 1995).
Andreeva 2014[6] Non-blinded cluster-randomised clinical trial, multicentre in 8 General Practice offices with a total of 18 doctors in Arkhangelsk and Murmansk regions, Russia	C-reactive protein test at point of care. Versus Usual care.	Inclusion criteria: adult patients (> 18 years) with index case of lower respiratory tract. Infection/acute cough for less than 28 days. Exclusion criteria: previously seen by GP for infection in question, immunocompromised status, on-going treatment with oral corticosteroids.	• Antibiotic use within the first 2 weeks after index consultation.	Included in Cochrane review.

Study, study design and setting	Intervention and comparison	Population	Outcomes	Comments
Cals 2009[14] Non-blinded, cluster-randomised (practice level) clinical trial, multicentre in 20 primary care practices in the Netherlands	C-reactive protein test at point of care vs. usual care	Inclusion criteria: adults (> 18 years) with suspected lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign). Exclusion criteria: aged less than 18 years, current antibiotic use or usage within previous 2 weeks. Hospitalisation in past 6 weeks, non-fluent in Dutch, previous participation in the study and the need for immediate hospitalisation.	• Antibiotic prescribing at index consultation. • Antibiotic use (any use for current infection) in 28 days. • Patient satisfaction.	Included in Cochrane review.
Cals 2010[17] Open randomised clinical trial, multicentre in 11 primary care practices in the Netherlands	C-reactive protein test at point of care vs. routine care	Inclusion criteria: adult (> 18 years) with index case of: 1) Lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign). 2) Rhinosinusitis < 4 weeks, + 2 symptoms or signs. Exclusion criteria: aged under 18 years, antibiotic use or hospitalisation within the previous14 days, non-fluent in Dutch, immune compromised status or need for immediate hospitalisation.	• Antibiotic use (delayed + immediate) at index consultation. • Antibiotic use (any use for current infection) in 28 days. • Patient satisfaction: Reported as number of patients who were at least very satisfied out of the total number of patients • Serious adverse events (death or hospitalisation).	Included in Cochrane review. There were no serious adverse events in both the groups.
Diederichsen 2000[22]	C-reactive protein test at point of	Inclusion criteria: all patients with index	• Antibiotic use at index consultation.	Included in Cochrane review.

Study, study design and setting	Intervention and comparison	Population	Outcomes	Comments
Open randomised clinical trial, multicentre in 35 single-handed primary care practices in Denmark	care. Versus No C-reactive protein test at point of care only (clinical assessment, no BNP).	case of respiratory infection. Median age 37 years (0-90). Exclusion criteria: previously seen by general practitioner for infection in question, patients who had streptococcal rapid testing performed and patients with chronic inflammatory diseases.		Study included both adults and children. But study does not report the exact number of children and adults in the study. We have used only data from adult patients in our analysis.
Little 2013[38] Non-blinded cluster-randomised (practice level) clinical trial, multinational with 246 primary care practices in Spain, England, Wales, Poland, Belgium, the Netherlands	C-reactive protein test at point of care. Versus Usual care.	Inclusion criteria for patients: lower respiratory tract infection; aged 18 years and over; consulting for the first time with acute cough (up to 28 days duration) as the main symptom, or alternatively where cough was not the most prominent symptom (for example, fever or malaise) but where the clinician considered acute LRTI was the main diagnosis. Pneumonia was not an exclusion criterion. Upper respiratory tract infection; aged 18years and over; consulting for the first time and judged by the physician to	• Antibiotic prescribing at index consultation. • Hospitalisation.	Included in Cochrane review.

Study, study design and setting	Intervention and comparison	Population	Outcomes	Comments
		be another acute respiratory infection (sore throat, otitis media, sinusitis, influenza and/or coryzal illness). Exclusion criteria: a non-infective working diagnosis (for example, pulmonary embolus; heart failure; oesophageal reflux; allergy); antibiotic use in the previous month; unable to provide informed consent (dementia; psychosis; severe depression); pregnant and immunological deficiencies.		
Melbye 1995[44] Open randomised clinical trial, multicentre in 10 primary care practices in Norway	C-reactive protein test at point of care. Versus Usual care.	Inclusion criteria: adult (> 18 years) with subjective complaint of 1) Pneumonia, bronchitis or asthma or 2) One of the following symptoms: cough, shortness of breath, chest pain on deep inspiration or cough. Exclusion criteria: aged under 18 years, patients with sore throat, blocked nose, pain in ears or sinuses. Patients with angina-like chest pain were also excluded.	• Antibiotic use at index consultation. • Antibiotic use (any use for current infection) in 21 days.	Included in Cochrane review.
Dahleriksen 1999[21] Randomised	C-reactive protein test at point of care.	The GPs filled out a registration card for each patient when a CRP was measured	• Antibiotic use.	No clinical guidelines for the use of CRP

Study, study design and setting	Intervention and comparison	Population	Outcomes	Comments
cross over trial in 41 general practice clinics in Denmark.	Versus No C-reactive protein test at point of care (order CRP as usual mailing a blood sample to the laboratory).	in the office or requested at laboratory (no further details reported on inclusion of patients).		were distributed to the clinics. Randomised to 2 groups - after 3 months the 2 groups interchanged their status.
BNP compared to standard care				
Burri 2012 [10] RCT including 29 Primary care physicians in Switzerland.	Point of care measurement of BNP. Versus Standard assessment without BNP.	Eligible patients presented with dyspnoea as their primary symptom. Dyspnoea had to be of new onset or clearly worsening if pre-existing. If multiple symptoms were present in an individual patient, dyspnoea had to be the main symptom. Patients younger than 18 years of age, or with an obvious traumatic cause of dyspnoea, sever renal disease or sepsis were excluded.	• Days in hospital at 3 months. • Days in hospital at 12 months. • Time to initiation appropriate therapy (surrogate outcome).	Only adult patients included.

Table 3: Clinical evidence summary: point of care CRP testing compared to standard care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with CRP testing (95% CI)
Antibiotics prescribed at index consultation. All trials	4146 (7 studies)	⨁⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.8 (0.69 to 0.93)	Moderate	
				519 per 1000	104 fewer per 1000 (from 36 fewer to 161 fewer)
Antibiotics prescribed at index consultation- Individually randomised trials	2171 (4 studies)	⨁⨁⨁⊖ MODERATE[a] due to risk of bias	RR 0.91 (0.83 to 1.01)	Moderate	
				503 per 1000	45 fewer per 1000 (from 86 fewer to 5 more)
Antibiotics prescribed at index consultation - Cluster-randomised trials (modified sample size) e	1975 (3 studies)	⨁⨁⨁⊖ MODERATE[a] due to risk of bias	RR 0.68 (0.61 to 0.75)	Moderate	
				525 per 1000	168 fewer per 1000 (from 131 fewer to 205 fewer)
Antibiotics prescribed within 28 days. All trials	708 (-4studies)	⨁⨁⨁⊖ MODERATE[a] due to risk of bias	**RR 0.8** (0.67 to 0.96)	Moderate	
				623 per 1000	**125 fewer per 1000** (from 25 fewer to 206

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with CRP testing (95% CI)
					fewer)
Antibiotics prescribed within 28 days - Individually randomised trials	497 (2studies)	⊕⊕⊕⊖ MODERATE[a] due to risk of bias	RR 0.87 (0.75 to 1.02)	Moderate	
				623 per 1000	81 fewer per 1000 (from 156 fewer to 12 more)
Antibiotics prescribed within 28 days - (cluster-randomised trials with modified sample size) e	211 (2 studies)	⊕⊕⊖⊖ LOW[a,c] due to risk of bias, imprecision	RR 0.68 (0.51 to 0.91)	Moderate	
				643 per 1000	206 fewer per 1000 (from 58 fewer to 315 fewer)
Patient satisfaction (reported as the number of patients who were at least very satisfied compared to total number of patients)	674 (2 studies)	⊕⊕⊖⊖ LOW[a,c] due to risk of bias, imprecision	RR 1.11 (0.97 to 1.27)	Moderate	
				649 per 1000	71 more per 1000 (from 19 fewer to 175 more)
Clinical recovery day 7 (number of patients substantially improved by day 7)	1264 (3 studies)	⊕⊕⊕⊖ MODERATE[a], due to risk of bias,	RR 0.95 (0.87 to 1.05)	Moderate	
				414 per 1000	21 fewer per 1000 (from 54 fewer to 21 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with CRP testing (95% CI)
Clinical recovery day 28 (number of patients substantially improved at follow-up within 28 days) (cluster-randomised trials with modified sample size) e	527 (3 studies)	⊕⊕⊖⊖ LOW [a,c,] due to risk of bias, imprecision	RR 1.01 (0.93 to 1.08)	Moderate	
				758 per 1000	8 more per 1000 (from 53 fewer to 61 more)
Serious adverse events	258 (1 study)	⊕⊕⊕⊖ MODERATE[a] due to risk of bias	Not estimable	-	-
Hospitalisation	2953 (1 study)	⊕⊖⊖⊖ VERY LOW[a,c,d] due to risk of bias, imprecision, indirectness	OR 2.91 (0.96 to 8.82)	11 per 1000	20 more per 1000 (from 0 fewer to 78 more)

(a) Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.

(b) Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

(c) Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis.

(d) Downgraded by 1 increment because majority of evidence had indirect outcomes, and downgraded by 2 increments if the majority of the evidence had very indirect outcomes (surrogate outcome for ED attendance).

(e) The unit of analysis was the individual patient. For cluster-RCTs the Cochrane review authors adjusted the unit of analysis by calculating the design effect to modify sample sizes and inflate confidence intervals (CIs) accordingly.

Table 4: Clinical evidence summary: point of care BNP testing compared to standard care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard care	Risk difference with BNP (95% CI)
Hospitalisation within 3 months	323 (1 study)	⨁⨁⨀⨀ LOW[a,c] due to imprecision, indirectness	RR 1.37 (0.81 to 2.34)	Moderate	
				125 per 1000	46 more per 1000 (from 24 fewer to 167 more)
Hospitalisation within 12 months	323 (1 study)	⨁⨁⨀⨀ LOW[a,c] due to imprecision, indirectness	RR 1.17 (0.83 to 1.65)	Moderate	
				263 per 1000	45 more per 1000 (from 45 fewer to 171 more)
Time to initiation of appropriate therapy (days)	323 (1 study)	⨁⨁⨁⨀ MODERATE[b] due to indirectness			The mean time to appropriate therapy (days) in the intervention groups was 11.9 lower (17.32 to 6.48 lower)

(a) Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

(b) Downgraded by 1 increment because majority of evidence had indirect outcomes, and downgraded by 2 increments if the majority of the evidence had very indirect outcomes (this outcome was used as a surrogate outcome for lab/diagnostic turn around for result to GP).

(c) Downgraded by 1 increment because majority of evidence had indirect outcomes, and downgraded by 2 increments if the majority of the evidence had very indirect outcomes (this is a surrogate outcome for ED attendance).

7.4 Economic evidence

Published literature

Three economic evaluations were identified with the relevant comparison and have been included in this review.[10,32,58] These are summarised in the economic evidence profile below (Table 5) and the economic evidence tables in Appendix E. A further study was selectively excluded since it was less applicable than the included studies[13] – see Appendix H.

The economic article selection protocol and flow chart for the whole guideline can found in the guideline's Appendix 41A and Appendix 41B.

Table 5: Economic evidence profile: GP access to laboratory investigations versus usual care

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Burri [10] Switzerland and Germany	Partially applicable[(a)]	Potentially serious limitations [(a)]	• Study design: RCT • Intervention: Receiving point of care B-type natriuretic peptide (BNP) measurement • Follow-up: 12 months	£317	**Hospitalisations (per 100 patients):** 4.42 **Diagnostic certainty (% of patients receiving appropriate treatment):** 13%	n/a	n/a
Hunter [32] UK	Directly applicable	No serious limitations[(c)]	• Study design: Probabilistic decision analytic model • Intervention: GP use of C-reactive protein (CRP) point of care test • Follow-up: 3 years (40 cycles)	-£0.42	**QALYs (mean per patient):** 0.0013 **Antibiotics prescribed (mean per patient):** -0.48	Probability CRP point of care testing cost-effective (£0/£20K/30k threshold): 50%/77%/ 80%	**Analysis of uncertainty:** One-way sensitivity analysis, changing key parameters in the model, had little impact on the conclusions.
Oppong[58] Sweden and Norway	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Study design: RCT • Intervention: Patients receiving C-reactive protein (CRP) point of care test • Follow-up: 28 days	£8.97	**QALYs (mean per patient):** 0.0012 **Antibiotics prescribed (mean per patient):** -0.1	£7,475 per QALY gained	n/a

Abbreviations: QALY: quality-adjusted life years; RCT: randomised controlled trial.

(a) Intervention may not be relevant. Cost-consequence analysis only. Clinical outcomes may not be important. Non-UK study.

(b) RCT-based analysis so from 1study by definition therefore not reflecting all evidence in area. No sensitivity analysis reported.

(c) Reliant on small number of studies, mostly collection of studies by Cals et al.

(d) Swedish/Norwegian health care system may not be representative of UK NHS. Only reported incremental QALY difference, not incremental QALYs of each intervention.

(e) Observational study using regression analysis. 28 day follow-up may not be sufficient. There was minimal sensitivity analysis.

7.5 Evidence statements

Clinical

Point of care CRP testing

- Nine studies comprising 4950 people evaluated the role of point of care CRP testing for improving outcomes in adults and young people at risk of an AME, or with a suspected or confirmed AME. The evidence suggested that point of care CRP testing may provide a benefit in reduced antibiotics prescribed at index consultation (7 studies, very low quality), antibiotics prescribed within 28 days (5 studies, moderate quality) and improved patient satisfaction (2 studies, low quality). The evidence suggested there was no effect on clinical recovery at day 7 (3 studies, moderate quality), clinical recovery at day 28 (3 studies, low quality) and hospitalisation (1 study, very low quality) for point of care CRP testing compared to standard care.

Point of care BNP testing

- One study comprising 323 people evaluated the role of point of care BNP testing for improving outcomes in adults and young people at risk of an AME, or with a suspected or confirmed AME. The evidence suggested that point of care BNP testing may provide a benefit for reduced time to initiation of appropriate therapy (moderate quality). However, the evidence suggested there was no effect either on hospitalisation within 3 months or hospitalisation within 12 months (low quality). The evidence was graded moderate to low quality for all outcomes due to imprecision and indirectness.

Economic

- One cost–utility analysis found that point of care CRP testing was dominant (less costly and more effective) compared to usual care for people with a suspected AME. This analysis was assessed as directly applicable with minor limitations.
- Another cost–utility analysis found that point of care CRP testing was cost effective compared to usual care for people with a suspected AME (ICER: £7,500 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.
- One cost-consequences analysis found that point of care BNP testing for patients presenting with new onset or clearly worsening dyspnoea was more costly (£317 per patient), had more hospitalisations (0.04 per patient) and greater diagnostic certainty (+13%) compared to usual care. This analysis was assessed as partially applicable with potentially serious limitations.

7.6 Recommendations and link to evidence

Recommendations	**2. Provide point-of-care C-reactive protein testing for people with suspected lower respiratory tract infections.**
Research recommendation	**-**
Relative values of different outcomes	Quality of life, patient and/or carer satisfaction, avoidable adverse events and ED attendance were considered by the committee to be critical outcomes. Antibiotic usage and lab/ diagnostic turn around for result to GP were considered by the committee to be important outcomes.
Trade-off between benefits and harms	There was evidence from 9 RCTs for this review question; 8 RCTs compared same day point of care CRP testing with standard care and 1 RCT compared same day point of care BNP testing with standard care, in primary care. <u>Point of care CRP testing:</u> The evidence from the review comparing CRP testing and standard care in patients with lower respiratory tract infections suggested that point of care CRP testing may provide a benefit in reduced antibiotics prescribed at index consultation, antibiotics prescribed within 28 days and improved patient satisfaction. The evidence suggested there was no effect on clinical recovery at day 7, clinical recovery at day 28 and hospitalisation. One study reported no serious adverse events; indicating that the reduction in antimicrobial use associated with CRP-POC testing was not harmful. No evidence was available for the outcomes quality of life, lab/diagnostic turn around for result to GP and ED attendance. <u>Point of care BNP testing:</u> The evidence from the review comparing BNP testing with standard care in patients presenting with dyspnoea suggested that there may be a benefit in reduced time to initiation of appropriate therapy. However, the evidence suggested there was no effect either on hospitalisation within 3 months or hospitalisation within 12 months. No evidence was available for the outcomes: antibiotic usage, avoidable adverse events, quality of life, patient and/or carer satisfaction and lab/ diagnostic turn around for result to GP and ED attendance. The outcomes of hospitalisation and time to appropriate therapy were non-protocol outcomes and these were considered as surrogate outcomes for ED attendance and lab/ diagnostic turn around for result to GP respectively. <u>Overall:</u> The committee agreed that the evidence for CRP testing in adult patients with lower respiratory tract infections was quite clear in demonstrating reduction in antibiotic prescription and increase in patient and/or carer satisfaction without a difference in serious adverse events. Therefore, the committee recommended CRP testing at point of care for patients with suspected lower respiratory tract infections. The committee also agreed that this recommendation fits with national strategy to reduce antibiotic prescribing for people with lower respiratory tract infections. The vast majority of respiratory infections are caused by viruses, against which antibiotics are ineffective and unnecessary and also there is a concern that antibiotics may cause side effects and are directly associated with antibiotic resistance in common bacteria, causing treatment failure and complications, including death. [3] The committee noted that all the evidence was from studies of tests conducted at

Recommendations	2. Provide point-of-care C-reactive protein testing for people with suspected lower respiratory tract infections.
Research recommendation	-
	point-of care within practice hours and no evidence was available for tests conducted out-of-hours. The committee acknowledged that there was some benefit of BNP testing on achieving drug therapy. However, they did not feel that there were sufficient data available on which to base a recommendation for primary care, particularly given the small size of the study. Studies of the diagnostic utility of BNP in the emergency department were not relevant for this review.[55,64] Given the lack of evidence for BNP testing in primary care, and the strong evidence for CRP, the committee formulated a recommendation solely for CRP-POC testing.
Trade-off between net effects and costs	The cost of point of care c-reactive protein testing is likely to be offset by a subsequent reduction in respiratory infections and antibiotic prescribing. Two economic evaluations were included evaluating GP access to CRP results through same day point of care testing compared to usual care. Both studies included cost-utility analysis, including 1 from a UK perspective, which was considered directly applicable and with only minor limitations. They both found that GP same day point of care testing would be cost-effective at the £20,000 per QALY threshold. The studies found that the intervention reduced the number of antibiotic prescriptions. Reducing unnecessary antibiotic prescription to avoid antimicrobial resistance has an uncertain, potentially large, economic benefit on top of any cost per QALY.[63] It is not clear whether point of care CRP testing will have a net increase or decrease in overall cost but it appears to be cost effective. There was one economic evaluation of point of care BNP testing. It found an increase in cost that was partly due to an increase in the average number of hospitalisations. This could be where admission to hospital based on earlier laboratory results could have a clinical benefit. An increase in diagnostic accuracy within the study provides potential evidence to support this. However, the study was not designed to evaluate whether the clinical benefits were large enough to justify the increased cost. In conclusion, there was cost effectiveness evidence to support CRP point of care testing but no evidence to support other tests.
Quality of evidence	The RCT evidence was moderate to very low quality. This was primarily due to risk of bias and imprecision. The outcomes hospitalisation and time to initiation of appropriate therapy were further downgraded for indirectness, as these outcomes were surrogates for ED attendance and lab/diagnostic turn around for result to GP respectively. One of the CRP economic evaluations was assessed as directly applicable with minor limitations. The other was partially applicable with potentially serious limitations as it was set in Scandinavia and based on observational evidence. The economic evaluation of BNP testing was assessed as partially applicable with potentially serious limitations as it was set in Scandinavia and based on observational evidence.
Other considerations	A review of CRP-POC testing reports good acceptance by doctors and patients; 50% of GP practices report minimal impact on workload.[20] It should be noted that CRP does not distinguish bacterial from viral infections, the latter not being susceptible to antimicrobial treatment, so a high level of CRP is not necessarily an indication for antimicrobial treatment. Adjunctive tests such as procalcitonin which may distinguish bacterial from viral infections have yet to show utility. This recommendation fits with the national strategy to reduce antibiotic prescribing

Recommendations	2. Provide point-of-care C-reactive protein testing for people with suspected lower respiratory tract infections.
Research recommendation	-
	for people with lower respiratory tract infections. The committee wished to note 3 other related NICE guidelines in this area: Pneumonia in adults: diagnosis and management,[50]Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use[52] and Respiratory tract infections (self-limiting): prescribing antibiotics.[54] For further guidance on BNP testing please see: Acute heart failure: diagnosis and management[49] and the Chronic heart failure in adults: management.[46] The committee agreed that all same day point of care tests must be subject to quality assurance. The committee recognised that other point of care tests in acute illness were available for use in primary care, including (but not limited to) creatinine to screen for acute kidney injury (Acute kidney injury: prevention, detection and management[48]), D-dimer for venous thrombosis or pulmonary embolism (Venous thromboembolic diseases: diagnosis, management and thrombophilia testing[47]); Pulmonary embolism,[53] and troponin for myocardial infarction.[51] Other tests could also become available with the development of new technologies. These tests have the potential to guide primary care-delivered treatments, rule out or refer serious illness or refine existing treatments. The utility of these tests is usually established in secondary care, for example, in the emergency department. Their utility in primary and community care requires independent evaluation to take into account the differing clinical contexts. The committee wished to note that the recommendation does not exclude services being set up to provide testing in a centralised manner. In cities this could be provided in hubs and in rural areas it may be achieved using kits within the healthcare setting. This testing may occur within GP practices, walk in centres, urgent care centres and other health care providers. The sampling processing times should be sufficiently rapid to provide results without delaying patient management. Results should be available within a few minutes.

References

Appendices

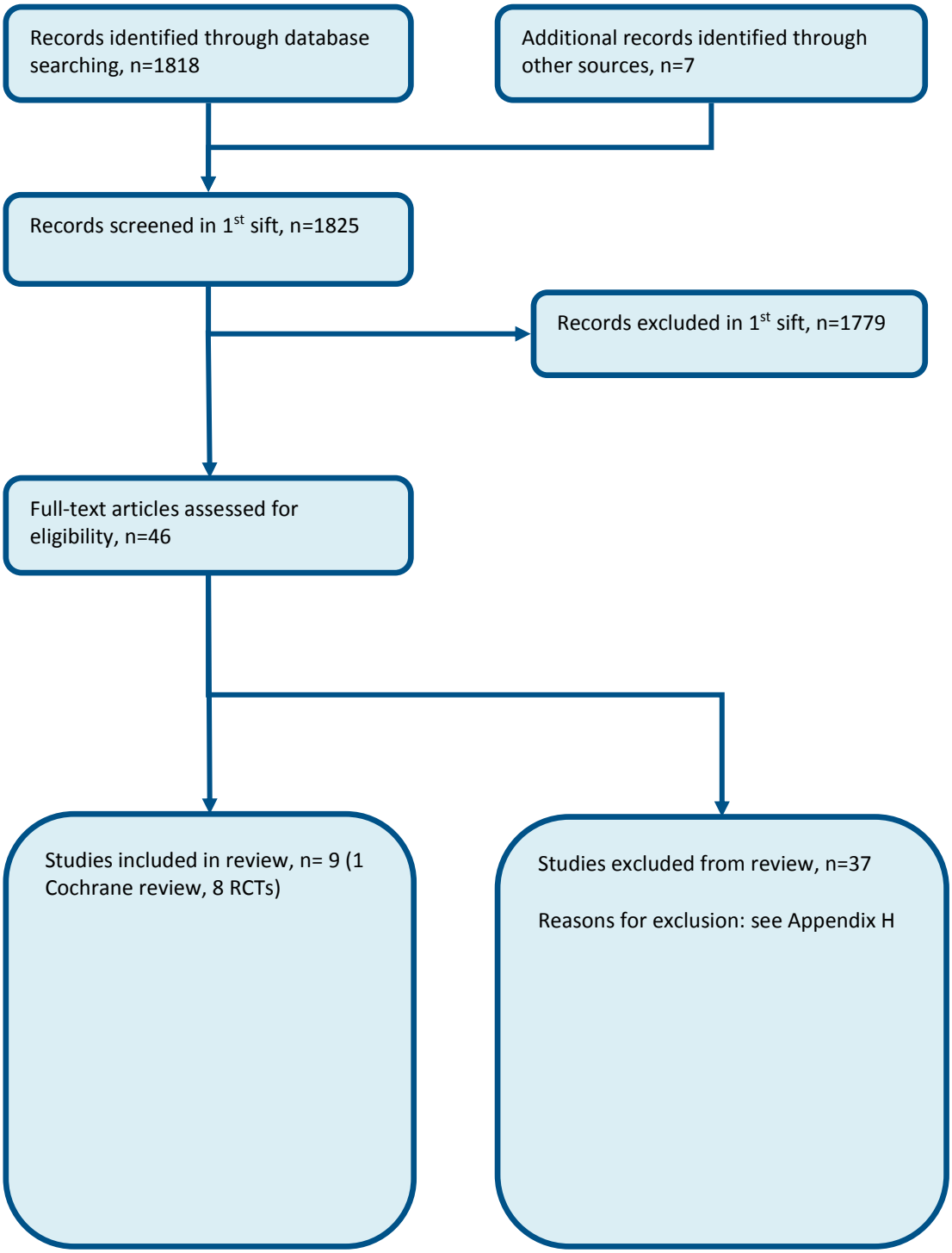
Appendix A: Review protocol

Table 6: Review protocol: GP access to laboratory investigations

Review question	Does primary care access to laboratory investigations with same day results improve outcomes?
Guideline condition and its definition	Acute Medical Emergencies. Definition: people with suspected or confirmed acute medical emergencies or at risk of an acute medical emergency.
Review population	Adults and young people (16 years and over) with a suspected or confirmed AME.
	Adults.
	Line of therapy not an inclusion criterion.
Interventions and comparators: generic/class; specific/drug (All interventions will be compared with each other, unless otherwise stated)	GP access to laboratory investigations within practice hours; GP access to phlebotomy and blood tests with same day results within practice hours including cardiac biomarkers including BNP and/or CRP and/or renal function and/or full blood count and/or LFT. GP access to laboratory investigations out of practice hours; GP access to phlebotomy and blood tests with same day results in out of practice hours including cardiac biomarkers including BNP and/or CRP and/or renal function and/or full blood count and/or LFT. Standard services; as defined in study. No GP access to laboratory investigations.
Outcomes	- Quality of life at end of follow-up (Continuous) CRITICAL - Patient satisfaction at end of follow- (Dichotomous) CRITICAL - Laboratory or diagnostic turnaround or result to GP at end of follow- (Continuous) CRITICAL - ED attendance at end of follow- (Dichotomous) CRITICAL - Antibiotic usage at end of follow- (Dichotomous) IMPORTANT - Avoidable adverse events at end of follow- (Dichotomous) CRITICAL
Study design	Systematic reviews (SRs) of RCTs, RCTs, observational studies only to be included if no relevant SRs or RCTs are identified.
Unit of randomisation	Patient. GP surgeries/practices.
Crossover study	Not permitted.
Minimum duration of study	Not defined.
Subgroup analyses if there is heterogeneity	- Frail elderly (frail elderly; no frail elderly); effects may be different in this subgroup.
Search criteria	Databases: Medline, Embase, the Cochrane Library. Date limits for search: None. Language: English.

Appendix B: Clinical article selection

Figure 1: Flow chart of clinical article selection for the review of primary care access to lab investigations



Appendix C: Forest plots

C.1 Point of care CRP testing vs. Standard care

Figure 2: Antibiotics prescribed at index consultation (all trials)

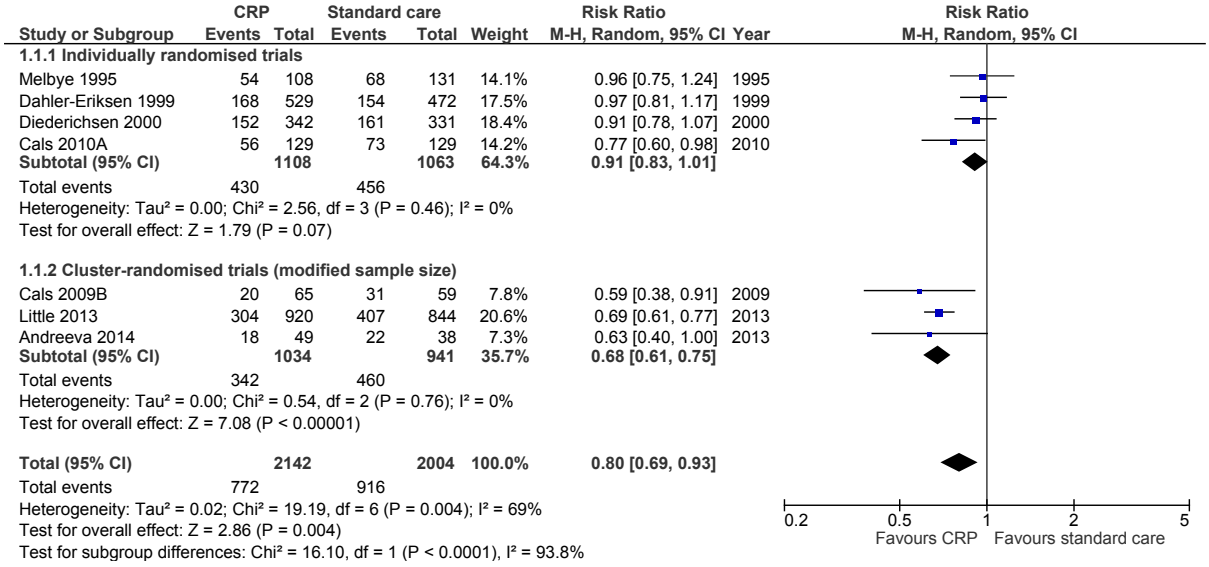


Figure 3: Antibiotics prescribed within 28 days (all trials)

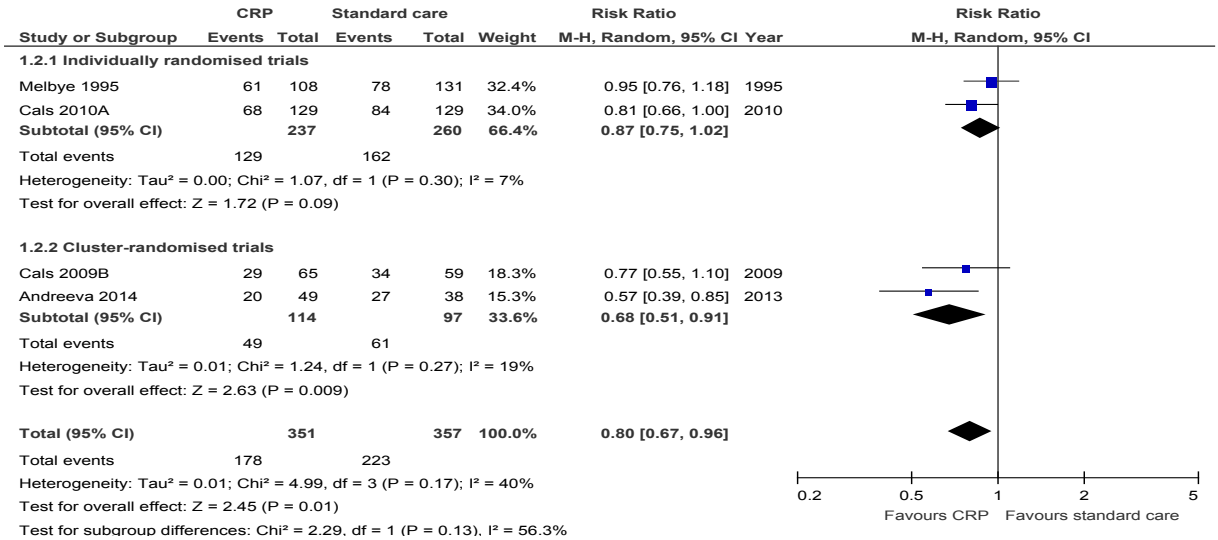


Figure 4: Patient satisfaction

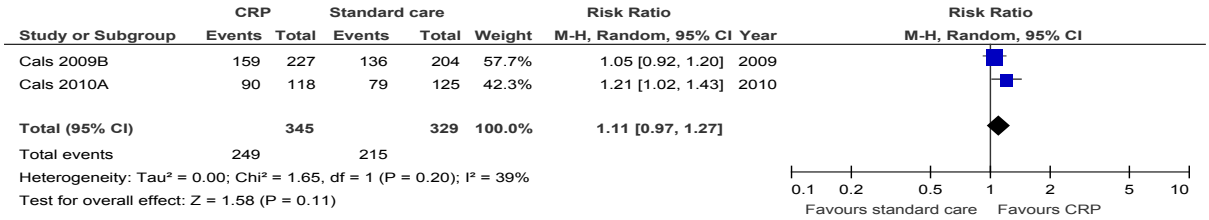


Figure 5: Clinical recovery day 7 (number of patients substantially improved by day 7)

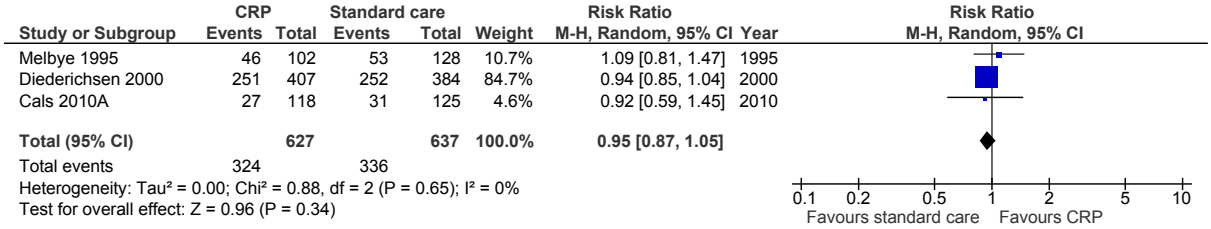


Figure 6: Clinical recovery day 28 (number of patients substantially improved within 28 days)

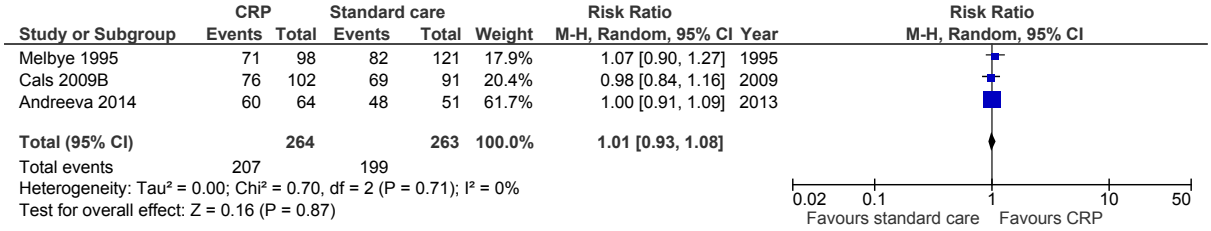


Figure 7: Serious adverse events

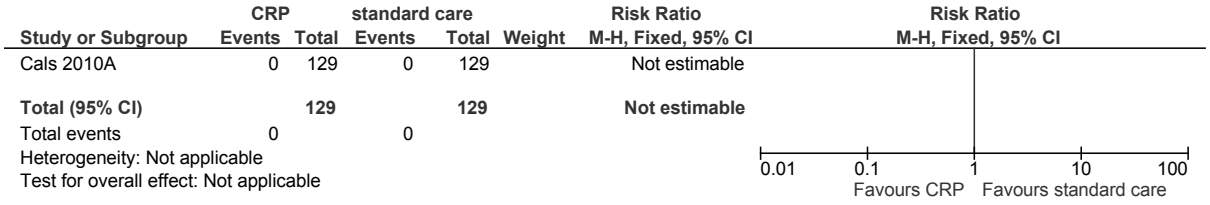
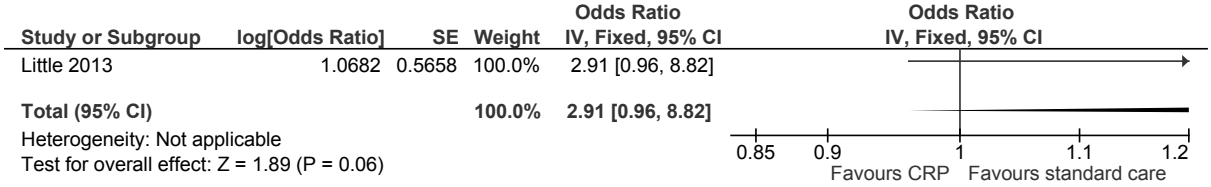


Figure 8: Hospitalisations



C.2 Point of care BNP testing versus standard care

Figure 9: Hospitalisation within 3 months

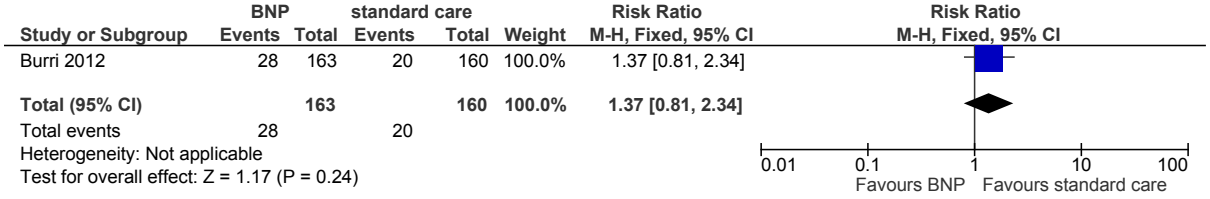


Figure 10: Hospitalisation within 12 months

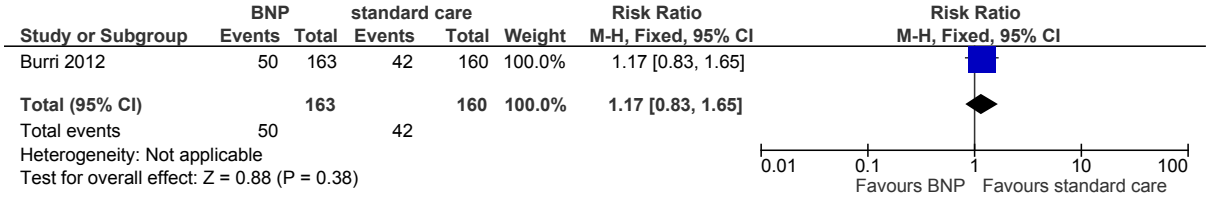
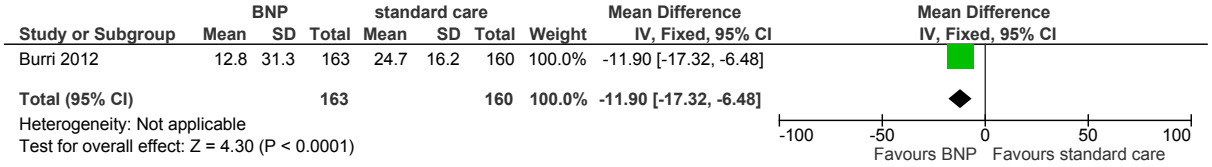


Figure 11: Time to initiation of appropriate therapy



Appendix D: Clinical evidence tables

Study	Aabenhus 2014[3] Cochrane review
Study type	Systematic review – effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers.
Number of studies (number of participants)	Six RCTs (3284 participants; 139 children).
Countries and setting	Russia, the Netherlands, Denmark, Spain, England, Wales, Poland, Belgium and Norway.
Duration of study	Databases were searched for papers published during the following time periods: CENTRAL (2013, Issue 12), MEDLINE (1946 to January 2014), EMBASE (2010 to January 2014), CINAHL (1981 to January 2014), Web of Science (1955 to January 2014) and LILACS (1982 to January 2014).
Stratum	-
Subgroup analysis within study	N/A.
Inclusion criteria	Randomised controlled trials (RCTs) in primary care patients with acute respiratory infections (ARI) that compared use of point-of-care biomarkers with standard of care. Trials that randomised individual patients as well as trials that randomised clusters of patients (cluster-RCTs) were included.
Exclusion criteria	Studies in which the analysis was not performed at the point-of-care, studies not conducted in a primary care setting and studies used a before-and-after design.
Recruitment/selection of patients	Primary care patients of all ages with symptoms from, or a diagnosis of, an ARI at study entry. Symptoms of ARI were defined as cough, discoloured/increased sputum, fever, runny nose, respiratory distress, feeling unwell, or combinations of focal and systemic symptoms having a duration of less than 4 weeks. Diagnoses included lower or upper respiratory tract infection, pneumonia, bronchitis, acute exacerbations of chronic obstructive pulmonary disease or asthma, pharyngitis, tonsillitis, laryngitis, rhinosinusitis, common cold, acute otitis media or influenza.
Age, gender and ethnicity	Age (mean, SD) intervention group: 45.3 (16.8), control group: 46.0 (17.2); % female intervention group: 62.8 control group: 64.3; ethnicity: not reported.

Study	Aabenhus 2014[3] Cochrane review
Further population details	Patients with acute respiratory infections (ARI).
Extra comments	Types of studies included in this review: 1. Patient or cluster randomised controlled trials (RCTs). 2. Patient or cluster controlled clinical trials (CCTs).
Indirectness of population	No indirectness.
Interventions	Biomarkers of infection act as surrogate measures of the immune response to infection and may reflect the severity of the condition A point-of-care test exists for some of these biomarkers to be performed at, or near, the site of patient care, delivering quick test results that can influence clinical decisions. The decision to prescribe antibiotics for an ARI is guided by pre-specified cut-off values specific to the individual point-of-care test but the test cannot replace clinical skills and expertise, and test results may be overruled on clinical grounds.
Funding	Not stated.

Study	Burri 2012[10]
Study type	RCT (Patient randomised; Parallel).
Number of studies (number of participants)	1 (n=323).
Countries and setting	Conducted in Switzerland; setting: the study was conducted by 29 primary care physicians in Switzerland and Germany and was co-ordinated at the University Hospital Basel, Switzerland. Sites were selected on the basis that patients could directly present to primary care physicians as a first point of consultation. Thus, the participating physicians represented a range of medical backgrounds from GPs to physicians with additional training in internal medicine, pneumology and cardiology. Participating practices were equally distributed in urban and suburban areas.
Line of therapy	1st line.
Duration of study	Intervention + follow up: point of care testing plus 12 months follow up.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis.
Stratum	Overall.

Subgroup analysis within study	Not applicable.
Inclusion criteria	Eligible patients presented with dyspnoea as their primary symptom. This had to be of new onset or clearly worsening if pre-existing. If multiple symptoms were present in an individual patient, dyspnoea had to be the main symptom.
Exclusion criteria	Patients younger than 18 years of age or with an obvious traumatic cause of dyspnoea, severe renal disease (serum creatinine level of more than 250 micromol/L) or sepsis were excluded.
Recruitment/selection of patients	323 consecutive patients were enrolled.
Age, gender and ethnicity	Age - Median (IQR): Intervention group: 73 (64-80), control group: 71 (62-79). Gender (M:F): Intervention group: 53% female, control group: 55% female. Ethnicity: not reported.
Further population details	-
Indirectness of population	No indirectness.
Interventions	(n=163) Intervention 1: GP access to laboratory investigations within practice hours - GP access to phlebotomy and blood tests with same day results within practice hours including cardiac biomarkers which included BNP and/or CRP and/or renal function and/or, full blood count and/or LFT. Rapid point-of-care testing measurement of BNP at initial presentation. 3ml of venous blood was collected into a potassium EDTA tube. Within a 15 minute period, BNP was measured using a rapid fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA). The same assay was used at all participating centres. All physicians were repeatedly trained in the most appropriate use of BNP levels in this indication. B-type natriuretic peptide was considered a quantitative marker of cardiac stress and heart failure. In the absence of BNP cut-off levels validated specifically inpatients presenting with dyspnoea to primary care physicians, we applied the cut-off levels validated inpatients presenting with acute dyspnoea to the ED. This decision was further supported by a large study performed in the primary care setting that demonstrated a comparable optimal cut-off level of NT-proB-NP as previously reported in studies conducted in the ED. Two cut-off levels of BNP to separate dyspnoea caused by heart failure from other causes of dyspnoea were suggested. In patients with a level below100 ng L)1, the diagnosis of heart failure was considered unlikely and alternative causes of dyspnoea had to be investigated. In patients with a BNP level above 400 ng L)1, heart failure was considered the most likely diagnosis and therapy with diuretics, nitro-glycerine, angiotensin-converting enzyme inhibitors (slow up-titration), beta blockers (slow up-titration) and spironolactone was recommended. BNP levels between 100 and 400 ng L)1 suggested the presence of mild heart failure, but clinical judgment and further diagnostic testing were recommended to exclude pulmonary embolism. Adjustments were recommended in patients with renal dysfunction and obesity (higher and lower cut-off levels, respectively). Duration: 12 months follow-up. Concurrent medication/care: all patients underwent an initial clinical assessment that, in general, included a clinical history, physical examination and electrocardiography. Chest radiography and pulmonary function tests were performed based on clinical decision. Diagnostic and therapeutic decisions were not based on BNP levels alone, instead this information was considered in the context of other clinical information obtained and the physician's clinical opinion.

	(n=160) Intervention 2: No GP access to laboratory investigations. Evaluation using the conventional diagnostic strategy without the measurement of BNP. Patients in the control group were evaluated and treated according to the most recent clinical guidelines. Duration: 12 months follow up. Concurrent medication/care: all patients underwent an initial clinical assessment that in general included a clinical history, physical examination and electrocardiography. Chest radiography and pulmonary function tests were performed based on clinical decision.
Funding	Equipment/drugs provided by industry (ALERE provided the rapid fluorescence immunoassay for the point of care measurement of BNP).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GP ACCESS TO PHLEBOTOMY AND BLOOD TESTS WITH SAME DAY RESULTS WITHIN PRACTICE HOURS INCLUDING CARDIAC BIOMARKERS INCLUDING BNP AND/OR, CRP AND/OR RENAL FUNCTION AND/OR, FULL BLOOD COUNT AND/OR LFT versus NO GP ACCESS TO LABORATORY INVESTIGATIONS. Protocol outcome 1: Laboratory or diagnostic turnaround or result to GP. - Actual outcome: Time to appropriate therapy at days; Group 1: mean 12.8 days (SD 31.3); n=163, Group 2: mean 24.7 days (SD 41.3); n=160; Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness Protocol outcome 2: ED attendance - Actual outcome: Hospitalisations after 3 months at 3 months; Group 1: 28/163, Group 2: 20/160; Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness - Actual outcome: Hospitalisations after 12 months at 12 months; Group 1: 50/163, Group 2: 42/160; Risk of bias: low; ; Risk of bias: All domain - high, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - - Low; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Quality of life; Antibiotic usage; Avoidable adverse events; Patient and/or carer satisfaction.

Study	**Cals 2009[14]**
Study type	RCT (GP surgeries/practices randomised; Parallel).
Number of studies (number of participants)	1 (n=431).
Countries and setting	Conducted in Netherlands; setting: 40 general practitioners based in 20 general practices in the Netherlands.
Line of therapy	1st line.
Duration of study	Intervention + follow up: 10 weeks.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.
Inclusion criteria	Suspected lower respiratory tract infection with a cough lasting less than 4 weeks together with 1 focal and 1 systemic symptom.
Exclusion criteria	None reported.
Recruitment/selection of patients	Sequential eligible adults with regular consultation hours during the winters of 2005-6 and 2006-7.
Age, gender and ethnicity	Age - Mean (SD): CRP test group: 49.4 (14.7), control group: 50.3 (16.0). Gender (M:F): CRP test group: 59%, control group: 64.2%. Ethnicity: not reported.
Further population details	-
Indirectness of population	No indirectness.
Interventions	(n=227) Intervention 1: GP access to laboratory investigations within practice hours - GP access to phlebotomy and blood tests with same day results within practice hours including cardiac biomarkers including BNP and/or CRP and/or renal function and/or, full blood count and/or LFT. Clinicians were given devices to test for CRP (NycoCard II Reader, Axis Shield, Norway) according to the manufacturer's instructions. A result can be available within 3 minutes, using a drop of blood obtained by finger prick. GPs were given guidance on how to use the test results within the consultation during a 30 minute practice based training session delivered by the study team. The additional value of C reactive protein in ruling out serious infection was emphasised. An 8 week run-in period enabled familiarisation with the devices before patient recruitment. Duration: 10 week follow up. Concurrent medication/care: n/a. (n=204) Intervention 2: No GP access to laboratory investigations. Usual care with no CRP testing. The Dutch guideline for managing acute cough, including diagnostic and therapeutic advice for lower respiratory tract infection, is distributed to all GPs in the Netherlands and informs usual care. Duration: 10 week follow-up. Concurrent medication/care: n/a.

Funding	Academic or government funding (Netherlands Organisation for Health Research and Development).
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GP ACCESS TO PHLEBOTOMY AND BLOOD TESTS WITH SAME DAY RESULTS WITHIN PRACTICE HOURS INCLUDING CARDIAC BIOMARKERS INCLUDING BNP AND/OR,CRP AND/OR RENAL FUNCTION AND/OR, FULL BLOOD COUNT AND/OR LFT versus NO GP ACCESS TO LABORATORY INVESTIGATIONS. Protocol outcome 1: Patient satisfaction. - Actual outcome: Patients very satisfied and above at NR; Group 1: 159/227, Group 2: 76/204; Risk of bias: All domain - high, Selection - Low, Blinding - high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no serious indirectness Protocol outcome 2: Antibiotic usage. - Actual outcome: Antibiotic prescription at first appointment at first appointment; Group 1: 70/227, Group 2: 108/204; Risk of bias: All domain - high, Selection - Low, Blinding - high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no serious indirectness - Actual outcome: Antibiotic prescribing within 28 days of first appointment at 28 days; Group 1: 102/227, Group 2: 119/204; Risk of bias: All domain - high, Selection - Low, Blinding - high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: no serious indirectness	
Protocol outcomes not reported by the study	Quality of life; ED attendance; Avoidable adverse events; Laboratory or diagnostic turnaround or result to GP.

Study	**Dahler-Eriksen 1999[21]**
Study type	RCT (GP surgeries/practices randomised; Parallel).
Number of studies (number of participants)	1 (n=1853).
Countries and setting	Conducted in Denmark; setting: 41 GP clinics in the catchment area of Vejle County Central (Denmark) hospital lab were invited to participate in the study. 29 clinics accepted. The clinics were randomised into 1 of 2 groups and after 3 months the 2 groups interchanged (crossover). The first period of intervention and control was 3 months April-June 1996 and the second period was 4 months (July-October 1996).
Line of therapy	1st line.
Duration of study	Intervention time.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis.
Stratum	Overall.
Subgroup analysis within study	Not applicable.
Inclusion criteria	Not reported.
Exclusion criteria	Incomplete registration of personal registration numbers.
Recruitment/selection of patients	The GP filled out a registration card for each patient when a CRP was measured or ordered.
Age, gender and ethnicity	Age - Other: mean: 53.7 CIs: 52.8-54.6. Gender (M:F): 60.2% women (CI 58.0-62.4). Ethnicity: not reported.
Further population details	-
Indirectness of population	No indirectness.
Interventions	(n=919) Intervention 1: GP access to laboratory investigations within practice hours - GP access to phlebotomy and blood tests with same day results within practice hours including cardiac biomarkers which included BNP and/or CRP and/or renal function and/or, full blood count and/or LFT. GP had access to a near-patient test for CRP (NycoCard CRP whole blood, Nycomed Pharma) in the office. Duration n/a. Concurrent medication/care: no clinical guidelines for the use of CRP were distributed to the clinics. (n=934) Intervention 2: Standard services - as defined in study. CRP had to be ordered as usual, by mailing a blood sample to the laboratory. Duration not reported. Concurrent medication/care: no clinical guidelines for the use of CRP were distributed to the clinics.
Funding	Academic or government funding (Danish Medical Research Council).

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: GP ACCESS TO PHLEBOTOMY AND BLOOD TESTS WITH SAME DAY RESULTS WITHIN PRACTICE HOURS INCLUDING CARDIAC BIOMARKERS INCLUDING BNP AND/OR,CRP AND/OR RENAL FUNCTION AND/OR, FULL BLOOD COUNT AND/OR LFT versus AS DEFINED IN STUDY. Protocol outcome 1: Antibiotic usage - Actual outcome: Antibiotics prescribed; Group 1: 168/529, Group 2: 154/472; Comments: Patients with infection as the tentative diagnosis and with unspecific diagnoses such as fever, cough or dyspnea are included in this analysis. Patients in a follow-up course and with appendicitis were excluded Risk of bias: All domain - high, selection- high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Intervention group purpose of CRP test was likely to be diagnosis of new disease, control group purpose of CRP test was likely to be follow-up	
Protocol outcomes not reported by the study	Quality of life; Laboratory or diagnostic turnaround or result to GP; ED attendance; Avoidable adverse events; Patient and/or carer satisfaction.

Appendix E: Economic evidence tables

Study	Burri[10]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: Hospital admission) **Study design:** RCT **Approach to analysis:** Analysis of individual resource use, with unit costs applied. **Perspective:** Switzerland and Germany primary care **Follow-up:** 12 months **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** Patients presenting with new onset or clearly worsening dyspnoea as their primary symptom **Cohort settings:** Start age: 72 Male: 13% **Intervention 1: (n=160)** Usual care (no BNP) **Intervention 2: (n=163)** Receiving point of care B-type natriuretic peptide (BNP) measurement	**Total costs (mean per patient):** Intervention 1: £5,607 Intervention 2: £5,924 Incremental (2−1): £317 (95% CI: NR; p=NR) **Currency & cost year:** 2007 US dollars (presented here as 2007 UK pounds35[(a)]) **Cost components incorporated:** Hospitalisations from dyspnoea, outpatient visits to a physician, medical treatment.	**Hospitalisations (per 100 patients):** Intervention 1: 26.25 Intervention 2: 30.67 Incremental (2−1): 4.42 (95% CI: NR; p=NR) **Diagnostic certainty (% of patients receiving appropriate treatment):** Intervention 1: 53% Intervention 2: 66% Incremental (2−1): 13% (95% CI: NR; p=NR)	Intervention 1, usual care (no BNP), was seen to have lower costs and fewer hospitalizations per 100 patients. However, diagnostic certainty was greater for intervention 2 using BNP.
Data sources				
Health outcomes: Resource use from questionnaires from referring physicians and telephone interviews with patients at 3 and 12 months. **Quality-of-life weights:** NA **Cost sources:** Participant's insurance company and hospital charges. Swiss health system.				
Comments				
Source of funding: NR **Applicability and limitations:** Intervention may not be relevant. Cost-consequence analysis only. Clinical outcomes may not be important. Unclear if hospital admissions through ED. Non-UK study. RCT-based analysis so from 1 study by definition therefore not reflecting all evidence in area. No sensitivity analysis reported.				
Overall applicability[(b)]: Partially applicable **Overall quality[(c)]:** Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; BNP: B-type natriuretic peptide; CCA: cost–consequence analysis; NR: not reported; for studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(a) Converted using 2007 purchasing power parities.[59]

(b) Directly applicable/Partially applicable/Not applicable.

(c) Minor limitations/Potentially serious limitations/Very serious limitations.

Study	**Hunter[32]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALY, antibiotic use) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Decision tree and Markov model of progression based on 2 severity states (Healthy and respiratory tract infection). 28 day cycles. **Perspective:** UK NHS **Time horizon:** 3 years (40 cycles) **Discounting:** Costs: 3.5% (0.26% per cycle); Outcomes: 3.5% (0.26% per cycle)	**Population:** Patients with respiratory tract infection symptoms as defined by NICE **Cohort settings:** Start age: NR Male: NR **Intervention 1: (n=100)** Usual care (no CRP) **Intervention 2: (n=100)** GP use of C-reactive protein (CRP) point of care test	**Total costs (mean per patient):** Intervention 1: £180.81 Intervention 2: £180.39 Incremental (2−1): -£0.42 (95% CI: NR; p=NR) **Currency & cost year:** 2013 UK pounds **Cost components incorporated:** Cost per CRP test, cost per minute GP, cost per antibiotic prescription	**QALYs (mean per patient):** Intervention 1: 2.5563 Intervention 2: 2.55761 Incremental (2−1): 0.0013 (95% CI: NR; p=NR) **Antibiotics prescribed (mean per patient):** Intervention 1: 1.84 Intervention 2: 1.36 Incremental (2−1): -0.48 (95% CI: NR; p=NR)	Intervention 2 marginally dominates. Probability Intervention 2 cost-effective (£20K/30k threshold): 77%/80% **Analysis of uncertainty:** pa: 5,000 iterations of discounted costs and QALYs for sets of 100 patients presented in a cost-effectiveness plane. Results found intervention 2, GP use of CRP, to be dominant compared to intervention 1, usual care, in 50% of simulations. One way sensitivity analysis, changing key parameters in the model, had little impact on the conclusions.
Data sources				
Health outcomes: Probabilities taken from Cals, Huang and Little [15,31,38] **Quality-of-life weights:** Health state utilities: utility scores from Kind, NICE and Oppong.[36,54,58] Duration of RTI from Cals [13] **Cost sources:** NHS reference costs and PSSRU.				
Comments				
Source of funding: NR **Limitations:** Reliant on small number of studies, mostly collection of studies by Cals et al.				
Overall applicability[(a)]: Directly applicable **Overall quality[(b)]:** Minor limitations				

Abbreviations: 95% CI: 95% confidence interval; CRP: C-reactive protein; CUA: cost–utility analysis; NR: not reported; pa: probabilistic analysis; PSSRU: personal social services research unit; QALYs: quality-adjusted life years.

(a) Directly applicable/Partially applicable/Not applicable.

(b) Minor limitations/Potentially serious limitations/Very serious limitations.

Study	Oppong[58]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs, antibiotic prescription) **Study design:** RCT **Approach to analysis:** Analysis of individual level resource use, with unit costs applied **Perspective:** Swedish and Norwegian health care systems. **Time horizon/Follow-up:** 28 days **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** Patients presenting to their GP for the first time with an acute or worsened cough as the main or dominant symptom for up to 28 days **Cohort settings:** Start age: 52 Male: NR **Intervention 1: (n=89)** Usual care (no CRP) **Intervention 2: (n=281)** Patients receiving C-reactive protein (CRP) point of care test	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): £8.97 (95% CI: £1.48 to £19.43; p=0.09) **Currency & cost year:** 2007 Euro (presented here as 2007 UK pounds(a))] **Cost components incorporated:** Primary care clinic visits, nurse visits, hospital admissions, medical investigations, referrals, antibiotics and other drug prescriptions	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): 0.0012 (95% CI: -0.001 to 0.004; p=0.35) **Antibiotics prescribed (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): -0.1 (95% CI: -0.2 to 0.01; p=0.08)	**ICER (Intervention 2 versus Intervention 1):** £7,475 per QALY gained; under the £20,000 per QALY gained threshold.
Data sources				
Health outcomes: Patient provided resource use through weekly updated diary over the 28 days. Clinician completed case reports. **Quality-of-life weights:** EQ-5D European harmonised value set **Cost sources:** 1. national and international publications on costs; 2. collaborators from the GRACE network; 3. British health economists who had participated in studies in the countries; 4. health economists in the countries.				
Comments				
Source of funding: Part of GRACE (Genomics to combat resistance against antibiotics in community-acquired LRTI in Europe) – European Commission funded project. **Limitations:** Swedish/Norwegian health care system may not be representative of UK NHS. Only reported incremental QALY difference, not incremental QALYs of each intervention. Observational study using regression analysis. 28 day follow-up may not be sufficient. Unit cost resources may not be reliable. No sensitivity analysis.				
Overall applicability(b): Partially applicable **Overall quality(c):** Potentially serious limitations				

Abbreviations: 95% CI: 95% confidence interval; CRP: C-reactive protein; CUA: cost–utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; NR: not reported; QALYs: quality-adjusted life years.

(a) Converted using 2007 purchasing power parities.[59]

(b) Directly applicable/Partially applicable/Not applicable.

(c) Minor limitations/Potentially serious limitations/Very serious limitations.

Appendix F: GRADE tables

Table 7: Clinical evidence profile: Point of care CRP testing versus standard care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRP	standard care	Relative (95% CI)	Absolute		
Antibiotics prescribed at index consultation. All trials (cluster-randomised with modified sample size) [6]												
7	randomised trials	serious[a]	serious[b]	no serious indirectness	serious[c]	None	772/2142 (36%)	51.9%	RR 0.8 (0.69 to 0.93)	104 fewer per 1000 (from 36 fewer to 161 fewer)	⊕OOO VERY LOW	IMPORTANT
Antibiotics prescribed at index consultation. All trials - Individually randomised trials												
4	randomised trials	Serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	430/1108 (38.8%)	50.3%	RR 0.91 (0.83 to 1.01)	45 fewer per 1000 (from 86 fewer to 5 more)	⊕⊕⊕O MODERATE	IMPORTANT
Antibiotics prescribed at index consultation. Cluster-randomised trials (modified sample size) [6]												
3	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	342/1034 (33.1%)	52.5%	RR 0.68 (0.61 to 0.75)	168 fewer per 1000 (from 131 fewer to 205 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Antibiotics prescribed within 28 days. All trials (cluster-randomised trials with modified sample size) [6]												
4	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	178/351 (50.7%)	62.3%	RR 0.8 (0.67 to 0.96)	125 fewer per 1000 (from 25 fewer to 206 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Antibiotics prescribed within 28 days - Individually randomised trials												

2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	129/237 (54.4%)	62.3%	RR 0.87 (0.75 to 1.02)	81 fewer per 1000 (from 156 fewer to 12 more)	⊕⊕⊕O MODERATE	IMPORTANT
Antibiotics prescribed within 28 days -cluster-randomised trials with modified sample size[6]												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	None	49/114 (43%)	64.3%	RR 0.68 (0.51 to 0.91)	206 fewer per 1000 (from 58 fewer to 315 fewer)	⊕⊕OO LOW	IMPORTANT
Patient satisfaction												
2	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	serious[c]	None	249/345 (72.2%)	64.9%	RR 1.11 (0.97 to 1.27)	71 more per 1000 (from 19 fewer to 175 more)	⊕⊕OO LOW	CRITICAL
Clinical recovery day 7 (number of patients substantially improved by day 7)												
3	randomised trials	serious[a]	no serious inconsistency	No serious indirectness	no serious imprecision	None	324/627 (51.7%)	41.4%	RR 0.95 (0.87 to 1.05)	21 fewer per 1000 (from 54 fewer to 21 more)	⊕⊕⊕O MODERATE	IMPORTANT ?
Clinical recovery day 28 (number of patients substantially improved at follow-up within 28 days) (cluster-randomised trials with modified sample size)[6]												
3	randomised trials	serious[a]	no serious inconsistency	No serious indirectness	serious[c]	None	207/264 (78.4%)	75.8%	RR 1.01 (0.93 to 1.08)	8 more per 1000 (from 53 fewer to 61 more)	⊕⊕OO LOW	IMPORTANT ?
Serious adverse events												
1	randomised trials	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	None	0/129 (0%)	0%	not pooled	not pooled	⊕⊕⊕O MODERATE	IMPORTANT
Hospitalisation												

1. Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias.
2. Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis.
3. Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
4. Downgraded by 1 or 2 increments because the point estimate varies widely across studies, unexplained by subgroup analysis.

[5.] Downgraded by 1 increment because majority of evidence had indirect outcomes, and downgraded by 2 increments if the majority of the evidence had very indirect outcomes (this is a surrogate outcome for ED attendance).

[6] The unit of analysis was the individual patient. For cluster-RCTs the Cochrane review authors adjusted the unit of analysis by calculating the design effect to modify sample sizes and inflate confidence intervals (CIs) accordingly

Table 11: Clinical evidence profile: Point of care BNP testing versus standard care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BNP	standard care	Relative (95% CI)	Absolute		
Hospitalisation within 3 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness[d]	serious[a]	None	28/163 (17.2%)	12.5%	RR 1.37 (0.81 to 2.34)	46 more per 1000 (from 24 fewer to 167 more)	⊕⊕OO LOW	IMPORTANT
Hospitalisation within 12 months												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious indirectness[d]	serious[a]	None	50/163 (30.7%)	26.3%	RR 1.17 (0.83 to 1.65)	45 more per 1000 (from 45 fewer to 171 more)	⊕⊕OO LOW	IMPORTANT
Time to initiation of appropriate therapy (days) (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[b,c]	no serious imprecision	None	163	160	-	MD 11.9 lower (17.32 to 6.48 lower)	⊕⊕⊕O MODERATE	IMPORTANT

[1.] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

[2.] Downgraded by 1 increment because majority of evidence had indirect outcomes, and downgraded by 2 increments if the majority of the evidence had very indirect outcomes (this outcome was used as a surrogate outcome for lab/diagnostic turn around for result to GP).

[3.] Result not reported as a hazard ratio.
[4.] Downgraded by 1 increment because majority of evidence had indirect outcomes, and downgraded by 2 increments if the majority of the evidence had very indirect outcomes (this is a surrogate outcome for ED attendance)

Appendix G: Excluded clinical studies

Table 8: Studies excluded from the clinical review

Study	Exclusion reason
Andersen 2015 [4]	Incorrect intervention. The study investigated the levels of interleukin (IL)-23 in patients with early rheumatoid arthritis and the effect of anti-tumour necrosis factor treatment on IL-23 levels.
Andreeva 2012[5]	Abstract
Anon 1984[1]	Incorrect interventions. Narrative paper. Use of serological tests in the EPI.
Anon 2005[2]	Article not in English
Bjerrum 2004[8]	Observational study
Bjerrum 2006[7]	Before-After study
Bjerrum 2011[9]	Before-After audit based study
Cadth 2013[11]	Incorrect interventions. A review of the clinical effectiveness of point of care testing technologies compared with central laboratory methods to assess patients' white blood cell counts.
Cals 2007[16]	Study protocol
Cals 2008[12]	Study protocol
Cals 2013[15]	No outcomes of interest
Chandrajay 2016 [18]	Incorrect study design- prospective cohort study (RCT evidence available). Incorrect intervention- evaluation of the effect of clinical validation of out of hours critical laboratory results
Cook2015A [19]	Narrative review of primary care point-of-care testing and anti-bacterial use in respiratory tract infection. RCTs included in this review have already been included in our evidence review.
Do2016[23]	Incorrect setting- primary health care centres in the community
Engel 2012[24]	Systematic review- screened for relevant references
Grodzinsky 2004[25]	Observational study (RCT data available)
Hanrahan 2015 [26]	Incorrect intervention. The study evaluated the effect of Xpert (MTB/RIF assay to diagnose TB rapidly) either at point of care or at an off-site laboratory for diagnosis of pulmonary TB. Tests for diagnosis of TB not included intervention of interest in our protocol.
Holm 2007 [27]	Observational study (RCT evidence available)
Hopstaken 2003 [29]	Observational study (RCT evidence available)
Hopstaken 2006 [28]	Observational study
Huang 2013[31]	Systematic review- screened for relevant references
Jakobsen 2010[33]	Observational study (RCT evidence available)
Joshi 2013[34]	Review paper checked for references
Kavanagh 2011[35]	Observational study (RCT evidence available)

Leber 2015 [37]	Incorrect intervention. This study assessed rapid HIV testing which was not included as an intervention of interest in our protocol.
Llor 2012[40]	Before-After audit based study
Llor 2012[42]	Before-After audit based study
Llor 2013[41]	Cross-sectional study
Llor 2013[39]	Observational study
Llor 2014[43]	Before- After audit based study
Mueller 2004[45]	Incorrect setting (patients in Emergency department)
Neumark 2010[56]	Observational study (RCT evidence available)
Oosterheert 2005[57]	Incorrect intervention and setting. Intervention is real time polymerase chain reaction (PCR) and setting is University hospital.
Peters 2013[60]	Case control study
Pluddemann 2011[61]	Review article
Rebnord 2015 [62]	Incorrect study design- observational study (RCT evidence available)
Strykowski 2015 [65]	Incorrect study design- before and after study (RCT evidence available)

Appendix H: Excluded economic studies

Table 9: Studies excluded from the health economic review

Reference	Reason for exclusion
Cals 2011[13]	This study was assessed as partially applicable with potentially serious limitations. However, given that 2 cost-utility analyses of CRP testing were available[32,58] including 1 set in the UK, this study was selectively excluded.

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