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Impact of point-of-care C-reactive protein in ambulatory care: a systematic review and meta-analysis.

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IMPACT OF POINT-OF-CARE C-REACTIVE PROTEIN IN AMBULATORY CARE: A

SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Objective: The aim of this review was to collate all available evidence on the impact of point-of-care CRP testing on patient-relevant outcomes in children and adults in ambulatory care.

Design: This was a systematic review to identify controlled studies assessing the impact of point-ofcare CRP in patients presenting to ambulatory care services. Ovid Medline, Embase, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, DARE, Science Citation Index were searched from inception to March 2017.

Elegibility criteria for selecting studies: controlled studies assessing the impact of point-of-care CRP in patients presenting to ambulatory care services, resulting in a change in clinical care, including but not limited to antibiotic prescribing rate, re-consultation, clinical recovery, patient satisfaction, referral and additional tests. No language restrictions were applied.

Data extraction: Data were extracted on setting, date of study, a description of the intervention and control group, patient characteristics and results. Methodological quality of selected studies and assessment of potential bias was assessed independently by two authors

Results: 11 randomised controlled trials and eight non-randomised controlled studies met the inclusion criteria, reporting on 16,064 patients. All included studies had a high risk of performance and selection bias. Compared to usual care, point-of-care CRP reduces immediate antibiotic prescribing (pooled risk ratio 0.81; 95% CI 0.71 to 0.92). This effect increased when guidance on antibiotic prescribing relative to the CRP level was provided (risk ratios of 0.68; 95%CI 0.63-0.74 in adults and 0.56; 95%CI 0.33-0.95 in children). We found no significant effect of point-of-care CRP testing on patient satisfaction, clinical recovery, re-consultation, further testing, and hospital admission.

Conclusions: Performing a point-of-care CRP test in ambulatory care accompanied by clinical guidance on interpretation reduces immediate antibiotic prescribing in both adults and children. As yet, available evidence does not suggest an effect on other patient outcomes or healthcare processes.

Trial Registration: CRD42016035426 (PROSPERO)

ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY

- This review focused on the clinical impact of POC CRP on patient-relevant outcomes in ambulatory care
- Performing a point-of-care CRP test in ambulatory care accompanied by clinical guidance can reduce immediate antibiotic prescribing rate
- Our comprehensive approach resulted in a heterogeneous group of outcomes, patient populations and study designs
- The paucity of data for children resulted in wide confidence intervals for our effect estimates, emphasizing the need for large trials in children in ambulatory care
- Lack of blinding of the clinicians and patients is inherent to trials examining the clinical impact of an intervention

INTRODUCTION

C-reactive protein (CRP) is an acute-phase protein, produced in the liver, which rises in response to tissue damage or inflammation, e.g. from infection, but also in other inflammatory processes such as an acute exacerbation of Crohn's disease.[1] Until recently, CRP blood tests have played only a minor role in ambulatory care because the delay between testing and result meant results were available too late to influence management decisions.[2] Point-of-care (POC) tests are being gradually introduced in different healthcare settings and their use is expected to increase dramatically,[3, 4] with POC CRP tests now available providing a result within 4 minutes.[5, 6] Ambulatory care deals with a large amount of non-specific presentations, such as infectious diseases. Diagnostic tools for acute conditions are fairly limited and mostly reliant on clinical assessment.[7-9] More precise assessment would be welcome to mitigate increasing rates of patients referred to secondary care, and render diagnostic assessment in ambulatory care safer.[10]

In addition, diagnostic uncertainty can lead to inappropriate antibiotic prescribing, unnecessary referrals to hospital, and unwarranted additional testing due to concern about potential serious infection.[8] Primary care is where the majority of antibiotics are prescribed, most of which are for respiratory infections. Children are a particularly high-risk group for unnecessary antibiotic prescribing.[11] As well as the global threat of widespread antimicrobial resistance, individuals with resistant infections in primary care are more likely to have clinical failure to subsequent antibiotic treatment.[12] Introducing better diagnostic tests might strengthen the assessment of infections in ambulatory care.[13] General practitioners (GP) have indicated that they would like to use these POC tests to help them decide whether or not to start antibiotic treatment for patients with respiratory tract infections if rigorous evidence of the impact on patient pathways are available.[14]

In ambulatory care, CRP has been evaluated (mostly diagnostic accuracy studies with only very few trials) for the diagnosis of lower respiratory tract infections in adults, identify serious infections in children and reduce inappropriate antibiotic prescribing.[9, 15] Since its introduction in routine care in Scandinavia in the early 1990s, prior to any solid evidence on the potential impact,[16] POC CRP

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has been incorporated in the Dutch and UK guidelines to assist antibiotic prescribing decisions in adults with symptoms of lower respiratory tract infections.[17, 18] Both recommendations are based on the same three RCTs (2 randomised at practice level and 1 at patient level), showing a significant reduction in immediate antibiotic prescribing rate when POC CRP was used (risk ratios ranging from 0.54 to 0.77).[19-21]

A recent Cochrane review, involving six trials, confirmed that POC CRP can reduce antibiotic prescribing in adults with acute respiratory tract infections by 22%,[14] however the broader impact on other clinically relevant outcomes, such as hospital admissions, missed diagnoses, inducing indication creep,[22] re-consultation, further testing and patient satisfaction and in other patient groups, such as children, has yet to be confirmed.[15]

This systematic review forms part of a series of reviews to assess the impact of any POC tests in ambulatory care. Here we aim to collate all available evidence on the impact of POC CRP testing in ambulatory care.

METHODS

Our objective was to assess the impact of POC CRP in patients presenting to ambulatory care services, resulting in a change in clinical care, including but not limited to antibiotic prescribing rate, re-consultation, clinical recovery, patient satisfaction, referral and additional tests.

Search strategy

We searched six electronic databases (MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Cochrane CENTRAL, DARE, Science Citation Index). The first search was undertaken in November 2015 with an update undertaken in March 2017. No time or language restrictions were applied. We checked reference lists of all retrieved articles included in the final review. The full search strategy is included in **Supplementary file 1**.

Selection of studies

Studies were eligible if they reported the impact of point-of-care testing in ambulatory care settings. Ambulatory care was defined as any outpatient setting including primary care, walk-in clinics, and emergency departments. Studies in hospitalised patients were excluded. In addition, we excluded conference abstracts, diagnostic accuracy studies (focussing only on the performance of a point-ofcare test versus a central lab test), qualitative studies, studies without a control group, and systematic reviews although their references were checked for potential relevance. Title and abstract screening was done in pairs by six independent reviewers (CG, PST, JV, TA, JL, PT). Discrepancies between the reviewers were resolved by a third independent reviewer of the team. For this paper, studies on point-of-care CRP testing were identified from the overall selection by two independent researchers (JV, CG). BMJ Open: first published as 10.1136/bmjopen-2018-025036 on 1 February 2019. Downloaded from http://bmjopen.bmj.com/ on April 28, 2024 by guest. Protected by copyright.

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Data extraction and assessment of methodological quality

Data were extracted by one reviewer (JV) and checked by a second reviewer (JL), and included setting, date of study, a description of the intervention and control group, patient characteristics and results.

Methodological quality of selected studies and assessment of potential bias was assessed independently by two authors (JV, JL). Any disagreements were resolved by discussion involving a third member of the team. We used the Cochrane Risk of Bias tool for RCTs,[23] extended for nonrandomised but experimental and controlled studies by an assessment of a set of pre-specified confounders, including whether baseline characteristics were reported, whether intervention and control groups were similar, and whether there was a detailed description of the usual care pathway. For case-control studies we applied the Newcastle-Ottawa scale.[24]

Outcome Assessment

The primary outcome of interest was the impact of POC on clinically relevant outcomes such as antibiotic prescribing rate at the index consultation and during follow up, re-consultation, referral or admission to hospital, and mortality. Secondary outcomes included clinical recovery, patient satisfaction, respiratory tract infections (RTI) during follow-up, referral for chest X-ray, additional tests performed, time to symptom resolution and adherence to antibiotic treatment.

Patient involvement

This paper is part of the NIHR Diagnostic Evidence Cooperative (DEC) Oxford portfolio, and as such benefits from reflection and advice from the DEC's standing Patient and Public Involvement panel. Our panel has shown great interest in the introduction of point-of-care tests in ambulatory care, especially in relation to the assessment of acutely ill children and the monitoring of anticoagulant therapy. Credibility of the test result, funding of testing strips, and how to deal with intermediate results have been raised by our PPI panel in relation to POC testing.

Data analysis and synthesis

Meta-analyses were conducted separately for randomised controlled trials and non-randomised studies. Individual study estimates were pooled in a meta-analysis using Mantel–Haenszel random-effects models for risk ratio estimates and inverse-variance random-effects models were used for mean difference estimates. Study-to-study heterogeneity was assessed using the I² test statistic in combination with visual inspection of the forest plots. For RTI during follow-up, antibiotics prescribed for RTI during follow-up, time to symptom resolution, adherence to antibiotic treatment, and antibiotic prescribing rate (if absolute numbers were unavailable) we used mean differences and their corresponding 95% confidence intervals (95% CI). Whenever data on mean differences was missing, we followed recommendations in the Cochrane Handbook of Systematic Reviews of Interventions to approximate the mean and standard deviation from the reported interquartile range.[23]

Subgroup analyses were limited to type of randomisation (at cluster (practice) or patient level), age group (children versus adults) and whether or not CRP cut-off guidance was applied. We performed meta-regression using the metareg function (meta package in R) to assess whether heterogeneity could be explained by age or the provision of CRP cut-off guidance. We created funnel plots to explore publication bias and small study effects when at least 10 studies were available for a particular outcome. Citation processing was done with Covidence (https://www.covidence.org/). Meta-analysis was undertaken with Revman version 5.3, meta-regression with R version 3.4.3.

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Description of studies

Databases were searched and yielded 26,124 records. After full text assessment in the overall review on POC testing in ambulatory care, 225 records were included, of which 19 studies were on POC CRP testing. These included studies comprising of 11 randomised controlled trials and eight nonrandomised studies reporting on 16,064 patients in total. **(Table 1)** Details of search strategy and screening are provided in **(Supplementary file 1 & 2)**. Sixteen studies on POC CRP testing were excluded at full-text screening, because: they were not in a

ambulatory care setting, [25, 26] no comparator group without POC CRP testing was present, [27-30] the effect of the POC CRP could not be assessed separately or did not guide treatment decisions, [31-33] the focus was cost-effectiveness modelling [34-36] or decision making analysis, [37, 38] or it was not a clinical trial (study protocol or response to systematic review). [39, 40] **(Supplementary file 3)**

Table 1: Baseline characteristics	of included studies
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Study	Country	Design	Device (Manufacturer)	Patient characteristics	Total sample size (CRP/no CRP)
	d controlled tria			0	
a) patients infectior	1 5	vith signs of	respiratory tract		
Andreeva	Russia	cluster	Afinion	adults with lower respiratory tract	179
2014[41]			(Axis Shield)	infection/acute cough for less than 28 days	(101/78)
Cals	the	cluster	Nycocard II (Axis	adults with suspected lower	431
2009[19]	Netherlands		Shield)	respiratory tract infection (cough < 4	(227/204)
				weeks, + 1 focal and + 1 systemic symptom or sign)	
Cals	the	individual	Nycocard II (Axis	adult with lower respiratory tract	258
2010[20]	Netherlands		Shield)	infection (cough < 4 weeks, + 1 focal	(129/129)
				and + 1 systemic symptom or sign) or	
				rhinosinusitis < 4 weeks, + 2	
				symptoms or signs	
Cals	the	cluster	Nycocard II (Axis	adults with suspected lower	379
2013[42]	Netherlands		Shield)	respiratory tract infection (cough < 4	(203/176)
				weeks, + 1 focal and + 1 systemic	
Diadariahaan	Demmeril	individual	Nuce cond II / Avia	symptom or sign)	812
Diederichsen	Denmark	individual	Nycocard II (Axis	children and adults with respiratory tract infection	
2000[43]			Shield)		(414/398)
Do	Vietnam	individual	Nycocard II (Axis	children and adults with at least one	2037
2016[44]			Shield)	focal and one systemic symptom of	(1017/1019)
				acute respiratory tract infection	

adults with upper or lower

respiratory tract infection less than

Quikread

(Orion

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Little

2013[21]

Spain,

England,

cluster

2013[21]	England, Wales (UK), Poland, Belgium, the Netherlands		(Orion Diagnostica)	28 days	(2224/2040)
Melbye 1995[45]	Norway	individual	Nycocard II (Axis Shield)	adults with subjective complaint of pneumonia, bronchitis or asthma or 1 of: cough, shortness of breath, chest pain on deep inspiration or cough	239 (108/131)
b) patients	s presenting with	signs of any ac	ute illness		
Lemiengre 2014[46] (also Verbakel 2016[9])	Belgium	cluster	Afinion (Alere)	children with an acute illness less than 5 days	3147 (1730/1417)
Rebnord 2017[47]	Norway	individual	Quikread Go (Orion Diagnostica)	children with fever and/or respiratory symptoms	397 (138/259)
Van den Bruel 2016[48]	UK	individual	Afinion (Alere)	children with an acute illness less than 5 days	54 (26/28)
a) patients infection		vith signs of	respiratory tract		
Bjerrum 2004[49]	Denmark	cohort	not specified	children and adults with acute sinusitis, acute tonsillitis, and acute otitis	367 (281/86)
Fagan 2001[50]	Norway	cohort	not specified	adults treated for acute bronchitis	324 (122/202)
Hughes 2016[51]	Wales (UK)	before-after	Afinion (Alere)	adults with symptoms of respiratory tract infection and other	94 (not specified)
Kavanagh 2011[52]	Ireland	before-after	Quikread (Orion Diagnostica)	adults with acute cough and/or sore throat less than one month	120 (60/60)
Llor 2010[53]	Spain	before-after	Nycocard II (Axis Shield)	adults with acute sinusitis, acute tonsillitis, and acute otitis	161 (43/118)
Llor 2012[54] (also Llor 2014[55])	Spain	before-after	Nycocard II (Axis Shield)	adults with uncomplicated acute illness (< 7 days) with cough as the main symptom and 2+ signs or symptoms of LRTI (increase in sputum volume or purulence, chest pain and/or worsening of dyspnoea)	836 (208/628)
Peters 2013[56]	the Netherlands	case-control	Nycocard II (Axis Shield)	children and adults with an intellectual disability suspected of lower respiratory tract infection	1472 (882/590)
b) patients	s presenting with	signs of any ac	ute illness		
Jakobsen 2010[57]	Norway, Sweden, Wales (UK)	cohort	Nycocard II (Axis Shield) & Quikread (Orion Diagnostica)	adults with an acute illness episode less than 28 days	503 (372/131)

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Included studies

Twelve studies included adult patients only (totaling 7778 patients),[19-21, 41, 42, 45, 50-54, 57] three studies included children only (3598 patients),[9, 47, 48] and four studies both (4688 patients).[43, 44, 49, 56] Of the 11 randomised trials, five were randomised at practice level (cluster-randomised)[19, 21, 41, 42, 46] and six at patient level only (individually randomised).[20, 43-45, 47, 48] Most studies included patients with respiratory tract infections (16 out of 19 in total), of which eight studies concerned lower respiratory tract only.[19, 20, 41, 42, 45, 50, 54, 56] Two studies included patients with sinusitis, tonsillitis or otitis media,[49, 53] whereas three studies included patients presenting with any acute illness.[46, 48, 57]

Ten studies tested CRP on the Nycocard Reader II (by Alere),[19, 20, 42-45, 53, 54, 56, 57] four studies on the Afinion AS100 Analyzer (Alere),[41, 46, 48, 51] three on the Quikread,[21, 52, 57] and one study tested CRP on the Quikread Go (both by Orion Diagnostica).[47] Antibiotic prescribing rate was reported as the primary outcome in 18 of the 19 studies,[19-21, 41, 43-52, 54, 56, 57] reconsultation within 28 days in six studies,[19-21, 41, 44, 52], clinical recovery within 7 and/or 28 days in five studies,[19, 20, 41, 43, 45] and referral[9, 21, 44] or admission[9, 21, 44] to hospital,[9, 44] both in three studies. **(Supplementary file 3)** Only one study reported on mortality, but none of the patients died during follow-up.[9]

Secondary outcomes were reported for patient satisfaction,[19, 20, 44, 52] respiratory tract infections (RTI) during follow-up,[42] referral for chest X-ray,[41] additional tests performed,[9, 48] time to symptom resolution,[44] and adherence to antibiotic treatment.[53]

Risk of bias for included studies

For the RCTs, overall methodological quality was high, with only two studies with an unclear or high risk of detection bias (lack of blinding of the outcome assessors), **[43, 47]** and two studies with an unclear risk of reporting bias (no study protocol available). **[43, 45]** Considering only studies that focussed on the impact of POC tests were included, blinding of doctors to testing status was

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inherently impossible in these studies, resulting in a high risk of performance bias in all studies. **(Supplementary file 4)** The non-randomised and before-after studies suffered from a high risk of selection, performance and detection bias, with an unclear risk of reporting bias, as there was no protocol available.**[49-54, 57]** For the single case-control study, the comparability of cases and controls was scored as "high risk", due to significant differences in sex, age and severity of intellectual disability, as well as an unclear risk due to non-reporting of the non-response rate.**[56]**

Antibiotic prescribing rate

Immediate prescribing at the index consultation

Based on ten RCTs, performing a POC CRP test resulted in a reduction of antibiotic prescriptions issued at the index consultation with a pooled effect estimate (risk ratio (RR)) of 0.81 (95% CI of 0.71 to 0.92), but heterogeneity was high (l² 72%) (**Figure 1a**).[19-21, 41, 43-48] The five non-randomised studies (all on adult populations) suggested an even larger reduction with a RR of 0.76 (95%CI of 0.63-0.91), again with high heterogeneity (l² 81%).[49, 50, 52, 54, 57] (**Figure 1b**) Subgroup analyses by age (adult vs children <18 years) showed that the largest reductions were seen in adult populations (RR 0.75; 95%CI 0.66-0.86, l²=63%).[19-21, 41, 43-45] Five RCTs examining antibiotic prescribing in children found a pooled RR of 0.93 (95% CI 0.72-1.21, l²=74%)

(Supplementary file 5).

Five studies (all in adults) providing guidance on when to initiate antibiotic treatment by CRP level, showed an overall RR of 0.68 (95%CI 0.63-0.74, I^2 =0%),[19-21, 41, 44] whereas two RCTs where no guidance was applied found no effect (RR of 0.93; 95%CI 0.81-1.06, I^2 =0%) (**Figure 2a**).[43, 45] A similar effect was seen in children, where two studies providing guidance resulted in fewer antibiotic prescriptions (RR 0.56; 95%CI 0.33-0.95),[44, 46] I^2 =79%), (**Figure 2b**) whereas no effect was found in the four remaining studies providing no guidance (RR 1.01; 95%CI 0.85-1.20, I^2 =0%).[43, 46-48]

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In addition to the ten RCTs mentioned above, we also identified one before-after study, which reported a significant decrease of antibiotic prescribing (mean percentage difference -21.4%; 95%CI -28.0 to -14.8%).[51]

Using meta-regression, heterogeneity could be explained by both the age group (adults versus children, 100% of between-study heterogeneity explained) and prescribing guidance (100% and 85.9% of between-study heterogeneity accounted for, in adults and children respectively, with residual between-study heterogeneity of 6.9% in children).

Prescribing during follow-up

Antibiotic prescriptions within 28 days of testing were slightly lower with a POC CRP test (RR 0.84; 95%CI 0.72-0.99) at moderate heterogeneity (I² 46%) for the five available RCTs.[19, 20, 41, 44, 45] One RCT, however, did not find a significant reduction in antibiotic treatments for RTIs during long-term follow up with a mean difference of -5% (95%CI -13 to +3%).[42] **(Supplementary file 6)** The single case-control study found a larger effect with a RR of 0.46 (95%CI 0.37-0.57).[56]

Referral and admission to hospital

We found no difference in the number of patients referred to hospital (overall RR of 0.84 (95%Cl 0.44-1.61) with low heterogeneity (I^2 of 18%).[9, 47, 48] **(Supplementary file 7)**Three RCTs reporting number of patients admitted to hospital showed a nonsignificant increase (due to wide 95%Cl) when POC CRP was used with a RR of 1.24 (95%Cl 0.64-2.43, I^2 =18%).[9, 44]

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Re-consultation

Re-consultations were not different for patients receiving POC CRP compared to usual care, in the five RCTs (RR of 1.09 (95%Cl 0.93-1.27, $l^2=0\%$ in each subgroup, l^2 for subgroup differences

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(individually randomized RCTs vs cluster RCTS was 45%))[19-21, 41, 44] and the before-after study (RR 1.56 (95% CI 0.73-3.32)).[52] (Supplementary file 8)

Secondary outcomes

Clinical recovery within 7 and 28 days, patient satisfaction, number of additional tests performed, and time to symptom resolution, did not differ between patients tested with POC CRP and usual care. **(Table 2)** A single RCT found a slight reduction (-16%) in number of RTIs (registered by the GP) during follow-up.[42] Another RCT detected a reduction in the number of patients referred for chest X-Ray in favour of POC CRP.[41] A before-after study in patients with acute sinusitis, tonsillitis and otitis found a higher adherence to antibiotic treatment (+9% of antibiotics containers opened) in patients tested with POC CRP.[53] **(Supplementary file 9)**

 Table 2: Secondary outcomes: results

Secondary outcome	Studies	(Pooled) Risk Ratio or mean difference (%) of POC CRP versus usual care	95% CI	Heterogeneity I ² (%)
clinical recovery within 7 days	[20, 43, 45]	1.03	0·93 to 1·14	0%
clinical recovery within 28 days	[19, 41, 45]	0.94	0.69 to 1.28	0%
patient satisfaction	[19, 20, 44]	0.82	0.55 to 1.21	48%
	[52]	1.00	0·43 to 2·34	NA
RTIs during follow-up (registered by the GP)	[42]	-16%	-30% to -2%	NA
number of additional tests	[9, 48]	1.17	0·79 to 1·72	0%
number of chest X-rays	[41]	0.72	0.53 to 0.98	NA
time to symptom resolution	[44]	+0 days	-19 to +19 days	NA
adherence to antibiotic treatment	[53]	+8.9%	+3·4% to +14·4%	NA

Publication bias

For the three primary outcomes where funnel plots were possible (antibiotic prescribing at index consultation, antibiotic prescribing within 28 days, and re-consultation within 28 days) there was no

apparent evidence of publication bias, although only studies with small effect sizes were identified in

this review. (Supplementary file 10)

DISCUSSION

Performing a point-of-care CRP test in ambulatory care accompanied by clinical guidance can reduce the immediate antibiotic prescribing rate in both adults and children presenting to their GP with an acute infection. POC in the absence of clinical guidance was effective at reducing antibiotic prescriptions in adults but not in children. We did not find a significant effect of POC CRP on clinical recovery, re-consultation, and subsequent management decisions, such as referral or delayed admission to hospital, although very few studies reported on the latter, resulting in residual uncertainty concerning safety of POC CRP.

This review focused on the clinical impact of POC CRP on patient-relevant outcomes in ambulatory care, emphasizing the importance of moving above and beyond the diagnostic accuracy of point-of-care tests and examining their effect on clinical decision making.[58] Our comprehensive approach regarding inclusion criteria, resulted in a heterogeneous group of outcomes, patient populations and study designs. However, our results were consistent across the different types of studies, suggesting these findings are robust. The paucity of data for children resulted in wide confidence intervals for our effect estimates, emphasizing the need for large trials in children in ambulatory care.[2] The issue of performance bias due to a lack of blinding of the clinicians and patients is inherent to trials examining the clinical impact of an intervention and therefore will not be improved in future studies.[59]

Before POC tests are widely adopted, GPs want evidence of their accuracy, rigorous testing of the impact on patient-relevant outcomes and consideration of test funding.[14]

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Previous studies have focused on the diagnostic accuracy of point-of-care CRP in ambulatory care,[9, 60] including a recent individual patient data meta-analysis that concluded that adding CRP measurements to the diagnostic work-up in ambulatory care improved risk classification of patients suspected of pneumonia.[60] Systematic reviews have mainly prioritized antibiotic prescribing rate in respiratory tract infections and found a significant reduction when POC CRP was used, similar to our findings.[15, 61] The current NICE pneumonia guideline advises GPs to consider a delayed prescription in patients with intermediate CRP values.[17] A recent umbrella review found that CRP is one of three effective strategies to reduce antibiotic prescribing, alongside shared decision making and procalcitonin-guided management.[62] The current systematic review included a wider range of patient-relevant outcomes, demonstrated the impact of clinical guidance in addition to POC CRP on prescribing and demonstrated the relative lack of evidence in paediatric populations. A recent nonrandomised study showed that having POC CRP results available influences the decision of GPs to prescribe antibiotic treatment in patients with acute cough, but not in GPs with a low antibiotic prescribing rate.[38] POC CRP testing has shown to be cost-effective in several studies, though this was not the focus of our review.[29, 33-36]

In order to justify adoption, point-of-care tests need to demonstrate an overall benefit to patients and healthcare providers, regulators and commissioners must also be satisfied. It is vital to have robust evidence to ensure the consequences to patients and healthcare systems are properly evaluated. Broad adoption would be appropriate if a test can be applied in a wide range of patients and conditions. Our findings show point-of-care CRP for use in ambulatory care meets these criteria as long as appropriate guidance is provided. GPs have indicated they require guidance on the use and interpretation of POC CRP cut-offs.[63, 64] Further testing assessing broader impact and cost-effectiveness in children is needed.

Furthermore, other interventions, such as educating GPs, facilitating patient-centered care, and decreasing diagnostic uncertainty often resulting in complex interventions, can be as effective in reducing antibiotic prescribing.[21, 65] Communication training has been shown to have an effect on

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antibiotic prescribing.[19] If implemented together with POC CRP, they even reinforced one another. However, a recent paper showed that communication intervention in children had the opposite effect, increasing the antibiotic prescribing rate.[66] Arguably, communication training, if applied in the wrong population (e.g. with an interest in decreasing prescribing behaviour), may have adverse effects. Similarly, when antibiotic prescribing rates are low from the outset, POC CRP may not be able to decrease rates further without becoming unsafe. Other safety issues associated with the use of POC CRP might still arise, especially in children. We found that mortality was generally underreported and the impact on hospital admission rates has yet to be confirmed. Future studies should focus on the potential harms and assess safety of implementing POC CRP in ambulatory care.

CONCLUSIONS

Performing a POC CRP test in ambulatory care accompanied by evidence-based clinical guidance on interpretation reduces immediate antibiotic prescribing rate in both adults and children. As yet the evidence of impact on other patient outcomes or healthcare usage is lacking.

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COMPETING INTERESTS STATEMENT

All authors have completed the ICMJE uniform disclosure form at <u>www.icmje.org/coi_disclosure.pdf</u> and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR'S CONTRIBUTIONS

JV and JL did data extraction. JV performed the analyses, which were discussed with JL, CG, PST, TA, PT, GH, AV. JV drafted this report and JL, CG, PST, TA, PT, GH, AV co-drafted and commented on the final version. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JV affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted. All authors have read and approved the final manuscript.

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1	DATA SHARING STATEMENT	
3	All data for these analyses are included in the manuscript or online appendices. No addition	nal
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FIGURES & SUPPLEMENTARY FILES

Figure 1: point-of-care CRP versus usual care: antibiotic prescribing at index consultation: all patients Figure 2: point-of-care CRP versus usual care: antibiotic prescribing at index consultation: if cut-off guidance applied

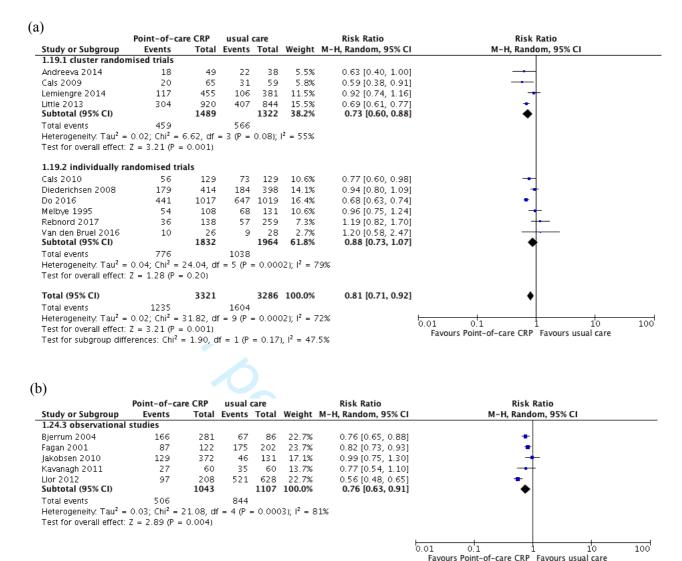
Online Supplementary Files

- Supplementary file 1: detailed search strategy
- Supplementary file 2: PRISMA flowchart
- Supplementary file 3: characteristics of included & excluded studies
- Supplementary file 4: risk of bias assessment (QUADAS 2)

Supplementary file 5: point-of-care CRP versus usual care: antibiotic prescribing at index consultation: adults

versus children

- Supplementary file 6: point-of-care CRP versus usual care: antibiotic prescribing within 28 days
- Supplementary file 7: point-of-care CRP versus usual care: referral and admission to hospital
- Supplementary file 8: point-of-care CRP versus usual care: re-consultation within 28 days
- Supplementary file 9: forest plots of secondary outcomes
- Supplementary file 10: funnel plots to assess publication bias



Test for subgroup differences: Not applicable

Figure 1: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) all patients, RCTs; (b) all patients, non-randomised studies.

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Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl M-H, Random 1.27.1 cluster randomised trials Andreeva 2014 (<20mg/L) 18 49 22 38 2.9% 0.63 [0.40, 1.00] Image: Cluster (Cluster) Cluster) Cluster)
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Test for overall effect: $Z = 6.61 (P < 0.00001)$
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Total events 612 847
Heterogeneity. Tau ² = 0.00; Chi ² = 1.47; df = 4 (P = 0.83); l ² = 0%
Test for overall effect: $Z = 9.68 (P < 0.00001)$ Test for subgroup differences: Chi ² = 0.08. df = 1 (P = 0.78), l ² = 0%
b) Point-of-care CRP usual care Risk Ratio Risk Rat
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random
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Heterogeneity. Not applicable
Heterogeneity: Not applicable Test for overall effect: Z = 6.20 (P < 0.00001) 1.25.2 cluster randomised trials
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Heterogeneity: Not applicable Test for overall effect: $Z = 6.20 (P < 0.00001)$ 1.25.2 cluster randomised trials Lemiengre 2014 (<5mg/L)
Heterogeneity: Not applicable Test for overall effect: $Z = 6.20$ (P < 0.00001)

Figure 2: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) RCTs, adults only, if cut-off guidance applied; (b) RCTs, children only, if cut-off guidance applied. CRP cut-off used to withhold antibiotic treatment between brackets.

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Online Supplementary Files

Supplementary file 1: detailed search strategy

Supplementary file 2: PRISMA flowchart

Supplementary file 3: characteristics of included & excluded studies

Supplementary file 4: risk of bias assessment (QUADAS 2)

Supplementary file 5: point-of-care CRP versus usual care: antibiotic prescribing at index consultation: adults

versus children

Supplementary file 6: point-of-care CRP versus usual care: antibiotic prescribing within 28 days

Supplementary file 7: point-of-care CRP versus usual care: referral and admission to hospital

Supplementary file 8: point-of-care CRP versus usual care: re-consultation within 28 days

Supplementary file 9: forest plots of secondary outcomes

Supplementary file 10: funnel plots to assess publication bias

Supplementary	file	1:	Search	strategy
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	dline
1	Ambulatory Care/
2	exp Ambulatory Care Facilities/
3	general practice/ or family practice/
4	general practitioners/ or physicians, family/ or physicians, primary care/
5	Primary Health Care/
6	Office Visits/
7	exp Emergency Service, Hospital/
8	Emergency Medical Services/
9	(ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
10	((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.
11	(primary care or primary health care or primary healthcare).ti,ab.
12	(emergency adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
13	(after hour? or afterhour? or "out of hour?" or ooh).ti,ab.
14	(clinic? or visit?).ti,ab.
15	((health* or medical) adj2 (center? or centre?)).ti,ab.
16	community health services/ or exp community health nursing/
17	Community Health Workers/
18	(community adj2 (health or health care or service? or program*)).ti,ab.
19	(community adj2 (worker? or aide? or volunteer? or assistant? or visitor?)).ti,ab.
20	((lay or volunteer) adj2 (health worker? or health aide? or health assistant?)).ti,ab.
21	((health* or medical) adj2 (facility or facilities)).ti,ab.
22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
23	16 or 17 or 18 or 19 or 20 or 21
24	Point-of-Care Systems/
25	(("point of care" or POC) adj3 (test* or diagnos*)).ti,ab.
26	(("point of care" or POC) and (test* or diagnos*)).ti.
27	poct.ti,ab.
28	((rapid or bedside or bed-side or "near patient") adj3 (test* or diagnos*)).ti,ab.
29	((rapid or bedside or bed-side or "near patient") and (test* or diagnos*)).ti.
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31	(istat or i-stat or afinion).ti,ab.
32	30 or 31
33	22 and 32
34	23 and 32
35	34 not 33

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2	outpatient department/
3	general practice/
4	general practitioner/
5	primary medical care/ or primary health care/
6	emergency ward/
7	emergency health service/
8	health center/
9	(ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
10	((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.
11	(primary care or primary health care or primary healthcare).ti,ab.
12	(emergency adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
13	(after hour? or afterhour? or "out of hour?" or ooh).ti,ab.
14	(clinic? or visit?).ti,ab.
15	((health* or medical) adj2 (center? or centre?)).ti,ab.
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17	community care/ or exp community health nursing/ or community program/
18	health auxiliary/
19	(community adj2 (health or health care or service? or program*)).ti,ab.
20	(community adj2 (worker? or aide? or volunteer? or assistant? or visitor?)).ti,ab.
21	((lay or volunteer) adj2 (health worker? or health aide? or health assistant?)).ti,ab.
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3	#1	MeSH descriptor: [Ambulatory Care] this term only
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25 26	#1	(emergency near/3 (care or setting? or facilit* or ward? or department? or
27	3	service?)):ti,ab,kw (Word variations have been searched)
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33	#1	((health* or medical) near/2 (center? or centre?)):ti,ab,kw (Word variations have been
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42	#1	MeSH descriptor: [Community Health Workers] explode all trees
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44	#2	(community near/2 (health or health care or service? or program*)):ti,ab,kw
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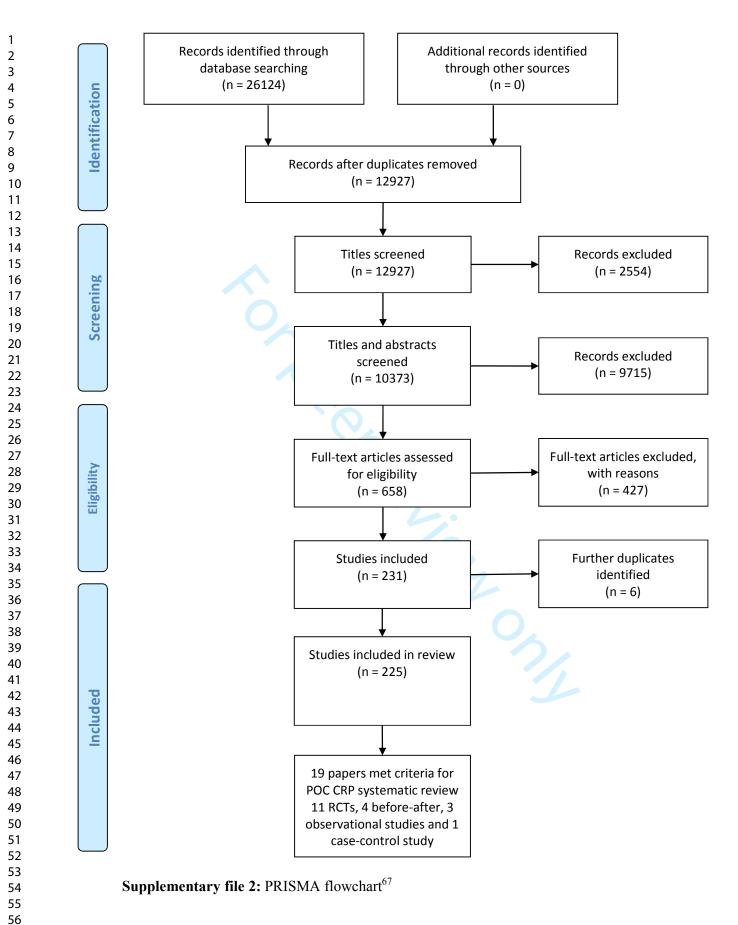
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Supplementary file 3: characteristics of included & excluded studies

study	title	reason for exclusion	
Cals 2011	C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial	cost-effectiveness modelling	
Hunter 2015	Cost-Effectiveness of Point-of-Care C-Reactive Protein Tests for Respiratory Tract Infection in Primary Care in England	cost-effectiveness modelling	
Oppong 2013	Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions	cost-effectiveness modelling	
Lindström 2015	What a difference a CRP makes. A prospective observational study on how point-of-care C-reactive protein testing influences antibiotic prescription for respiratory tract infections in Swedish primary health care	decision making analysis	
Minnaard 2016	C-reactive protein point-of-care testing and associated antibiotic prescribing	decision making analysis	
Dahler-Eriksen 1999	Near-Patient Test for C-Reactive Protein in General Practice: Assessment of Clinical, Organizational, and Economic Outcomes	effect of POC CRP cannot be assessed seperately	
Elfving 2016	Acute Uncomplicated Febrile Illness in Children Aged 2-59 months in Zanzibar - Aetiologies, Antibiotic Treatment and Outcome	effect of POC CRP cannot be assessed seperately	
Gonzales 2011	C-REACTIVE PROTEIN TESTING DOES NOT DECREASE ANTIBIOTIC USE FOR ACUTE COUGH ILLNESS WHEN COMPARED TO A CLINICAL ALGORITHM	effect of POC CRP cannot be assessed seperately	
Kankaanpaa 2016	Use of point-of-care testing and early assessment model reduces length of stay for ambulatory patients in an emergency department	effect of POC CRP cannot be assessed seperately	
Nijman 2015	C-Reactive Protein Bedside Testing in Febrile Children Lowers Length of Stay at the Emergency Department	effect of POC CRP cannot be assessed seperately	
Cohen 2006	Impact of CRP rapid test in management of febrile children in paediatric emergency units of Ile-de-France	no comparator with no POCT CRP	
Cohen 2008	Evaluation of impact of CRP rapid test in management of febrile children in ambulatory pediatric practice	no comparator with no POCT CRP	
Kokko 2014	Rapid C-reactive protein and white cell tests decrease cost and shorten emergency visits	no comparator with no POCT CRP	
Muszynska 2007	Rational antibiotic therapy - rapid CRP tests value on the effect on antiobitic prescribing - initial results	no comparator with no POCT CRP	
Cals 2007	Improving management of patients with acute cough by C- reactive protein point of care testing and communication training (IMPAC3T): study protocol of a cluster randomised controlled trial	not a clinical trial (protocol only)	
Azevedo 2014	[Analysis of the Cochrane review: biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database Syst Rev. 2014,11:CD10130]	not a clinical trial (response to s review)	

Supplementary file 3a: characteristics of excluded studies

Author / Year	Participant inclusion criteria	Participant exclusion criteria	Comparator	Outcome measures
Andreeva 2014	adults with lower respiratory tract infection/acute cough for less than 28 days	previously seen by GP for infection in question, immunocompromised status, ongoing treatment with oral corticosteroids	usual care	Primary outcome • Antibiotic use within the first 2 weeks after index consultation Secondary outcomes • Reported morbidity after 2 weeks (ordinal data) • Chest X-ray referrals (number) • Re-consultations (number) • Complications including hospitalisation (number) In the intervention group, the antibiotic prescribing rate was 37.6%, which was significantly lower than that in the control group (58.9%) (P = 0.006). Referral for chest X-ray was also significantly lower in the intervention group (55.4%) than in the control group (75.6%) (P = 0.004). The recovery rate, as recorded by the GPs, was 92.9% and 93.6% in the intervention and control groups, respectively
Bjerrum 2004	children and adults with acute sinusitis, acute tonsillitis, and acute otitis	none stated	usual care	antibiotic prescribing rate for patients with acute sinusitis, acute tonsillitis, and acute otitis The antibiotic prescribing rate for patients with acute sinusitis in the group of GPs who used rapid CRP testir was 59% (95%CI=56to62)comparedwith78%(95%CI=73to82), the chance of being treated with antibiotics for sinusitis was significantly lower (odds ratio [OR] = 0.43)
Cals 2009	adults with suspected lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	aged under 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	usual care	 Primary outcome Antibiotic prescribing at index consultation Secondary outcomes Antibiotic use (any use for current infection) in 28 days Number of additional consultations Patient satisfaction: number of patients at least very satisfied; number with intent to return in future if similar symptoms develop Enablement (median score) Clinical recovery: no. of patients recovered on day 7; median of symptom scores per day; median reported time to full recovery General practitioners in the C reactive protein test group prescribed antibiotics to 31% of patients compared with 53% in the no test group (P=0.02). General practitioners trained in enhanced communication skills prescribed antibiotics to 27% of patients compared with 54% in the no training group (P<0.01). Both interventions showed a statistically significant effect on antibiotic prescribing at any point during the 28 days follow-up. Clinicians in the combined intervention group prescribed antibiotics to 23% of patients (interaction term was non- significant). Patients' recovery and satisfaction were similar in all study groups.
Cals 2010	adult with lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign) or rhinosinusitis < 4 weeks, + 2 symptoms or signs	aged under 18 years, antibiotic use or hospitalisation within the previous 14 days, non-fluent in Dutch, immunocompromised status or need for immediate hospitalisation	usual care	 Primary outcome Antibiotic use (delayed and immediate) at index consultation Secondary outcomes Antibiotic use (any use for current infection) in 28 days Number of additional consultations Patient satisfaction: number of patients at least very satisfied; number with intent to return in future if similar symptoms develop Enablement (median score) Clinical recovery: no. of patients recovered on day 7; median of symptom scores per day; median reported time to full recovery Patients in the CRP-assisted group used fewer antibiotics (43.4%) than control patients (56.6%) after the inde consultation (relative risk [RR] = 0.77; 95% con dence interval [CI], 0.56-0.98). This difference remained signi cant during follow-up (52.7% vs 65.1%; RR=0.81; 95% CI, 0.62-0.99). Delayed pre- scriptions in the CRP- assisted group were lled only in a minority of cases (23% vs 72% in control group, P <.001). Recovery was

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				similar across groups. Satisfaction with care was higher in patients managed with CRP assistance (P = .03).
Cals 2013	adults with suspected lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	aged under 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	usual care	The primary outcome was the average number of episodes of respiratory tract infection during the follow-up period for which patients consulted their physician per patient per year (PPPY) and the proportion of these episodes that resulted in an antibiotic prescription. The mean number of episodes of respiratory tract infections during follow-up was 0.40 PPPY in the CRP test group and 0.56 PPPY in the no CRP test group (P=.12). In the communication skills training group, there was a mean of 0.36 PPPY episodes of respiratory tract infections, and in the no training group the mean was 0.57 PPPY (P=.09). During follow-up 30.7% of all episodes of respiratory tract infection were treated with antibiotics in the CRP test group compared with 35.7% in the no test group (P=.36). Family physicians trained in communication skills treated 26.3% of all episodes of respiratory tract infection with antibiotics compared with 39.1% treated by family physicians without train- ing in communication skills (P = .02)
Diederichsen 2000	children and adults with respiratory tract infection	previously seen by general practitioner for infection in question, patients who had streptococcal rapid testing performed, patients with chronic inflammatory diseases	usual care	 Primary outcome Antibiotic use at index consultation Secondary outcome Patient-reported morbidity after 1 week In the CRP group the frequency of antibiotic prescriptions was 43% (179/414) compared with 46% (184/398) in the control group (odds ratio (OR)=0.9, NS). After 1 week, increased or unchanged morbidity was stated more frequently in the CRP group (12%) than in the control group (8%) (OR = 1.6, p = 0.05). In the control group, the variable having the greatest influence on whether the GP prescribed antibiotics was the patients' general well-being (OR = 2.9, p B 0.0001), whereas in the CRP group the CRP value had the greatest influence (OR = 1.1 per unit increase (mg/l), p B 0.0001).
Do 2016	children and adults with at least one focal and one systemic symptom of acute respiratory tract infection	patients with sever acute respiratory tract infection	usual care	 primary outcome number of patients receiving any antibiotic within 2 weeks of enrolment antimicrobial activity in urine (day 3, 4, or 5), the proportion of patients with immediate antibiotic prescription at enrolment, any antibiotic usage in patients without immediate prescription (subsequent antibiotic prescription, the source of any antibiotic taken but not prescribed at enrolment or day 4 (self-medication, drug seller, doctor, or other), the frequency o reconsultations, serious adverse events (hospital admission or death), time to resolution of symptoms, and reported patient satisfaction with participating in the trial on day 14 (measured on a scale from 0 to 10) The number of patients who used antibiotics within 14 days was 581 (64%) of 902 patients in the C-reactive protein group versus 738 (78%) of 947 patients in the control group (odds ratio [OR] 0.49, 95% Cl 0.40–0.61; p<0.0001). Highly significant differences were seen in both children and adults, with substantial heterogeneity of the intervention effect across the 10 sites (I2=84%, 95% Cl 66–96). 140 patients in the C-reactive protein group and 137 patients in the routine care group missed the urine test on day 3, 4, or 5. Antibiotic activity in urine on day 3, 4, or 5 was found in 267 (30%) of 877 patients in the C-reactive protein group versus 314 (36%) of 882 patients in the routine treatment group (OR 0.78, 95% Cl 0.63–0.95; p=0.015). Time to resolution of symptoms was similar in both groups. Adverse events were rare, with no deaths and a total of 14 hospital admissions (six in the C-reactive protein group and eight in the control group).
Fagan 2001	adults treated for acute bronchitis	telephone consultations and home visits	usual care	antibiotic prescribing at index consultation In period 1, 87% (175/202) of the patients in Arendal with the diagnosis of acute bronchitis were treated with antibiotics. Doccycline was prescribed to 47% followed by penicillin (28%) and erythromycin (14%) (Figure 1). In Tønsberg, 135 patients (78%) were treated with antibiotics. Here, penicillin was most commonly prescribed (31%), then doxycycline (30%). 18% received erythromycin. 21% were treated with other antibiotics, mainly amoxicillin. In period 2, 71% of the patients in Arendal received antibiotics (87/122). The reduction in prescribing from period 1 was statically significant (p <0.001). In Tønsberg, 74% of patients in period 2

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				received antibiotics. The difference from period 1 was not statistically significant ($p = 0.34$). There were no significant changes in which antibiotics were prescribed, except for a decrease in the use of other antibiotics from 21% to 7% in Tønsberg ($p < 0.05$).
Hughes 2016	adults with symptoms of respiratory tract infection and other	none stated	usual care	overall antibiotic prescribing rate A mean reduction in items of 21.39%, compared to 10.6% reduction across all practices during the same period
Jakobsen 2010	adults with an acute illness episode less than 28 days	none stated	usual care	GPs' decision to prescribe antibiotics for acute cough A total of 803 patients were recruited in the three networks. Among the 372 patients tested with a POCT for CRP, the CRP value was the strongest independent predictor of antibiotic prescribing, with an odds ratio (OR of CRP 50 mg/L of 98.1. Crackles on auscultation and a patient preference for antibiotics perceived by the Gi were the strongest predictors of antibiotic prescribing when the CRP test was not used
Kavanagh 2011	adults with acute cough and/or sore throat less than one month	none stated	usual care	Primary outcome was antibiotic prescription at the index consultation. Secondary outcomes were number of delayed prescrip- tions issued, re-consultation (referring to both 'in per- son' an telephone consultations) and antibiotic prescription, both during 28 days of follow-up, and patient satisfaction Thirty-five (58%) patients in the no-test group received antibiotic prescriptions compared to 27 (45%) in the test group. Both groups demonstrated similarly high level of patient satisfaction (85%). Fourteen (23%) patients in the CRP test group re-attended within 28 days compared to 9 (15%) in the no-CRP test group
Lemiengre 2014	children with an acute illness less than 5 days	acute illness is caused by merely traumatic or neuro- logical conditions, intoxication, psychiatric or behav- ioural problem, or an exacerbation of a known chronic condition	usual care	immediate and total antibiotic prescribing rate In comparison to usual care, POC CRP didn't influence antibiotic prescribing (adjusted odds ratio (aOR) 0.77 (95% Confidence Interval (CI) 0.42 to 1.44) for immediate and 1.31 (95%CI 0.71-2.40) for total prescribing). BISNA increased antibiotic prescribing (aOR 2.13 (95% CI 1.24 to 3.69) for immediate and 2.02 (95%CI 1.15 to 3.56) for total prescribing). In combination with POC CRP, this increase disappeared.
(also Verbakel 2016)				hospital admission (> 24 hours) for a serious infection within 5 days after initial presentation Restricting CRP testing to those identified as at clinical risk substantially reduced the number of children tested by 79.9 % (95 % Cl, 77.8–82.0 %). There was no significant difference between arms in the number of children with serious infection who were referred to hospital immediately (0.16 % vs. 0.14 %, P = 0.88). Only one child with a CRP < 5 mg/L had an illness requiring admission (a child with viral gastroenteritis admitted f rehydration). However, of the 80 children referred to hospital to rule out serious infection, 24 (30.7 %, 95 % Cl 19.6–45.6 %) had a CRP < 5 mg/L.
Little 2013	adults with upper or lower respiratory tract infection less than 28 days	Exclusion criteria: a non-infective working diagnosis (e.g. pulmonary embolus; heart failure; oesophageal reflux; allergy); antibiotic use in the previous month; unable to pro- vide informed consent (dementia; psychosis; severe depression); pregnant; immunological	usual care	 Primary outcome Antibiotic prescribing at index consultation Secondary outcomes New or worsening symptoms, defined as re-consultation within 28 days with worsening symptoms, new symptoms, new signs, or hospital admission Symptom severity and duration, defined as a) the severity of symptoms in the 2 to 4 days after seeing the physician and b) the duration of symptoms rated moderately bad or worse by patients, both based on patient self completed diaries The baseline audit, done in 259 practices, provided data for 6771 patients with lower-respiratory-tract infections (3742 [55:3%]) and upper-respiratory-tract infections (1416 [20:9%]), of whom 5355 (79.1%) were prescribed antibiotics. After randomisation, 246 practices were included and 4264 patients were recruited. Th antibiotic prescribing rate was lower with CRP training than without (33% vs 48%, adjusted risk ratio 0.54, 95% Cl 0.42–0.69) and with enhanced-communication training than without (36% vs 45%, 0.69, 0.54–0.87). The combined intervention was associated with the greatest reduction in prescribing rate (CRP risk ratio 0.53, 95%

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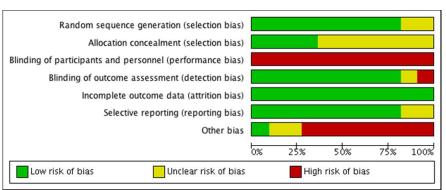
		deficiencies Patients with lower respiratory tract infection (up to the first 30 presenting in each practice) and upper respiratory tract infection (up to the first 5 presenting) were recruited following informed consent		Cl 0·36–0·74, p<0·0001; enhanced communication 0·68, 0·50–0·89, p=0·003; combined 0·38, 0·25–0·55, p<0·0001)
Llor 2012 & 2014	adults with acute sinusitis, acute tonsillitis, and acute otitis	none stated	pre- intervention and usual care group	antibiotic prescription the use of the CRP was a significant protective factor for antibiotic prescription. Thus, with CRP results <10 mg/l, the odds ratio (OR) of antibiotic prescription was 0.008 compared with the no use of this test [95% confidence interval (CI): 0–0.015]. After adjusting for the remain- ing variables, no statistically significant differences were found in antibiotic prescription between the two pre-intervention and the control groups. In contrast, the post-intervention ORs were lower than those of the control and pre-intervention groups, but it was on- ly significant among physicians assigned to FIG. In comparison with the control group, the OR for antibi- otic prescription was 0.115 (95% CI: 0.008–0.321).
Llor 2010	adults with uncomplicated acute illness (< 7 days) with cough as the main symptom and 2+ signs or symptoms of LRTI (increase in sputum volume or purulence, chest pain and/or worsening of dyspnoea)	none stated	pre- intervention	Three outcome measures were taken into account; • taking adherence • correct dosing • good timing adherence during at least 80% of the antibiotic course The rate of failures was also taken into account when the patient was seen at the end of the treatment. Adherence was better when patients underwent CRP rapid testing prior to administration of the antibiotic, both in terms of the percentage of container openings (83.3% ± 14.8% vs. 74.4% ± 17.7%; p<0.01) and the goot timing adherence during at least 80% of the antibiotic course (32.6% vs. 16.9%; p<0.05). The percentage of patients who took at least 80% of the doses was slightly better when the patient underwent rapid testing (72.1% vs. 55.1%), although this difference was not statistically significant. The percentage of patients who opened the container a satisfactory number of times – at least three times per day throughout the treatment course – was always greater when the patient had undergone CRP testing prior to antibiotic administration (see Figure 2). The differences between those who underwent the point-of-care test and those who did not were statistically significant for days 4 and 5 (p<0.01). A disappearance of the differences after the fifth day of the antibiotic treatment schedule was observed.
Melbye 1995	adults with subjective complaint of pneumonia, bronchitis or asthma or 1 of: cough, shortness of breath, chest pain on deep inspiration or cough	aged under 18 years, patients with sore throat, blocked nose, pain in ears or sinuses. Patients with angina-like chest pain were also excluded	usual care	 Primary outcome Antibiotic use at index consultation Secondary outcomes Antibiotic use (any use for current infection) in 21 days Clinical recovery: no. of patients recovered on day 7 and day 21 No significant difference was found in the number of antibiotic prescriptions between the groups (RR 0.96, CI 0.75 to 1.24). No difference in patient recovery rate on rate of improvement was observed on day 7 (RR 0.94, C 0.75 to 1.18) or day 21 (RR 0.85, CI 0.57 to 1.29). Management decisions were changed by C-reactive protein testing in 10% (11/108) of the cases; estimated algorithm adherence 42%
Peters 2013	children and adults with an intellectual disability suspected of lower respiratory tract infection	none stated	usual care	antibiotic prescriptions for LRTIs by physicians specialising in the care of individuals with intellectual disabilities Of the 48 patients in the control group who were diagnosed as having an LRTI, 43 (90%) received antibiotics, compared with 59 out of the 144 patients (41%) in the case group (OR = 12.0; 95% CI = 4.1–35.3). There were no significant differences between the case and control groups regarding changes in antibiotic prescriptions during follow-up

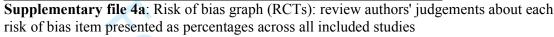
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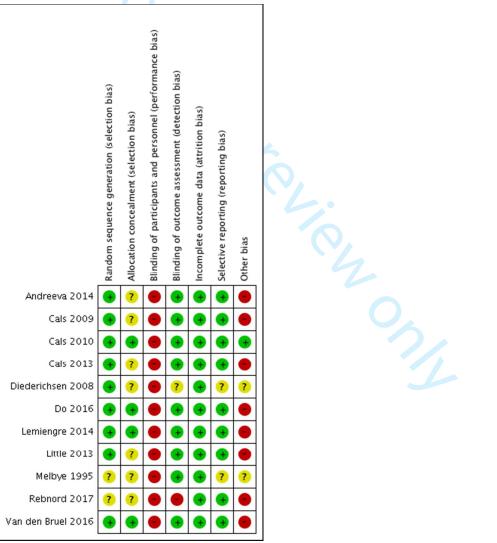
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den el 2016	and/or respiratory symptoms children with an acute illness less than 5 days	Children were excluded if they had consulted for acute trauma, were clinically unstable warranting	usual care	In the group pretested with CRP, the antibiotic prescription rate was 26%, compared with 22% in the control group. In the group pretested with CRP, 5% were admitted to hospital, compared with 9% in the control group. These differences were not statistically significant Secondary outcomes included antibiotic prescribing, hospital referral or admis- sion, additional testing in primary care, or re-consultation in primary or secondary care Antibiotics were prescribed to 60 children (30%, 95% Cl 23.6% to 36.4%) at the index consultation, 70 (35%) received explicit safety-netting advice and 11 (5.5%) were referred to hospital. There was no statistically significant difference in any outcome between those tested or not tested with CRP point-of-care. In the 10-day
				studies
Su	pplementary file 3b	: characteristics o	f included	studies
				12

Supplementary file 4: Risk of bias assessment (QUADAS 2)







Supplementary file 4b: Risk of bias summary (RCTs): review authors' judgements about each risk of bias item for each included study.

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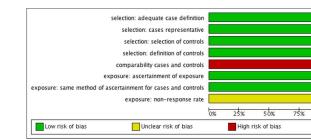
Random sequence generation (selection bias)

Allocation concealment (selection bias)



Supplementary file 4d: Risk of bias summary (non-randomised studies).

100%



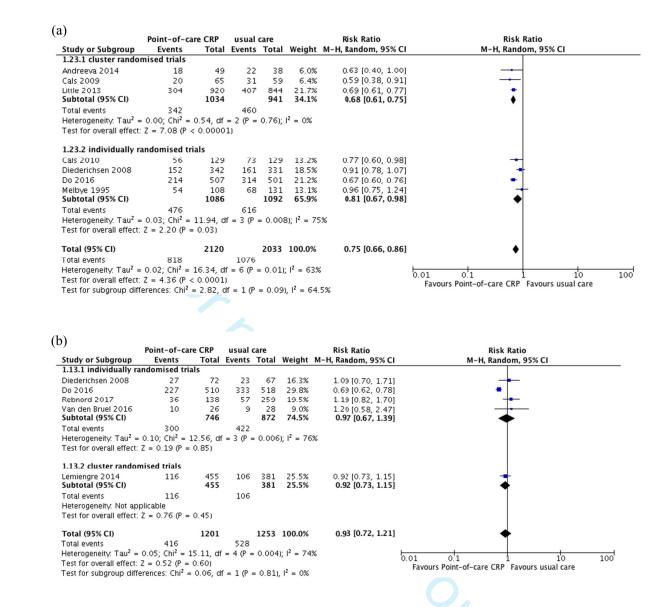
Supplementary file 4e: Risk of bias graph (case-control studies).

Supplementary file 4f: Risk of bias summary (case-control studies).

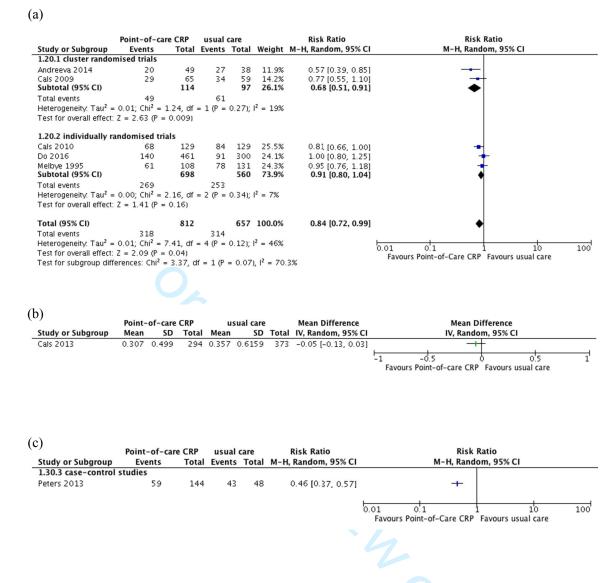
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L.C.L.

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Supplementary file 5: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) RCTs, adults only; (b) RCTs, children only.

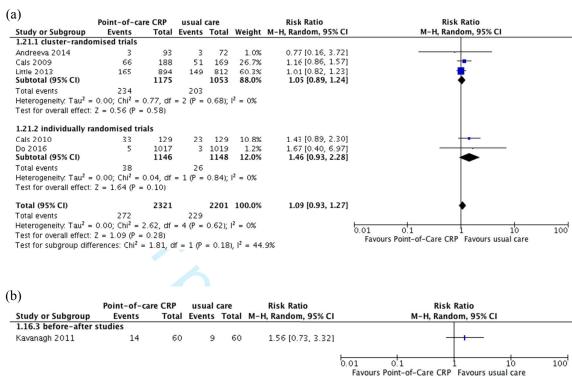


Supplementary file 6: Forest plot of comparison: point-of-care CRP versus usual care, outcome: (a) antibiotic prescribing within 28 days (all patients, RCTs); (b) antibiotic treatment for respiratory tract infection during follow-up (RCT); (c) antibiotic prescribing within 28 days (all patients, non-randomised study).

(a)

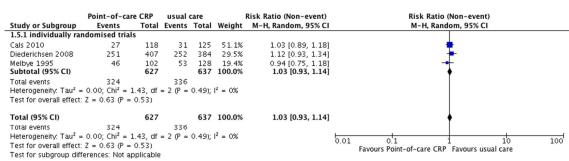
	Point-of-car		usual			Risk Ratio	Risk Ratio
Study or Subgroup	Events		Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.9.1 individually rar							_
Rebnord 2017	7	138		259	46.3%	0.55 [0.24, 1.24]	
Van den Bruel 2016 Subtotal (95% CI)	3	26 164	4	28 287	19.1% 65.4%	0.81 [0.20, 3.27] 0.60 [0.30, 1.22]	
Total events	10		28				
Heterogeneity: Tau ² =			= 1 (P =	0.64);	$ ^2 = 0\%$		
Test for overall effect:	Z = 1.40 (P =	0.16)					
1.9.2 cluster random	ised trials						
Verbakel 2016	11	566	6	470	34.6%	1.52 [0.57, 4.09]	
Subtotal (95% CI)		566		470	34.6%	1.52 [0.57, 4.09]	
Total events	11		б				
Heterogeneity: Not ap Test for overall effect:		0.40)					
Total (95% CI)		730		757	100.0%	0.84 [0.44, 1.61]	•
Total events	21		34				
Heterogeneity: Tau ² =	0.06; $Chi^2 = 2$.45, df	= 2 (P =	0.29);	$l^2 = 18\%$		0.01 0.1 1 10
Test for overall effect:	Z = 0.53 (P =	0.601					Favours point-of-care CRP Favours usual care
Test for subgroup diff	erences. cm =	2.25, U	$u = \pm 0$	- 0.14	,, i - 55.	1/0	
2 1							
))	Point-of-car		usual c			Risk Ratio	Risk Ratio
)) Study or Subgroup	Events	Total			Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
)) Study or Subgroup 1.14.1 individually ra	Events andomised tria	Total Is	Events	Total		M-H, Random, 95% CI	
) Study or Subgroup 1.14.1 individually ra Do 2016	Events	Total Is 901		Total 874	33.2%	M-H, Random, 95% Cl 0.73 [0.25, 2.09]	
)) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI)	Events Indomised tria	Total Is	Events 8	Total		M-H, Random, 95% CI	
) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events	Events andomised tria	Total Is 901	Events	Total 874	33.2%	M-H, Random, 95% Cl 0.73 [0.25, 2.09]	
)) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI)	Events andomised tria 6 6 plicable	Total Is 901 901	Events 8	Total 874	33.2%	M-H, Random, 95% Cl 0.73 [0.25, 2.09]	
) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity. Not ap	Events andomised tria 6 plicable Z = 0.59 (P =	Total Is 901 901	Events 8	Total 874	33.2%	M-H, Random, 95% Cl 0.73 [0.25, 2.09]	
) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity. Not ap Test for overall effect:	Events andomised tria 6 plicable Z = 0.59 (P =	Total Is 901 901	Events 8 8	Total 874	33.2%	M-H, Random, 95% CI 0.73 [0.25, 2.09] 0.73 [0.25, 2.09]	
5) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity. Not ap Test for overall effect: 1.14.2 cluster randor	Events andomised tria 6 plicable Z = 0.59 (P = nised trials	Total 901 901 0.55)	Events 8	874 874	33.2% 33.2%	M-H, Random, 95% Cl 0.73 [0.25, 2.09]	
) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity. Not ap Test for overall effect: 1.14.2 cluster randor Little 2013	Events andomised tria 6 plicable Z = 0.59 (P = nised trials 9	Total 901 901 0.55) 920	Events 8 8 3	Total 874 874 874	33.2% 33.2% 23.2%	M-H, Random, 95% CI 0.73 [0.25, 2.09] 0.73 [0.25, 2.09] 2.75 [0.75, 10.13]	
b) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity. Not ap Test for overall effect: 1.14.2 cluster randor Little 2013 Verbakel 2016 Subtotal (95% CI) Total events	Events indomised tria 6 plicable Z = 0.59 (P = mised trials 9 12 21	Total 901 901 0.55) 920 649 1569	Events 8 8 3 3 11	Total 874 874 874 844 532 1376	33.2% 33.2% 23.2% 43.6% 66.8%	M-H, Random, 95% CI 0.73 [0.25, 2.09] 0.73 [0.25, 2.09] 2.75 [0.75, 10.13] 1.23 [0.51, 2.99]	
5) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: 1.14.2 cluster randor Little 2013 Verbakel 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	Events indomised tria 6 plicable 2 = 0.59 (P = nised trials 9 12 0.00; Chl ² = 1	Total 901 901 901 0.55) 920 649 1569 01, df =	Events 8 8 3 3 11	Total 874 874 874 844 532 1376	33.2% 33.2% 23.2% 43.6% 66.8%	M-H, Random, 95% CI 0.73 [0.25, 2.09] 0.73 [0.25, 2.09] 2.75 [0.75, 10.13] 1.23 [0.51, 2.99]	
b) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity. Not ap Test for overall effect: 1.14.2 cluster randor Little 2013 Verbakel 2016 Subtotal (95% CI) Total events	Events indomised tria 6 plicable 2 = 0.59 (P = nised trials 9 12 0.00; Chl ² = 1	Total 901 901 901 0.55) 920 649 1569 01, df =	Events 8 8 3 3 11	Total 874 874 874 844 532 1376	33.2% 33.2% 23.2% 43.6% 66.8%	M-H, Random, 95% CI 0.73 [0.25, 2.09] 0.73 [0.25, 2.09] 2.75 [0.75, 10.13] 1.23 [0.51, 2.99]	
5) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: 1.14.2 cluster randor Little 2013 Verbakel 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	Events indomised tria 6 plicable 2 = 0.59 (P = nised trials 9 12 0.00; Chl ² = 1	Total 901 901 901 0.55) 920 649 1569 01, df =	Events 8 8 3 3 11	Total 874 874 532 1376 0.32); 1	33.2% 33.2% 23.2% 43.6% 66.8%	M-H, Random, 95% CI 0.73 [0.25, 2.09] 0.73 [0.25, 2.09] 2.75 [0.75, 10.13] 1.23 [0.51, 2.99]	
Study or Subgroup 1.1.4.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity. Not ap Test for overall effect: 1.1.4.2 cluster randor Little 2013 Verbakel 2016 Subtotal (95% CI) Total events Heterogeneity. Tau ² = Test for overall effect:	Events indomised tria 6 plicable 2 = 0.59 (P = nised trials 9 12 0.00; Chl ² = 1	Total 901 901 901 0.55) 920 649 1569 01, df = 0.22)	Events 8 8 3 3 11	Total 874 874 532 1376 0.32); 1	33.2% 33.2% 23.2% 43.6% 66.8% ² = 1%	M-H, Random, 95% CI 0.73 [0.25, 2.09] 0.73 [0.25, 2.09] 2.75 [0.75, 10.13] 1.23 [0.51, 2.99] 1.59 [0.76, 3.32]	
5) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: 1.14.2 cluster randor Little 2013 Verbakel 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: Total (95% CI)	Events indomised tria 6 plicable Z = 0.59 (P = nised trials 9 12 21 0.00; Chi ² = 1 Z = 1.23 (P = 27	Total 901 901 0.55) 920 649 1569 0.22) 2470	Events 8 8 3 8 11 = 1 (P = 19	Total 874 874 532 1376 0.32); 1 2250	33.2% 33.2% 23.2% 43.6% 66.8% ² = 1% 100.0%	M-H, Random, 95% CI 0.73 [0.25, 2.09] 0.73 [0.25, 2.09] 2.75 [0.75, 10.13] 1.23 [0.51, 2.99] 1.59 [0.76, 3.32]	M-H, Random, 95% CI
5) Study or Subgroup 1.14.1 individually ra Do 2016 Subtotal (95% CI) Total events Heterogeneity. Not ap Test for overall effect: 1.14.2 cluster randor Little 2013 Verbakel 2016 Subtotal (95% CI) Total events Heterogeneity. Tau ² = Test for overall effect: Total (95% CI) Total events	Events indomised tria 6 plicable Z = 0.59 (P = nised trials 9 12 0.00; Chi ² = 1 Z = 1.23 (P = 27 0.06; Chi ² = 2	Total 901 901 0.55) 920 649 1569 01, df 0.22) 2470	Events 8 8 3 8 11 = 1 (P = 19	Total 874 874 532 1376 0.32); 1 2250	33.2% 33.2% 23.2% 43.6% 66.8% ² = 1% 100.0%	M-H, Random, 95% CI 0.73 [0.25, 2.09] 0.73 [0.25, 2.09] 2.75 [0.75, 10.13] 1.23 [0.51, 2.99] 1.59 [0.76, 3.32]	M-H, Random, 95% CI
Study or Subgroup 1.1.4.1 individually ra Do 2016 Subtotal (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: 1.4.2 cluster randor Little 2013 Verbakel 2016 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: Total events Heterogeneity: Tau ² = Total events Heterogeneity: Tau ² =	Events indomised tria 6 plicable 2 = 0.59 (P = mised trials 9 12 0.00; Chi ² = 1 2 = 1.23 (P = 27 0.06; Chi ² = 2 Z = 0.64 (P =	Total 901 901 0.55) 920 649 1569 0.22) 2470 43, df = 0.52)	Events 8 8 8 11 11 19 2 (P =	Total 874 874 532 1376 0.32); 1 2250 0.30); 1	33.2% 33.2% 23.2% 43.6% 66.8% ² = 1% 100.0% ² = 18%	M-H, Random, 95% CI 0.73 [0.25, 2.09] 0.73 [0.25, 2.09] 2.75 [0.75, 10.13] 1.23 [0.51, 2.99] 1.59 [0.76, 3.32] 1.24 [0.64, 2.43]	M-H, Random, 95% CI

Supplementary file 7: Forest plot of comparison: point-of-care CRP versus usual care, outcome: (a) referral to hospital (RCTs); (b) hospital admission (RCTs).



Supplementary file 8: Forest plot of comparison: 1 POC CRP versus usual care, outcome: re-consultations within 28 days.: (a) all patients, RCTs; (b) all patients, non-randomised study.

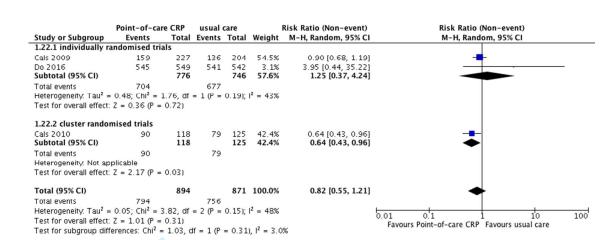
Supplementary file 9: Forest plots secondary outcomes (Figure a-j)



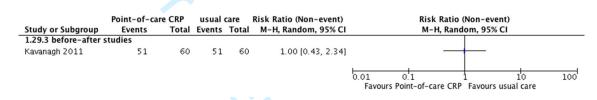
Supplementary file 9a: Forest plot of comparison: 1 POC CRP versus usual care, outcome: clinical recovery day 7 (all studies).

	Point-of-care	CRP	usual	care	1	Risk Ratio (Non-event)	Risk Ratio (Non-event)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.6.1 individually rai	ndomised trials						
Melbye 1995 Subtotal (95% CI)	71	98 98	82	121 121	56.1% 56.1%	0.85 [0.57, 1.29] 0.85 [0.57, 1.29]	
Total events	71		82				
Heterogeneity. Not ap	plicable						
Test for overall effect:	Z = 0.75 (P = 0)	.46)					
1.6.2 cluster random	nised trials						
Andreeva 2014	60	64	48	51	4.5%	1.06 [0.25, 4.53]	
Cals 2009	76	102	69	91	39.3%	1.05 [0.64, 1.73]	
Subtotal (95% CI)		166		142	43.9%	1.06 [0.66, 1.68]	◆
Total events	136		117				
Heterogeneity: Tau ² -	- 0.00; Chi ² = 0.0	00, df -	- 1 (P -	0.99);	$ ^2 = 0\%$		
Test for overall effect:	Z = 0.23 (P = 0)	.82)					
Total (95% CI)		264		263	100.0%	0.94 [0.69, 1.28]	•
Total events	207		199				
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0.4	44, df :	= 2 (P =	0.80);	$ ^2 = 0\%$		
Test for overall effect:	Z = 0.41 (P = 0)	.68)					0.01 0.1 1 10 100' Favours Point-of-care CRP Favours usual care
Test for subgroup diff	ferences: $Chi^2 = 0$	0.44. d	f = 1 (P)	= 0.51	$ ^2 = 0\%$		Favours Point-of-Care CRP Favours usual care
2		.,			,		

Supplementary file 9b: Forest plot of comparison: 1 POC CRP versus usual care, outcome: clinical recovery day 28 (all studies).



Supplementary file 9c: Forest plot of comparison: 1 POC CRP versus usual care, outcome: patient satisfaction (RCTs).



Supplementary file 9d: Forest plot of comparison: 1 POC CRP versus usual care, outcome: patient satisfaction (non-randomised study).

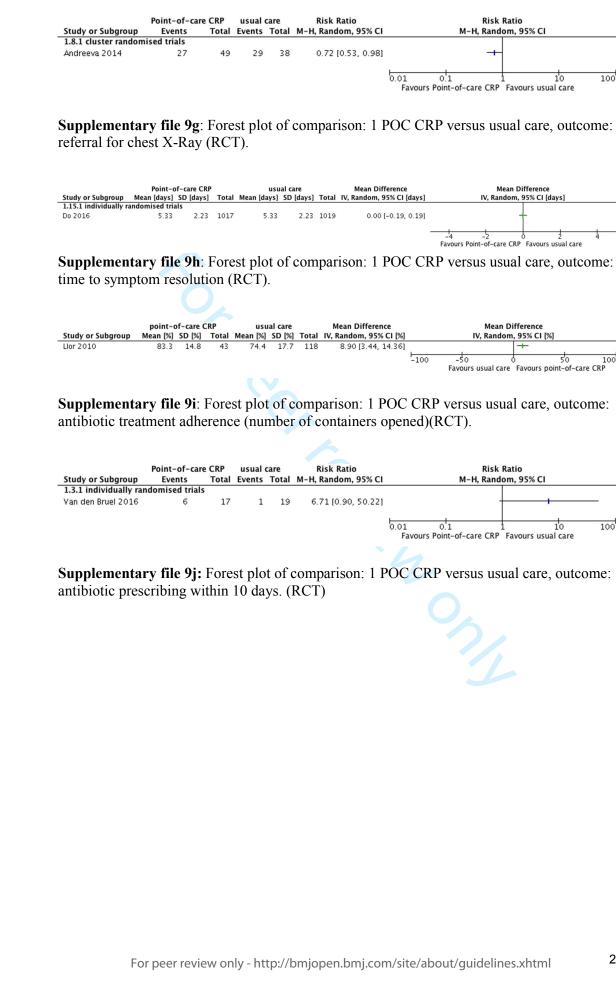
	Point-of-care CRP		Point-of-care CRP usual care Mean Difference				Mean Difference	Mean D	ifference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Rando	m, 95% CI	
Cals 2013	0.4	0.51	203	0.56	0.85	176	-0.16 [-0.30, -0.02]			
								-1 -0.5	0 0.5	1
								Favours Point-of-care CRP	Favours usual care	

Supplementary file 9e: Forest plot of comparison: 1 POC CRP versus usual care, outcome: respiratory tract infection during follow-up. (RCT)

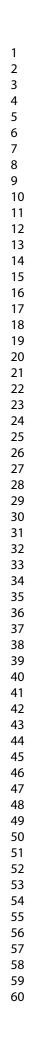
	Point-of-car	e CRP	usual	care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.10.1 individually rai	ndomised tria	ls					
Van den Bruel 2016 Subtotal (95% CI)	3	26 26	1	28 28	3.1% 3.1%	3.23 [0.36, 29.14] 3.23 [0.36, 29.14]	
Total events	3		1				
Heterogeneity. Not app	licable						
Test for overall effect: 2	Z = 1.05 (P =	0.30)					
1.10.2 cluster random	nised trials						
Verbakel 2016	53	524	39	437	96.9%	1.13 [0.76, 1.68]	
Subtotal (95% CI)		524		437	96.9%	1.13 [0.76, 1.68]	
Total events	53		39				
Heterogeneity. Not app	licable						
Test for overall effect: 2	Z = 0.62 (P =	0.53)					
Total (95% CI)		550		465	100.0%	1.17 [0.79, 1.72]	•
Total events	56		40				
Heterogeneity: Tau ² =	0.00 ; $Chi^2 = 0$.85, df	= 1 (P =	0.36);	$ ^2 = 0\%$		0.01 0.1 1 10 100
Test for overall effect: 2	Z = 0.80 (P =	0.43)					0.01 0.1 1 10 100 Favours Point-of-care CRP Favours usual care
Test for subgroup diffe	rences: Chi ² =	0.84, d	lf = 1 (P	= 0.36	$, ^2 = 0\%$		ravours rome-or-care cive ravours usual care

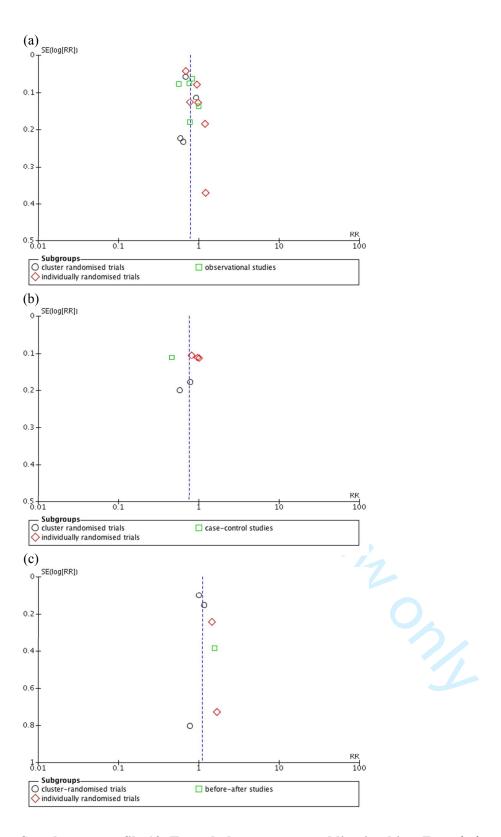
Supplementary file 9f: Forest plot of comparison: 1 POC CRP versus usual care, outcome: additional tests performed (RCTs).

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Supplementary file 10: Funnel plots to assess publication bias: Funnel plots (for the following outcomes: (a) antibiotic prescribing at index consultation, (b) antibiotic prescribing

within 28 days, (c) re-consultation within 28 days)

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Report on pag
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	6-7



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

41 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. 42 doi:10.1371/journal.pmed1000097 For more information, visit: www.prisma-statement.org.

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IMPACT OF POINT-OF-CARE C-REACTIVE PROTEIN IN AMBULATORY CARE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Objective: The aim of this review was to collate all available evidence on the impact of point-of-care CRP testing on patient-relevant outcomes in children and adults in ambulatory care.

Design: This was a systematic review to identify controlled studies assessing the impact of point-ofcare CRP in patients presenting to ambulatory care services. Ovid Medline, Embase, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, DARE, Science Citation Index were searched from inception to March 2017.

Eligibility criteria for selecting studies: controlled studies assessing the impact of point-of-care CRP in patients presenting to ambulatory care services, measuring a change in clinical care, including but not limited to antibiotic prescribing rate, re-consultation, clinical recovery, patient satisfaction, referral and additional tests. No language restrictions were applied.

Data extraction: Data were extracted on setting, date of study, a description of the intervention and control group, patient characteristics and results. Methodological quality of selected studies and assessment of potential bias was assessed independently by two authors using the Cochrane Risk of Bias tool.

Results: 11 randomised controlled trials and eight non-randomised controlled studies met the inclusion criteria, reporting on 16,064 patients. All included studies had a high risk of performance and selection bias. Compared to usual care, point-of-care CRP reduces immediate antibiotic prescribing (pooled risk ratio 0.81; 95% CI 0.71 to 0.92), however at considerable heterogeneity (I² 72%). This effect increased when guidance on antibiotic prescribing relative to the CRP level was provided (risk ratios of 0.68; 95%CI 0.63-0.74 in adults and 0.56; 95%CI 0.33-0.95 in children). We found no significant effect of point-of-care CRP testing on patient satisfaction, clinical recovery, reconsultation, further testing, and hospital admission.

Conclusions: Performing a point-of-care CRP test in ambulatory care accompanied by clinical guidance on interpretation reduces immediate antibiotic prescribing in both adults and children. As yet, available evidence does not suggest an effect on other patient outcomes or healthcare processes.

Trial Registration: CRD42016035426 (PROSPERO)

ARTICLE SUMMARY: STRENGTHS AND LIMITATIONS OF THIS STUDY

- A systematic review and meta-analysis to assess the impact of point-of-care CRP on patient-relevant outcomes in ambulatory care
- Our comprehensive approach resulted in a heterogeneous group of outcomes, patient populations and study designs.
- A paucity of data for children resulted in wide confidence intervals around effect estimates
- A lack of blinding of the clinicians and patients is inherent to trials examining the clinical impact of an intervention

INTRODUCTION

C-reactive protein (CRP) is an acute-phase protein, produced in the liver, which rises in response to tissue damage or inflammation, e.g. from infection, but also in other inflammatory processes such as an acute exacerbation of Crohn's disease.[1] Until recently, CRP blood tests have played only a minor role in ambulatory care because the delay between testing and result meant results were available too late to influence management decisions.[2] Point-of-care (POC) tests are being gradually introduced in different healthcare settings and their use is expected to increase dramatically,[3, 4] with POC CRP tests now available providing a result within 4 minutes.[5, 6] Ambulatory care deals with a large amount of non-specific presentations, such as infectious diseases. Diagnostic tools for acute conditions are fairly limited and mostly reliant on clinical assessment.[7-9] More precise assessment would be welcome to mitigate increasing rates of patients referred to secondary care, and render diagnostic assessment in ambulatory care safer.[10]

In addition, diagnostic uncertainty can lead to inappropriate antibiotic prescribing, unnecessary referrals to hospital, and unwarranted additional testing due to concern about potential serious infection.[8] Primary care is where the majority of antibiotics are prescribed, most of which are for respiratory infections. Children are a particularly high-risk group for unnecessary antibiotic prescribing.[11] As well as the global threat of widespread antimicrobial resistance, individuals with resistant infections in primary care are more likely to have clinical failure to subsequent antibiotic treatment.[12] Introducing better diagnostic tests might strengthen the assessment of infections in ambulatory care.[13] General practitioners (GP) have indicated that they would like to use these POC tests to help them decide whether or not to start antibiotic treatment for patients with respiratory tract infections if rigorous evidence of the impact on patient pathways are available.[14]

In ambulatory care, CRP has been evaluated (mostly diagnostic accuracy studies with only very few trials) for the diagnosis of lower respiratory tract infections in adults, identify serious infections in children and reduce inappropriate antibiotic prescribing.[9, 15] Since its introduction in routine care in Scandinavia in the early 1990s, prior to any solid evidence on the potential impact,[16] POC CRP has been incorporated in the Dutch and UK guidelines to assist antibiotic prescribing decisions in

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adults with symptoms of lower respiratory tract infections.[17, 18] Both recommendations are based on the same three RCTs (2 randomised at practice level and 1 at patient level), showing a significant reduction in immediate antibiotic prescribing rate when POC CRP was used (risk ratios ranging from 0.54 to 0.77).[19-21]

A recent Cochrane review, involving six trials, confirmed that POC CRP can reduce antibiotic prescribing in adults with acute respiratory tract infections by 22%,[14] however the broader impact on other clinically relevant outcomes, such as hospital admissions, missed diagnoses, inducing indication creep,[22] re-consultation, further testing and patient satisfaction and in other patient groups, such as children, has yet to be confirmed.[15]

This systematic review forms part of a series of reviews to assess the impact of any POC tests in ambulatory care. Here we aim to collate all available evidence on the impact of POC CRP testing in ambulatory care.

METHODS

Our objective was to assess the impact of POC CRP in patients presenting to ambulatory care services, resulting in a change in clinical care, including but not limited to antibiotic prescribing rate, re-consultation, clinical recovery, patient satisfaction, referral and additional tests.

Search strategy

We searched six electronic databases (MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Cochrane CENTRAL, DARE, Science Citation Index). The first search was undertaken in November 2015 with an update undertaken in March 2017. No time or language restrictions were applied. We checked reference lists of all retrieved articles included in the final review. The full search strategy is included in **Supplementary file 1**.

Selection of studies

Studies were eligible if they reported the impact of point-of-care testing on clinically relevant outcomes in ambulatory care settings. Ambulatory care was defined as any outpatient setting including primary care, walk-in clinics, and emergency departments. Studies in hospitalised patients were excluded. In addition, we excluded conference abstracts, diagnostic accuracy studies (focussing only on the performance of a point-of-care test versus a central lab test), qualitative studies, studies without a control group, and systematic reviews although their references were checked for potential relevance. Title and abstract screening was done in pairs by six independent reviewers (CG, PST, JV, TA, JL, PT). Discrepancies between the reviewers were resolved by a third independent reviewer of the team. For this paper, studies on point-of-care CRP testing were identified from the overall selection by two independent researchers (JV, CG).

Data extraction and assessment of methodological quality

Data were extracted by one reviewer (JV) and checked by a second reviewer (JL), and included setting, date of study, a description of the intervention and control group, patient characteristics and results.

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Methodological quality of selected studies and assessment of potential bias was assessed independently by two authors (JV, JL). Any disagreements were resolved by discussion involving a third member of the team. We used the Cochrane Risk of Bias tool for RCTs,[23] extended for nonrandomised but experimental and controlled studies by an assessment of a set of pre-specified confounders, including whether baseline characteristics were reported, whether intervention and control groups were similar, and whether there was a detailed description of the usual care pathway. For case-control studies we applied the Newcastle-Ottawa scale.[24]

Outcome Assessment

The primary outcome of interest was the impact of POC on clinically relevant outcomes such as antibiotic prescribing rate at the index consultation and during follow up, re-consultation, referral or admission to hospital, and mortality. Secondary outcomes included clinical recovery, patient satisfaction, respiratory tract infections (RTI) during follow-up, referral for chest X-ray, additional tests performed, time to symptom resolution and adherence to antibiotic treatment.

Patient involvement

This paper is part of the NIHR Diagnostic Evidence Cooperative (DEC) Oxford portfolio, and as such benefits from reflection and advice from the DEC's standing Patient and Public Involvement panel. Our panel has shown great interest in the introduction of point-of-care tests in ambulatory care, especially in relation to the assessment of acutely ill children and the monitoring of anticoagulant therapy. Credibility of the test result, funding of testing strips, and how to deal with intermediate results have been raised by our PPI panel in relation to POC testing.

Data analysis and synthesis

Meta-analyses were conducted separately for randomised controlled trials and non-randomised studies. For cluster-RCTs, we adjusted the unit of analysis by calculating the design effect to modify

sample sizes (with the formula "1 + (M – 1)*ICC" with M representing the number of clusters and ICC the intracluster correlation coefficient, both extracted from the original publication) and inflate confidence intervals accordingly.[25] Individual study estimates were pooled in a meta-analysis using Mantel–Haenszel random-effects models for risk ratio estimates and inverse-variance randomeffects models were used for mean difference estimates. Study-to-study heterogeneity was assessed using the I² test statistic in combination with visual inspection of the forest plots. For RTI during follow-up, antibiotics prescribed for RTI during follow-up, time to symptom resolution, adherence to antibiotic treatment, and antibiotic prescribing rate (if absolute numbers were unavailable) we used mean differences and their corresponding 95% confidence intervals (95% CI). Whenever data on mean differences was missing, we followed recommendations in the Cochrane Handbook of Systematic Reviews of Interventions to approximate the mean and standard deviation from the reported interquartile range.[23]

Subgroup analyses were limited to type of randomisation (at cluster (practice) or patient level), age group (children versus adults) and whether or not CRP cut-off guidance was applied. We performed meta-regression using the metareg function (meta package in R) to assess whether heterogeneity could be explained by age or the provision of CRP cut-off guidance. We created funnel plots to explore publication bias and small study effects when at least 10 studies were available for a particular outcome. Citation processing was done with Covidence (https://www.covidence.org/). Meta-analysis was undertaken with Revman version 5.3, meta-regression with R version 3.4.3.

RESULTS

Description of studies

Databases were searched and yielded 26,124 records. After full text assessment in the overall review on POC testing in ambulatory care, 225 records were included, of which 19 studies were on POC CRP testing. These included studies comprising of 11 randomised controlled trials and eight nonrandomised studies reporting on 16,064 patients in total. **(Table 1)** Details of search strategy and

screening are provided in (Supplementary file 1 & 2).

Sixteen studies on POC CRP testing were excluded at full-text screening, because: they were not in a ambulatory care setting, [26, 27] no comparator group without POC CRP testing was present, [28-31] the effect of the POC CRP could not be assessed separately or did not guide treatment decisions, [32-34] the focus was cost-effectiveness modelling [35-37] or decision making analysis, [38, 39] or it was not a clinical trial (study protocol or response to systematic review). [40, 41] **(Supplementary file 3)**

Table 1: Baseline characteristics of included studies

Study	Country	Design	Device (Manufacturer)	Patient characteristics	Total sample siz (CRP/no CRP)
1. randomise	d controlled tria	ls		0	
a) patients	presenting with	signs of respir	atory tract infection		
Andreeva	Russia	cluster	Afinion	adults with lower respiratory tract	179
2014[42]			(Axis Shield)	infection/acute cough for less than 28 days	(101/78)
Cals	the	cluster	Nycocard II (Axis	adults with suspected lower	431
2009[19]	Netherlands		Shield)	respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	(227/204)
Cals	the	individual	Nycocard II (Axis	adult with lower respiratory tract	258
2010[20]	Netherlands		Shield)	infection (cough < 4 weeks, + 1 focal	(129/129)
				and + 1 systemic symptom or sign) or rhinosinusitis < 4 weeks, + 2	
				symptoms or signs	
Cals	the	cluster	Nycocard II (Axis	adults with suspected lower	379
2013[43]	Netherlands		Shield)	respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	(203/176)
Diederichsen	Denmark	individual	Nycocard II (Axis	children and adults with respiratory	812
2000[44]			Shield)	tract infection	(414/398)
Do	Vietnam	individual	Nycocard II (Axis	children and adults with at least one	2037
2016[45]			Shield)	focal and one systemic symptom of acute respiratory tract infection	(1017/1019)

Little 2013[21]	Spain, England, Wales (UK), Poland, Belgium, the Netherlands	cluster	Quikread (Orion Diagnostica)	adults with upper or lower respiratory tract infection less than 28 days	4264 (2224/2040)
Melbye 1995[46]	Norway	individual	Nycocard II (Axis Shield)	adults with subjective complaint of pneumonia, bronchitis or asthma or 1 of: cough, shortness of breath, chest pain on deep inspiration or cough	239 (108/131)
b) patients	presenting with	n signs of any ac	ute illness		
Lemiengre 2014[47] (also Verbakel 2016[9])	Belgium	cluster	Afinion (Alere)	children with an acute illness less than 5 days	3147 (1730/1417)
Rebnord 2017[48]	Norway	individual	Quikread Go (Orion Diagnostica)	children with fever and/or respiratory symptoms	397 (138/259)
Van den Bruel 2016[49]	UK	individual	Afinion (Alere)	children with an acute illness less than 5 days	54 (26/28)
 non-randon a) patients Bjerrum 2004[50] 		n signs of respira cohort	ntory tract infection not specified	children and adults with acute sinusitis, acute tonsillitis, and acute	367 (281/86)
Fagan 2001[51]	Norway	cohort	not specified	otitis adults treated for acute bronchitis	324 (122/202)
Hughes 2016[52]	Wales (UK)	before-after	Afinion (Alere)	adults with symptoms of respiratory tract infection and other	94 (not specified
Kavanagh 2011[53]	Ireland	before-after	Quikread (Orion Diagnostica)	adults with acute cough and/or sore throat less than one month	120 (60/60)
Llor 2010[54]	Spain	before-after	Nycocard II (Axis Shield)	adults with acute sinusitis, acute tonsillitis, and acute otitis	161 (43/118)
Llor 2012[55] (also Llor 2014[56])	Spain	before-after	Nycocard II (Axis Shield)	adults with uncomplicated acute illness (< 7 days) with cough as the main symptom and 2+ signs or symptoms of LRTI (increase in sputum volume or purulence, chest pain and/or worsening of dyspnoea)	836 (208/628)
Peters 2013[57]	the Netherlands	case-control	Nycocard II (Axis Shield)	children and adults with an intellectual disability suspected of lower respiratory tract infection	1472 (882/590)
b) patients	presenting with	n signs of any ac	ute illness		
Jakobsen	Norway, Sweden,	cohort	Nycocard II (Axis Shield) &	adults with an acute illness episode less than 28 days	503 (372/131)

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Included studies

Twelve studies included adult patients only (totaling 7778 patients),[19-21, 42, 43, 46, 51-55, 58] three studies included children only (3598 patients),[9, 48, 49] and four studies both (4688 patients).[44, 45, 50, 57] Of the 11 randomised trials, five were randomised at practice level (cluster-randomised)[19, 21, 42, 43, 47] and six at patient level only (individually randomised).[20, 44-46, 48, 49] Most studies included patients with respiratory tract infections (16 out of 19 in total), of which eight studies concerned lower respiratory tract only.[19, 20, 42, 43, 46, 51, 55, 57] Two studies included patients with sinusitis, tonsillitis or otitis media,[50, 54] whereas three studies included patients presenting with any acute illness.[47, 49, 58]

Ten studies tested CRP on the Nycocard Reader II (by Alere),[19, 20, 43-46, 54, 55, 57, 58] four studies on the Afinion AS100 Analyzer (Alere),[42, 47, 49, 52] three on the Quikread,[21, 53, 58] and one study tested CRP on the Quikread Go (both by Orion Diagnostica).[48] Antibiotic prescribing rate was reported as the primary outcome in 17 of the 19 studies,[19-21, 42, 44-53, 55, 57, 58] reconsultation within 28 days in six studies,[19-21, 42, 45, 53], clinical recovery within 7 and/or 28 days in five studies,[19, 20, 42, 44, 46] and referral[9, 48, 49] or admission to hospital,[9, 21, 45] both in three studies. **(Supplementary file 3)** Only one study reported on mortality, but none of the patients died during follow-up.[9]

Secondary outcomes were reported for patient satisfaction, [19, 20, 45, 53] respiratory tract infections (RTI) during follow-up, [43] referral for chest X-ray, [42] additional tests performed, [9, 49] time to symptom resolution, [45] and adherence to antibiotic treatment. [54]

Risk of bias for included studies

For the RCTs, overall methodological quality was high, with only two studies with an unclear or high risk of detection bias (lack of blinding of the outcome assessors),[44, 48] and two studies with an unclear risk of reporting bias (no study protocol available).[44, 46] Considering only studies that focussed on the impact of POC tests were included, blinding of doctors to testing status was inherently impossible in these studies, resulting in a high risk of performance bias in all

studies. (Supplementary file 4) The non-randomised and before-after studies suffered from a high risk of selection, performance and detection bias, with an unclear risk of reporting bias, as there was no protocol available.[50-55, 58] For the single case-control study, the comparability of cases and controls was scored as "high risk", due to significant differences in sex, age and severity of intellectual disability, as well as an unclear risk due to non-reporting of the non-response rate.[57]

Antibiotic prescribing rate

Immediate prescribing at the index consultation

Based on ten RCTs, performing a POC CRP test resulted in a reduction of antibiotic prescriptions issued at the index consultation with a pooled effect estimate (risk ratio (RR)) of 0.81 (95% CI of 0.71 to 0.92), but heterogeneity was high (l² 72%) (**Figure 1a**).[19-21, 42, 44-49] The five non-randomised studies (all on adult populations) suggested an even larger reduction with a RR of 0.76 (95%CI of 0.63-0.91), again with high heterogeneity (l² 81%).[50, 51, 53, 55, 58] (**Figure 1b**) Subgroup analyses by age (adult vs children <18 years) showed that the largest reductions were seen in adult populations (RR 0.75; 95%CI 0.66-0.86, l²=63%).[19-21, 42, 44-46] Five RCTs examining antibiotic prescribing in children found a pooled RR of 0.93 (95% CI 0.72-1.21, l²=74%)

(Supplementary file 5).

Five studies (all in adults) providing guidance on when to initiate antibiotic treatment by CRP level, showed an overall RR of 0.68 (95%Cl 0.63-0.74, l²=0%),[19-21, 42, 45] whereas two RCTs where no guidance was applied found no effect (RR of 0.93; 95%Cl 0.81-1.06, l²=0%) (**Figure 2a**).[44, 46] A similar effect was seen in children, where two studies providing guidance resulted in fewer antibiotic prescriptions (RR 0.56; 95%Cl 0.33-0.95),[45, 47] l²=79%), (**Figure 2b**) whereas no effect was found in the four remaining studies providing no guidance (RR 1.01; 95%Cl 0.85-1.20, l²=0%).[44, 47-49]

In addition to the ten RCTs mentioned above, we also identified one before-after study, which reported a significant decrease of antibiotic prescribing (mean percentage difference -21.4%; 95%Cl -28.0 to -14.8%).[52]

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Using meta-regression, heterogeneity could be explained by both the age group (adults versus children, 100% of between-study heterogeneity explained) and prescribing guidance (100% and 85.9% of between-study heterogeneity accounted for, in adults and children respectively, with residual between-study heterogeneity of 6.9% in children). **(Supplementary file 6)**

Prescribing during follow-up

Antibiotic prescriptions within 28 days of testing were slightly lower with a POC CRP test (RR 0.84; 95%CI 0.72-0.99) at moderate heterogeneity (I² 46%) for the five available RCTs.[19, 20, 42, 45, 46] One RCT, however, did not find a significant reduction in antibiotic treatments for RTIs during long-term follow up with a mean difference of -5% (95%CI -13 to +3%).[43] **(Supplementary file 7)** The single case-control study found a larger effect with a RR of 0.46 (95%CI 0.37-0.57).[57]

Referral and admission to hospital

We found no difference in the number of patients referred to hospital (overall RR of 0.84 (95%Cl 0.44-1.61) with low heterogeneity (I² of 18%).[9, 48, 49] **(Supplementary file 8)** Three RCTs reporting number of patients admitted to hospital showed a nonsignificant increase when POC CRP was used with a RR of 1.24 (95%Cl 0.64-2.43, I²=18%).[9, 21, 45]

Re-consultation

Re-consultations were not different for patients receiving POC CRP compared to usual care, in the five RCTs (RR of 1.09 (95%CI 0.93-1.27, I²=0% in each subgroup, I² for subgroup differences (individually randomized RCTs vs cluster RCTS was 45%))[19-21, 42, 45] and the before-after study (RR 1.56 (95% CI 0.73-3.32)).[53] **(Supplementary file 9)**

Clinical recovery within 7 and 28 days, patient satisfaction, number of additional tests performed, and time to symptom resolution, did not differ between patients tested with POC CRP and usual care. **(Table 2)** A single RCT found a slight reduction (-16%) in number of RTIs (registered by the GP) during follow-up.[43] Another RCT detected a reduction in the number of patients referred for chest X-Ray in favour of POC CRP.[42] A before-after study in patients with acute sinusitis, tonsillitis and otitis found a higher adherence to antibiotic treatment (+9% of antibiotics containers opened) in patients tested with POC CRP.[54] **(Supplementary file 10)**

Table 2: Secondary outcomes: results

Secondary outcome	Studies	(Pooled) Risk Ratio or mean difference (%) of POC CRP versus usual care	95% CI	Heterogeneity I ² (%)
clinical recovery within 7 days	[20, 44, 46]	1.03	0·93 to 1·14	0%
clinical recovery within 28 days	[19, 42, 46]	0.94	0.69 to 1.28	0%
patient satisfaction	[19, 20, 45]	0.82	0·55 to 1·21	48%
	[53]	1.00	0·43 to 2·34	NA
RTIs during follow-up	[43]	-16%	-30% to -2%	NA
(registered by the GP)				
number of additional tests	[9, 49]	1.17	0·79 to 1·72	0%
number of chest X-rays	[42]	0.72	0·53 to 0·98	NA
time to symptom resolution	[45]	+0 days	-19 to +19 days	NA
adherence to antibiotic treatment	[54]	+8.9%	+3·4% to +14·4%	NA

Publication bias

For the three primary outcomes where funnel plots were possible (antibiotic prescribing at index consultation, antibiotic prescribing within 28 days, and re-consultation within 28 days) there was no apparent evidence of publication bias, although only studies with small effect sizes were identified in this review. **(Supplementary file 11)**

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DISCUSSION

Performing a point-of-care CRP test in ambulatory care accompanied by clinical guidance can reduce the immediate antibiotic prescribing rate in both adults and children presenting to their GP with an acute infection. POC in the absence of clinical guidance was effective at reducing antibiotic prescriptions in adults but not in children. We did not find a significant effect of POC CRP on clinical recovery, reconsultation, and subsequent management decisions, such as referral or delayed admission to hospital, although very few studies reported on the latter, resulting in residual uncertainty concerning safety of POC CRP.

This review focused on the clinical impact of POC CRP on patient-relevant outcomes in ambulatory care, emphasizing the importance of moving above and beyond the diagnostic accuracy of point-of-care tests and examining their effect on clinical decision making.[59] Our comprehensive approach resulted in a heterogeneous group of outcomes, patient populations and study designs. However, our results were consistent across the different types of studies, suggesting these findings are robust and reflect clinical reality. Our subgroup analyses and meta-regression has shown much of the statistical heterogeneity could be explained by patient age and prescribing guidelines. When implementing POC CRP these factors should be taken into account, guidance should be considered, especially in children. The paucity of data for children resulted in wide confidence intervals around our effect estimates, emphasizing the need for large trials in children in ambulatory care.[2] Our search was updated in March 2017, potentially overlooking relevant papers published in the past 12 months.

The issue of performance bias due to a lack of blinding of the clinicians and patients is inherent to trials examining the clinical impact of an intervention and therefore will not be improved in future studies.[60]

Before POC tests are widely adopted, GPs want evidence of their accuracy, rigorous testing of the impact on patient-relevant outcomes and consideration of test funding.[14] Previous studies have focused on the diagnostic accuracy of point-of-care CRP in ambulatory care,[9, 61] including a recent individual patient data meta-analysis that concluded that adding CRP

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measurements to the diagnostic work-up in ambulatory care improved risk classification of patients suspected of pneumonia.[61] Systematic reviews have mainly prioritized antibiotic prescribing rate in respiratory tract infections and found a significant reduction when POC CRP was used, similar to our findings.[15, 62] The current NICE pneumonia guideline advises GPs to consider a delayed prescription in patients with intermediate CRP values.[17] A recent umbrella review found that CRP is one of three effective strategies to reduce antibiotic prescribing, alongside shared decision making and procalcitonin-guided management.[63] The current systematic review included a wider range of patient-relevant outcomes, demonstrated the impact of clinical guidance in addition to POC CRP on reactibing and demonstrated the relative lack of evidence in paediatric populations. A recent non-randomised study showed that having POC CRP results available influences the decision of GPs to prescribe antibiotic treatment in patients with acute cough, but not in GPs with a low antibiotic prescribing rate.[39] POC CRP testing has shown to be cost-effective in several studies, though this was not the focus of our review.[30, 34-37]

In order to justify adoption, point-of-care tests need to demonstrate an overall benefit to patients and healthcare providers, regulators and commissioners must also be satisfied. It is vital to have robust evidence to ensure the consequences for patients and healthcare systems are properly evaluated. Broad adoption would be appropriate if a test can be applied in a wide range of patients and conditions. Our findings show point-of-care CRP for use in ambulatory care meets these criteria as long as appropriate guidance is provided. GPs have indicated they require guidance on the use and interpretation of POC CRP cut-offs.[64, 65] Further testing assessing broader impact and cost-effectiveness in children is needed.

Furthermore, other interventions, such as educating GPs, facilitating patient-centered care, and decreasing diagnostic uncertainty often resulting in complex interventions, can be as effective in reducing antibiotic prescribing.[21, 66] Communication training has been shown to have an effect on antibiotic prescribing.[19] If implemented together with POC CRP, they even reinforced one another. However, a recent paper showed that communication intervention in children had the opposite effect, increasing the antibiotic prescribing rate.[67] Arguably, communication training, if applied in

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the wrong population (e.g. with an interest in decreasing prescribing behaviour), may have adverse effects. Similarly, when antibiotic prescribing rates are low from the outset, POC CRP may not be able to decrease rates further without becoming unsafe. Other safety issues associated with the use of POC CRP might still arise, especially in children. We found that mortality was generally underreported and the impact on hospital admission rates has yet to be confirmed. Future studies should focus on the potential harms and assess safety of implementing POC CRP in ambulatory care.

CONCLUSIONS

Performing a POC CRP test in ambulatory care accompanied by evidence-based clinical guidance on interpretation reduces immediate antibiotic prescribing rate in both adults and children. As yet the evidence of impact on other patient outcomes or healthcare usage is lacking.

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COMPETING INTERESTS STATEMENT

All authors have completed the ICMJE uniform disclosure form at <u>www.icmje.org/coi_disclosure.pdf</u> and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR'S CONTRIBUTIONS

JV and JL did data extraction. JV performed the analyses, which were discussed with JL, CG, PST, TA, PT, GH, AV. JV drafted this report and JL, CG, PST, TA, PT, GH, AV co-drafted and commented on the final version. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JV affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted. All authors have read and approved the final manuscript.

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All data for these analyses are included in the manuscript or online appendices. No additional

data available.

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FIGURES & SUPPLEMENTARY FILES

Figure 1: point-of-care CRP versus usual care: antibiotic prescribing at index consultation: all patients Figure 2: point-of-care CRP versus usual care: antibiotic prescribing at index consultation: if cut-off guidance applied

Online Supplementary Files

Supplementary file 1: detailed search strategy

Supplementary file 2: PRISMA flowchart

Supplementary file 3: characteristics of included & excluded studies

Supplementary file 4: risk of bias assessment (QUADAS 2)

Supplementary file 5: point-of-care CRP versus usual care: antibiotic prescribing at index consultation: adults

versus children

Supplementary file 6: point-of-care CRP versus usual care: antibiotic prescribing within 28 days

Supplementary file 7: point-of-care CRP versus usual care: referral and admission to hospital

Supplementary file 8: point-of-care CRP versus usual care: re-consultation within 28 days

Supplementary file 9: forest plots of secondary outcomes

Supplementary file 10: funnel plots to assess publication bias

1(2)								
$^{1}_{2}(a)$		Point-of-ca	re CRP	usual e	care		Risk Ratio	Risk Ratio
3 -	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
	cluster rando							
4	Andreeva 2014	18	49	22	38	5.5%	0.63 [0.40, 1.00]	
5	Cals 2009	20	65	31	59	5.8%	0.59 [0.38, 0.91]	
6	Lemiengre 2014 Little 2013	117 304	455 920	106 407	381 844	11.5% 15.5%	0.92 [0.74, 1.16] 0.69 [0.61, 0.77]	- ·
7	Subtotal (95% CI)		1489	407	1322	38.2%	0.73 [0.60, 0.88]	• • • • • • • • • • • • • • • • • • •
8	Total events	459		566				•
9	Heterogeneity: Tau ² =	= 0.02; Chi ² =	6.62, df	= 3 (P =	0.08);	$^{2} = 55\%$		
10	Test for overall effect	: Z = 3.21 (P =	0.001)					
11	individually ra	andomised tri	als					
12	Cals 2010	56	129	73	129	10.6%	0.77 [0.60, 0.98]	
	Diederichsen 2008	179	414	184	398	14.1%	0.94 [0.80, 1.09]	
13	Do 2016	441	1017		1019	16.4%	0.68 [0.63, 0.74]	
14	Melbye 1995	54	108	68	131	10.6%	0.96 [0.75, 1.24]	— —
15	Rebnord 2017	36	138	57	259	7.3%	1.19 [0.82, 1.70]	
16	Van den Bruel 2016	10	26	9	28	2.7%	1.20 [0.58, 2.47]	
17	Subtotal (95% CI)	776	1832	1038	1964	61.8%	0.88 [0.73, 1.07]	
18	Total events Heterogeneity: Tau ² =		24.04 di		- 0 000	(2) $I^2 = 7$	9%	
19	Test for overall effect				- 0.000	2), 1 - 7	570	
20								
	Total (95% CI)		3321		3286	100.0%	0.81 [0.71, 0.92]	\bullet
21	Total events	1235	ىلە دە د	1604	0 000	2), 1 ² 7	20/	
22	Heterogeneity: Tau ² = Test for overall effect			= 9 (P =	= 0.000	$(2); 1^{-} = 7$	Ζ%	0.1 0.2 0.5 1 2 5 10
23	Test for subgroup dif			df = 1 (P)	= 0.17), $ ^2 = 47$.	5%	Favours Point-of-care CRP Favours usual care
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29	Study or Subgroup	Point-of-ca Events		usual o		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
30	observationa		Total	Events	Total	weight	M 11, Randolli, 55% Cl	
31	Bjerrum 2004	166	281	67	86	22.7%	0.76 [0.65, 0.88]	-
	Fagan 2001	87	122	175	202	23.7%	0.82 [0.73, 0.93]	-
32	Jakobsen 2010	129	372	46	131	17.1%	0.99 [0.75, 1.30]	-+-
33	Kavanagh 2011	27	60	35	60	13.7%	0.77 [0.54, 1.10]	
34	Llor 2012 Subtotal (95% CI)	97	208 1043	521	628 1107	22.7% 100.0%	0.56 [0.48, 0.65] 0.76 [0.63, 0.91]	
35	Total events	506	_0.5	844		10000		▼
36	Heterogeneity: Tau ² =		21.08, di		= 0.000	3); I ² = 83	1%	
37	Test for overall effect							
38								
39								0.1 0.2 0.5 1 2 5 10
40	Test for subgroup dif	ferences: Not a	applicable	2				Favours Point-of-care CRP Favours usual care
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43	Figura 1 · I	Forest plat	of co	mnaria	20n. 1	nint_0	f-care CRP versu	is usual care, outcome: antibiotic prescribing
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45	at index co	nsultation	: (a) al	ii patie	ents,	KUIS;	(b) all patients, r	non-randomised studies.
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$\frac{3}{4}(a)$								
		Point-of-car		usual o			Risk Ratio	Risk Ratio
5	Study or Subgroup cluster randomised	Events trials	Total	Events	Total	weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
6	Andreeva 2014 (<20mg/L)	18	49	22	38	2.9%	0.63 [0.40, 1.00]	
7	Cals 2009 (<20mg/L)	20	65	31	59	3.1%	0.59 [0.38, 0.91]	
8	Little 2013 (<20mg/L)	304	920	407	844	44.6%	0.69 [0.61, 0.77]	• •
9	Subtotal (95% CI)		1034		941	50.5%	0.68 [0.61, 0.75]	\bullet
10	Total events Heterogeneity: Tau ² = 0.00;			460 ⊧ 0.76); I	$^{2} = 0\%$			
11	Test for overall effect: $Z = 7$.	.08 (P < 0.0000	1)					
12	individually random	ised trials						
13	Cals 2010 (<20mg/L)	56	129	73	129	9.6%	0.77 [0.60, 0.98]	
14	Do 2016 (<10mg/L)	214	507	314	501	39.8%	0.67 [0.60, 0.76]	+
15	Subtotal (95% CI)		636		630	49.5%	0.69 [0.62, 0.77]	◆
16	Total events	270		387				
17	Heterogeneity: $Tau^2 = 0.00$;			= 0.36); I	$^{2} = 0\%$			
	Test for overall effect: $Z = 6$.	.61 (P < 0.0000	1)					
18	Total (95% CI)		1670		1571	100.0%	0.68 [0.63, 0.74]	•
19	Total events	612		847				
20	Heterogeneity: $Tau^2 = 0.00;$			= 0.83); I	$^{2} = 0\%$			
21	Test for overall effect: $Z = 9$.							Favours Point-of-care CRP Favours usual care
22	Test for subgroup difference	es: $Chi^2 = 0.08$,	dt = 1 (1)	P = 0.78	$, ^2 = 0$	1%		
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25 26 _{(h})	Point of cor		ucual			Pick Patio	Pick Patio
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25 26 _{(b} 27 28) Study or Subgroup individually random	Events				Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
25 26 _{(b} 27 28 29	Study or Subgroup individually random Do 2016 (<10mg/L)	Events	Total		Total	59.1%	M-H, Random, 95% Cl 0.69 [0.62, 0.78]	
25 26 _{(b} 27 28	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI)	Events ised trials 227	Total	Events 333	Total		M-H, Random, 95% Cl	
25 26 _{(b} 27 28 29	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events	Events ised trials 227 227	Total	Events	Total	59.1%	M-H, Random, 95% Cl 0.69 [0.62, 0.78]	
25 26 _{(b} 27 28 29 30	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl	Events ised trials 227 227 le	Total 510 510	Events 333	Total	59.1%	M-H, Random, 95% Cl 0.69 [0.62, 0.78]	
25 26 _{(b} 27 28 29 30 31 32	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events	Events ised trials 227 227 le	Total 510 510	Events 333	Total	59.1%	M-H, Random, 95% Cl 0.69 [0.62, 0.78]	
25 26 27 28 29 30 31 32 33	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl	Events ised trials 227 227 le .20 (P < 0.0000	Total 510 510	Events 333	Total	59.1%	M-H, Random, 95% Cl 0.69 [0.62, 0.78]	
25 26 _{(b} 27 28 29 30 31 32 33 34	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L)	Events ised trials 227 227 le .20 (P < 0.0000	Total 510 510 (1) 260	Events 333	Total 518 518 518 422	59.1% 59.1% 40.9%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.62, 0.78]	
25 26 27 28 29 30 31 32 33	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L) Subtotal (95% CI)	Events ised trials 227 227 le .20 (P < 0.0000 trials 19	Total 510 510 (1)	Events 3333 333 76	Total 518 518	59.1% 59.1%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78]	
25 26(b 27 28 29 30 31 32 33 34 35 36	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L)	Events ised trials 227 le .20 (P < 0.0000 trials 19 19	Total 510 510 (1) 260	Events 333 333	Total 518 518 518 422	59.1% 59.1% 40.9%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.62, 0.78]	
25 26(b 27 28 29 30 31 32 33 34 35 36 37	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L) Subtotal (95% CI) Total events	Events ised trials 227 le .20 (P < 0.0000 trials 19 19 le	Total 510 510 11) 260 260 260	Events 3333 333 76	Total 518 518 518 422	59.1% 59.1% 40.9%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.62, 0.78]	
25 26(b 27 28 29 30 31 32 33 34 35 36 37 38	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 3	Events ised trials 227 le .20 (P < 0.0000 trials 19 19 le	Total 510 510 (1) 260 260 260 260 260	Events 3333 333 76	Total 518 518 422 422 422	59.1% 59.1% 40.9% 40.9%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.25, 0.65] 0.41 [0.25, 0.65]	
25 26(b 27 28 29 30 31 32 33 34 35 36 37 38 39	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl	Events ised trials 227 le .20 (P < 0.0000 trials 19 19 le	Total 510 510 11) 260 260 260	Events 3333 333 76	Total 518 518 422 422 422	59.1% 59.1% 40.9%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.62, 0.78]	
25 26(b 27 28 29 30 31 32 33 34 35 36 37 38 39 40	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 3 Total (95% CI) Total events Heterogeneity: Tau ² = 0.12;	Events ised trials 227 227 le .20 (P < 0.0000 trials 19 le .70 (P = 0.0002 246 Chi ² = 4.87, df	Total 510 510 (1) 260 260 260 270	Events 333 333 76 76 76 409	Total 518 518 422 422 422 940	59.1% 59.1% 40.9% 40.9% 100.0%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.25, 0.65] 0.41 [0.25, 0.65]	M-H, Random, 95% CI
25 26(b 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 3 Total (95% CI) Total events Heterogeneity: Tau ² = 0.12; Test for overall effect: Z = 2	Events ised trials 227 227 le .20 (P < 0.0000 trials 19 le .70 (P = 0.0002 246 Chi ² = 4.87, df .15 (P = 0.03)	Total 510 510 (1) 260 260 260 (1) 770 (1) 770 (1) (1)	Events 333 333 76 76 76 26 9 9	Total 518 518 422 422 422 940 ° ² = 799	59.1% 59.1% 40.9% 40.9% 100.0%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.25, 0.65] 0.41 [0.25, 0.65]	
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25 26(b 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 3 Total (95% CI) Total events Heterogeneity: Tau ² = 0.12; Test for overall effect: Z = 2	Events ised trials 227 227 le .20 (P < 0.0000 trials 19 le .70 (P = 0.0002 246 Chi ² = 4.87, df .15 (P = 0.03)	Total 510 510 (1) 260 260 260 (1) 770 (1) (1) (2) (2) (2) (2) (2) (2) (2) (2) (2) (2	Events 333 333 76 76 76 26 9 9	Total 518 518 422 422 422 940 ° ² = 799	59.1% 59.1% 40.9% 40.9% 100.0%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.25, 0.65] 0.41 [0.25, 0.65]	M-H, Random, 95% CI
25 26(b 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 3 Total (95% CI) Total events Heterogeneity: Tau ² = 0.12; Test for overall effect: Z = 2	Events ised trials 227 227 le .20 (P < 0.0000 trials 19 le .70 (P = 0.0002 246 Chi ² = 4.87, df .15 (P = 0.03)	Total 510 510 (1) 260 260 260 (1) 770 (1) (1) (2) (2) (2) (2) (2) (2) (2) (2) (2) (2	Events 333 333 76 76 76 26 9 9	Total 518 518 422 422 422 940 ° ² = 799	59.1% 59.1% 40.9% 40.9% 100.0%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.25, 0.65] 0.41 [0.25, 0.65]	M-H, Random, 95% CI
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25 26(b 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	Study or Subgroup individually random Do 2016 (<10mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 6 cluster randomised Lemiengre 2014 (<5mg/L) Subtotal (95% CI) Total events Heterogeneity: Not applicabl Test for overall effect: Z = 3 Total (95% CI) Total events Heterogeneity: Tau ² = 0.12; Test for overall effect: Z = 2	Events ised trials 227 227 le .20 (P < 0.0000 trials 19 le .70 (P = 0.0002 246 Chi ² = 4.87, df .15 (P = 0.03)	Total 510 510 (1) 260 260 260 (1) 770 (1) (1) (2) (2) (2) (2) (2) (2) (2) (2) (2) (2	Events 333 333 76 76 76 26 9 9	Total 518 518 422 422 422 940 ° ² = 799	59.1% 59.1% 40.9% 40.9% 100.0%	M-H, Random, 95% Cl 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.62, 0.78] 0.69 [0.25, 0.65] 0.41 [0.25, 0.65]	M-H, Random, 95% CI

Figure 2: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) RCTs, adults only, if cut-off guidance applied; (b) RCTs, children only, if cut-off guidance applied.

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CRP cut-off used to withhold antibiotic treatment between brackets.

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Online Supplementary Files

Supplementary file 1: detailed search strategy

Supplementary file 2: PRISMA flowchart

Supplementary file 3: characteristics of included & excluded studies

Supplementary file 4: risk of bias assessment (QUADAS 2)

Supplementary file 5: point-of-care CRP versus usual care: antibiotic prescribing at index consultation: adults

versus children

Supplementary file 6: statistical heterogeneity: I-squared for overall results and different subgroups after meta-regression

Y.C. ONL

Supplementary file 7: point-of-care CRP versus usual care: antibiotic prescribing within 28 days

Supplementary file 8: point-of-care CRP versus usual care: referral and admission to hospital

Supplementary file 9: point-of-care CRP versus usual care: re-consultation within 28 days

Supplementary file 10: forest plots of secondary outcomes

Supplementary file 11: funnel plots to assess publication bias

Medline

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general practitioners/ or physicians, family/ or physicians, primary care/

((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.

(primary care or primary health care or primary healthcare).ti,ab.

(after hour? or afterhour? or "out of hour?" or ooh).ti,ab.

community health services/ or exp community health nursing/

(community adj2 (health or health care or service? or program*)).ti,ab.

1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

((rapid or bedside or bed-side or "near patient") adj3 (test* or diagnos*)).ti,ab.

((rapid or bedside or bed-side or "near patient") and (test* or diagnos*)).ti.

(community adj2 (worker? or aide? or volunteer? or assistant? or visitor?)).ti,ab.

((lay or volunteer) adj2 (health worker? or health aide? or health assistant?)).ti,ab.

((health* or medical) adj2 (center? or centre?)).ti,ab.

((health* or medical) adj2 (facility or facilities)).ti,ab.

(("point of care" or POC) adj3 (test* or diagnos*)).ti,ab.

(("point of care" or POC) and (test* or diagnos*)).ti.

(ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.

(emergency adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.

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Supplementary file 1: Search strategy

exp Ambulatory Care Facilities/

general practice/ or family practice/

exp Emergency Service, Hospital/

Emergency Medical Services/

Ambulatory Care/

Primary Health Care/

(clinic? or visit?).ti,ab.

Community Health Workers/

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Point-of-Care Systems/

poct.ti,ab.

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Office Visits/

(ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.

(emergency adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.

((general or family) adj2 (practi* or physician? or doctor?)).ti,ab. (primary care or primary health care or primary healthcare).ti,ab.

1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 community care/ or exp community health nursing/ or community program/

(community adj2 (health or health care or service? or program*)).ti,ab.

(community adj2 (worker? or aide? or volunteer? or assistant? or visitor?)).ti,ab. ((lay or volunteer) adj2 (health worker? or health aide? or health assistant?)).ti,ab.

((rapid or bedside or bed-side or "near patient") adj5 (test* or diagnos*)).ti,ab. ((rapid or bedside or bed-side or "near patient") and (test* or diagnos*)).ti.

(after hour? or afterhour? or "out of hour?" or ooh).ti,ab.

((health* or medical) adj2 (center? or centre?)).ti,ab.

((health* or medical) adj2 (facility or facilities)).ti,ab.

(("point of care" or POC) adj5 (test* or diagnos*)).ti,ab. (("point of care" or POC) and (test* or diagnos*)).ti.

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24 or 25 or 26 or 27 or 28 or 29 (istat or i-stat or afinion).ti,ab.

"point of care testing"/

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ambulatory care/

general practice/ general practitioner/

emergency ward/

health center/

emergency health service/

(clinic? or visit?).ti,ab.

health auxiliary/

outpatient department/

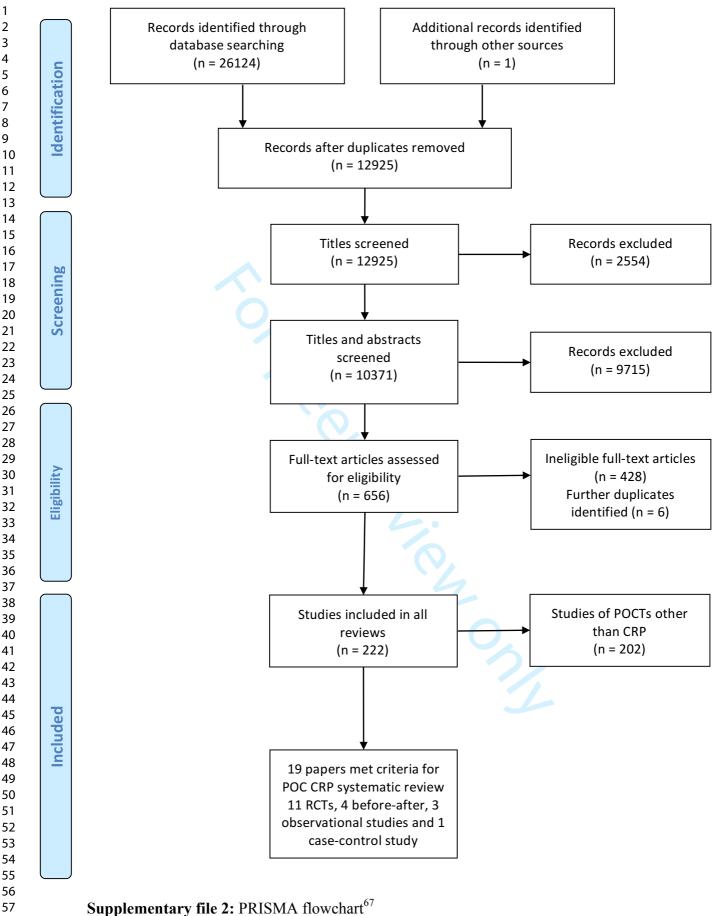
primary medical care/ or primary health care/

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5 6	#2	MeSH descriptor: [Ambulatory Care Facilities] explode all trees
7	#3	MeSH descriptor: [General Practice] explode all trees
8 9	#4	MeSH descriptor: [General Practitioners] explode all trees
10	#5	MeSH descriptor: [Physicians, Family] explode all trees
11 12	#6	MeSH descriptor: [Physicians, Primary Care] explode all trees
13	#7	MeSH descriptor: [Primary Health Care] this term only
14 15	#8	MeSH descriptor: [Office Visits] explode all trees
16	#9	MeSH descriptor: [Emergency Service, Hospital] explode all trees
17	#1	MeSH descriptor: [Emergency Medical Services] this term only
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23	1 #4	service?)):ti,ab,kw (Word variations have been searched)
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26	2	been searched)
27 28	#1	(emergency near/3 (care or setting? or facilit* or ward? or department? or
20	3	service?)):ti,ab,kw (Word variations have been searched)
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31 32	4	searched)
33	#1	clinic or clinics or visit or visits:ti,ab,kw (Word variations have been searched)
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36	#1	((health* or medical) near/2 (center? or centre?)):ti,ab,kw (Word variations have been
37 38	6	searched)
39	#1	MeSH descriptor: [Community Health Services] this term only
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44 45	#1	MeSH descriptor: [Community Health Workers] explode all trees
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47 48	#2	(community near/2 (health or health care or service? or program*)):ti,ab,kw
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	NEAR/3 (test* or diagnos*))) OR TI=(((rapid or bedside or bed-side or "near patient") and (test*
	or diagnos*))) OR TS=((istat or i-stat or afinion))
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	primary health care or primary healthcare)) OR TS=((emergency NEAR/3 (care or setting? or
	facilit* or ward? or department? or service?))) OR TS=(("after hour?" or afterhour? or "out of
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Supplementary file 3: characteristics of included & excluded studies

Excluded studies	s: reasons for exclusion	
study	title	reason for exclusion
Cals 2011	C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial	cost-effectiveness modelling
Hunter 2015	Cost-Effectiveness of Point-of-Care C-Reactive Protein Tests for Respiratory Tract Infection in Primary Care in England	cost-effectiveness modelling
Oppong 2013	Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions	cost-effectiveness modelling
Lindström 2015	What a difference a CRP makes. A prospective observational study on how point-of-care C-reactive protein testing influences antibiotic prescription for respiratory tract infections in Swedish primary health care	decision making analysis
Minnaard 2016	C-reactive protein point-of-care testing and associated antibiotic prescribing	decision making analysis
Dahler-Eriksen 1999	Near-Patient Test for C-Reactive Protein in General Practice: Assessment of Clinical, Organizational, and Economic Outcomes	effect of POC CRP cannot be assessed seperately
Elfving 2016	Acute Uncomplicated Febrile Illness in Children Aged 2-59 months in Zanzibar - Aetiologies, Antibiotic Treatment and Outcome	effect of POC CRP cannot be assessed seperately
Gonzales 2011	C-REACTIVE PROTEIN TESTING DOES NOT DECREASE ANTIBIOTIC USE FOR ACUTE COUGH ILLNESS WHEN COMPARED TO A CLINICAL ALGORITHM	effect of POC CRP cannot be assessed seperately
Kankaanpaa 2016	Use of point-of-care testing and early assessment model reduces length of stay for ambulatory patients in an emergency department	effect of POC CRP cannot be assessed seperately
Nijman 2015	C-Reactive Protein Bedside Testing in Febrile Children Lowers Length of Stay at the Emergency Department	effect of POC CRP cannot be assessed seperately
Cohen 2006	Impact of CRP rapid test in management of febrile children in paediatric emergency units of Ile-de-France	no comparator with no POCT CRP
Cohen 2008	Evaluation of impact of CRP rapid test in management of febrile children in ambulatory pediatric practice	no comparator with no POCT CRP
Kokko 2014	Rapid C-reactive protein and white cell tests decrease cost and shorten emergency visits	no comparator with no POCT CRP
Muszynska 2007	Rational antibiotic therapy - rapid CRP tests value on the effect on antiobitic prescribing - initial results	no comparator with no POCT CRP
Cals 2007	Improving management of patients with acute cough by C- reactive protein point of care testing and communication training (IMPAC3T): study protocol of a cluster randomised controlled trial	not a clinical trial (protocol only)
Azevedo 2014	[Analysis of the Cochrane review: biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database Syst Rev. 2014,11:CD10130]	not a clinical trial (response to sys review)

Supplementary file 3a: characteristics of excluded studies

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Author / Year	Participant inclusion criteria	Participant exclusion criteria	Comparator	Outcome measures	25036
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Andreeva 2014	adults with lower respiratory tract infection/acute cough for less than 28 days	previously seen by GP for infection in question, immunocompromised status, ongoing treatment with oral	usual care	Primary outcome • Antibiotic use within the first 2 weeks after index consultation Secondary outcomes • Reported morbidity after 2 weeks (ordinal data) • Chest X-ray referrals (number) • Re-consultations (number) • Commissions including to exist list in (number)	1 February 20
		corticosteroids		• Complications including hospitalisation (number) In the intervention group, the antibiotic prescribing rate was the control group (58.9%) (P = 0.006). Referral for chest X-ray group (55.4%) than in the control group (75.6%) (P = 0.004). T 92.9% and 93.6% in the intervention and control groups, resp	v was also significantly lower in the intervention The recovery rate, as recorded by the GPs, was been tively
Bjerrum 2004	children and adults with acute sinusitis, acute tonsillitis, and acute otitis	none stated	usual care	antibiotic prescribing rate for patients with acute sinusitis, acute to The antibiotic prescribing rate for patients with acute sinusiti was 59% (95%CI=56 to 62) compared with78%(95%CI=73 to 8 sinusitis was significantly lower (odds ratio [OR] = 0.43)	ວາຣີillitis, and acute otitis iເ ຊີn the group of GPs who used rapid CRP tes
Cals 2009	adults with suspected lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	aged under 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	usual care	 Primary outcome Antibiotic prescribing at index consultation Secondary outcomes Antibiotic use (any use for current infection) in 28 days Number of additional consultations Patient satisfaction: number of patients at least very satisfied; nutor return in future if similar symptoms develop Enablement (median score) Clinical recovery: no. of patients recovered on day 7; median of per day; median reported time to full recovery General practitioners in the C reactive protein test group prewith 53% in the no test group (P=0.02). General practitioners prescribed antibiotics to 27% of patients compared with 54% interventions showed a statistically significant effect on antii follow-up. Clinicians in the combined intervention group presterm was non-significant). Patients' recovery and satisfaction 	symptom scores seribed antibiotics to 31% of patients compare trained in enhanced communication skills in the no training group (P<0.01). Both betic prescribing at any point during the 28 da seribed antibiotics to 23% of patients (interacti
Cals 2010	adult with lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign) or rhinosinusitis < 4 weeks, + 2 symptoms or signs	aged under 18 years, antibiotic use or hospitalisation within the previous 14 days, non-fluent in Dutch, immunocompromised status or need for immediate hospitalisation	usual care	 Primary outcome Antibiotic use (delayed and immediate) at index consultation Secondary outcomes Antibiotic use (any use for current infection) in 28 days Number of additional consultations Patient satisfaction: number of patients at least very satisfied; not to return in future if similar symptoms develop Enablement (median score) Clinical recovery: no. of patients recovered on day 7; median of per day; median reported time to full recovery Patients in the CRP-assisted group used fewer antibiotics (4: consultation (relative risk [RR] = 0.77; 95% confidence interv significant during follow-up (52.7% vs 65.1%; RR=0.81; 95% confidence 	symptom scores 3.4%) than control patients (56.6%) after the inc adCI], 0.56-0.98). This difference remained
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				assisted group were filled only in a minority of cases (23% vs 2% in control group, P <.001). Recovery was similar across groups. Satisfaction with care was higher in pattern managed with CRP assistance (P = .03	
Cals 2013	adults with suspected lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	aged under 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	usual care	The primary outcome was the average number of episodes of respentory tract infection during the follow-up period which patients consulted their physician per patient per year (PPPY) and the proportion of these episodes that result in an antibiotic prescription. The mean number of episodes of respiratory tract infections during follow-up was 0.40 PPPY in the CRP te group and 0.56 PPPY in the no CRP test group (P=.12). In the communication skills training group, there we mean of 0.36 PPPY episodes of respiratory tract infections, and in the no training group the mean was 0.57 PPPY (P=.09). During follow-up 30.7% of all episodes of respiratory tract infection were treated with antibiot in the CRP test group compared with 35.7% in the no test group? (P=.36). Family physicians trained in communication skills treated 26.3% of all episodes of respiratory tract infection with antibiotics compared 39.1% treated by family physicians without training in communication skills (P = .02)	d for ulted est vas a 7 otics
Diederichsen 2000	children and adults with respiratory tract infection	previously seen by general practitioner for infection in question, patients who had streptococcal rapid testing performed, patients with chronic inflammatory diseases	usual care	Primary outcome • Antibiotic use at index consultation Secondary outcome • Patient-reported morbidity after 1 week In the CRP group the frequency of antibiotic prescriptions was 43% (179/414) compared with 46% (184/398 the control group (odds ratio (OR)=0.9, NS). After 1 week, increased or unchanged morbidity was stated more frequently in the CRP group (12%) than i the control group (8%) (OR = 1.6, p = 0.05). In the control group, the variable having the greatest influence whether the GP prescribed antibiotics was the patients' general well-being (OR = 2.9, p B 0.0001), whereas the CRP group the CRP value had the greatest influence (OR = 1.1 per unit increase (mg/l), p B 0.0001).	in
Do 2016	children and adults with at least one focal and one systemic symptom of acute respiratory tract infection	patients with sever acute respiratory tract infection	usual care	primary outcome - number of patients receiving any antibiotic within 2 weeks of enroment secondary outcome - antimicrobial activity in urine (day 3, 4, or 5), the proportion of patients with immediate antibiotic prescription at enrolment, any antibiotic usage in patients without immediate prescription (subsequent antibiotic use or interventio failure), and prescriptions on the second visit in patients without an immediate antibiotic prescription, the source of antibiotic taken but not prescribed at enrolment or day 4 (self-mediation, drug seller, doctor, or other), the frequent re-consultations, serious adverse events (hospital admission or death), time to resolution of symptoms, and reporter patient satisfaction with participating in the trial on day 14 (measured on a scale from 0 to 10) The number of patients who used antibiotics within 14 days was 581 (64%) of 902 patients in the C-reactive protein group versus 738 (78%) of 947 patients in the control group (odds ratio [OR] 0.49, 95% CI 0.40–0.64 p<0.0001). Highly significant differences were seen in both children and adults, with substantial heterogen of the intervention effect across the 10 sites (I2=84%, 95% CI 09–96). 140 patients in the C-reactive protein group and 137 patients in the routine care group missed the urine test on day 3, 4, or 5. Antibiotic activity i urine on day 3, 4, or 5 was found in 267 (30%) of 877 patients in the C-reactive protein group versus 314 (30 of 882 patients in the routine treatment group (OR 0.78, 95% CE0.63–0.95; p=0.015). Time to resolution of symptoms was similar in both groups. Adverse events were rate, with no deaths and a total of 14 hospital admissions (six in the C-reactive protein group and eight in the control group).	f any ncy c ed f; neity in
Fagan 2001	adults treated for acute bronchitis	telephone consultations and home visits	usual care	antibiotic prescribing at index consultation In period 1, 87% (175/202) of the patients in Arendal with the diagnosis of acute bronchitis were treated wit antibiotics. Doxycycline was prescribed to 47% followed by pericillin (28%) and erythromycin (14%) (Figur In Tønsberg, 135 patients (78%) were treated with antibiotics. Here, penicillin was most commonly prescrik (31%), then doxycycline (30%). 18% received erythromycin. 21% were treated with other antibiotics, mainly amoxicillin. In period 2, 71% of the patients in Arendal received antibiotics (87/122). The reduction in	re 1) bed

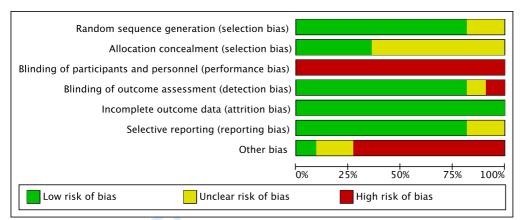
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				prescribing from period 1 was statically significant (p <0.001). Tonsberg, 74% of patients in period 2 received antibiotics. The difference from period 1 was not statistically significant (p = 0.34). There were no significant changes in which antibiotics were prescribed, except for a decrease in the use of other antibiotic from 21% to 7% in Tønsberg (p <0.05).
Hughes 2016	adults with symptoms of respiratory tract infection and other	none stated	usual care	overall antibiotic prescribing rate A mean reduction in items of 21.39%, compared to 10.6% reduction across all practices during the same period
Jakobsen 2010	adults with an acute illness episode less than 28 days	none stated	usual care	GPs' decision to prescribe antibiotics for acute cough A total of 803 patients were recruited in the three networks. Among the 372 patients tested with a POCT for CRP, the CRP value was the strongest independent predictor of antibiotic prescribing, with an odds ratio (OI of CRP 50 mg/L of 98.1. Crackles on auscultation and a patier preference for antibiotics perceived by the C were the strongest predictors of antibiotic prescribing when the CRP test was not used
Kavanagh 2011	adults with acute cough and/or sore throat less than one month	none stated	usual care	Primary outcome was antibiotic prescription at the index consultation. Secondary outcomes were number of delayed prescriptions issued re-consultation (referring to both 'in per- son' and telephone consultations) and antibiotic prescription, both during 28 days of follow-up, and patient satisfaction Thirty-five (58%) patients in the no-test group received antibiodic prescriptions compared to 27 (45%) in the test group. Both groups demonstrated similarly high level of patient satisfaction (85%). Fourteen (23%) patients in the CRP test group re-attended within 28 days compared to 9 (15%) in the no-CRP test group
Lemiengre 2014	children with an acute illness less than 5 days	acute illness is caused by merely traumatic or neuro- logical conditions, intoxication, psychiatric or behav- ioural problem, or an exacerbation of a known chronic condition	usual care	immediate and total antibiotic prescribing rate In comparison to usual care, POC CRP didn't influence antibiotic prescribing (adjusted odds ratio (aOR) 0.7' (95% Confidence Interval (CI) 0.42 to 1.44) for immediate and 1.31 (95%CI 0.71-2.40) for total prescribing). BISNA increased antibiotic prescribing (aOR 2.13 (95% CI 1.24) to 3.69) for immediate and 2.02 (95%CI 1.15 to 3.56) for total prescribing). In combination with POC CRP, this increase disappeared.
(also Verbakel 2016)				hospital admission (> 24 hours) for a serious infection within 5 days after initial presentation Restricting CRP testing to those identified as at clinical risk substantially reduced the number of children tested by 79.9 % (95 % Cl, 77.8–82.0 %). There was no significant difference between arms in the number of children with serious infection who were referred to hospital in mediately (0.16 % vs. 0.14 %, P = 0.88). Only one child with a CRP < 5 mg/L had an illness requiring admission (a child with viral gastroenteritis admitted rehydration). However, of the 80 children referred to hospital torule out serious infection, 24 (30.7 %, 95 % C 19.6–45.6 %) had a CRP < 5 mg/L.
Little 2013	adults with upper or lower respiratory tract infection less than 28 days	Exclusion criteria: a non-infective working diagnosis (e.g. pulmonary embolus; heart failure; oesophageal reflux; allergy); antibiotic use in the previous month; unable to pro- vide informed consent (dementia; psychosis; severe depression); pregnant;	usual care	Primary outcome • Antibiotic prescribing at index consultation Secondary outcomes • New or worsening symptoms, defined as re-consultation within 28 days with worsening symptoms, new symptoms, new signs, or hospital admission • Symptom severity and duration, defined as a) the severity of symptoms in the 2 to 4 days after seeing the physician and b) the duration of symptoms in the 2 to 4 days after seeing the physician and b) the duration of symptoms in the 2 to 5 The baseline audit, done in 259 practices, provided data for 671 patients with lower-respiratory-tract infections (3742 [55·3%]) and upper-respiratory-tract infections (1416 [20·9%]), of whom 5355 (79·1%) were prescribed antibiotics. After randomisation, 246 practices were included and 4264 patients were recruited. The antibiotic prescribing rate was lower with CRP training than without (33% vs 48%, adjusted risk ratio 0·54, 95 CI 0·42–0·69) and with enhanced-communication training than without (36% vs 45%, 0·69, 0·54–0·87). The
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		immunological deficiencies Patients with lower respiratory tract infection (up to the first 30 presenting in each practice) and upper respiratory tract infection (up to the first 5 presenting) were recruited following informed consent		combined intervention was associated with the greatest reduction CI 0·36–0·74, p<0·0001; enhanced communication 0·68, 0·50–089 p<0·0001) 1 February 2019. 0 9	
Llor 2012 & 2014	adults with acute sinusitis, acute tonsillitis, and acute otitis	none stated	pre- intervention and usual care group	antibiotic prescription the use of the CRP was a significant protective factor for antibiotic mg/l, the odds ratio (OR) of antibiotic prescription was 0.008 com confidence interval (CI): 0–0.015]. After adjusting for the reman- differences were found in antibiotic prescription between the for contrast, the post-intervention ORs were lower than those of the was only significant among physicians assigned to FIG. In comp antibiotic prescription was 0.115 (95% CI: 0.008–0.321).	npared with the no use of this test [95% ing variables, no statistically significant o pre-intervention and the control groups. In control and pre-intervention groups, but it
Llor 2010	adults with uncomplicated acute illness (< 7 days) with cough as the main symptom and 2+ signs or symptoms of LRTI (increase in sputum volume or purulence, chest pain and/or worsening of dyspnoea)	none stated	pre- intervention	Three outcome measures were taken into account; • taking adherence • correct dosing • good timing adherence during at least 80% of the antibiotic course The rate of failures was also taken into account when the patient was Adherence was better when patients underwent CRP rapid testin both in terms of the percentage of container openings (83.3% ± 1 timing adherence during at least 80% of the antibiotic course (32 patients who took at least 80% of the doses was slightly better (72.1% vs. 55.1%), although this difference was not statistically s The percentage of patients who opened the container a satisfie day throughout the treatment course – was always greater when to antibiotic administration (see Figure 2). The differences betwee and those who did not were statistically significant for days 4 and differences after the fifth day of the antibiotic treatment schedene	In prior to administration of the antibiotic, 14.8% vs. 74.4% \pm 17.7%; p<0.01) and the good 2.6% vs. 16.9%; p<0.05). The percentage of when the patient underwent rapid testing significant. Bory number of times – at least three times per the patient had undergone CRP testing prior the patient had undergone CRP testing prior the point-of-care test ad 5 (p<0.01). A disappearance of the
Melbye 1995	adults with subjective complaint of pneumonia, bronchitis or asthma or 1 of: cough, shortness of breath, chest pain on deep inspiration or cough	aged under 18 years, patients with sore throat, blocked nose, pain in ears or sinuses. Patients with angina-like chest pain were also excluded	usual care	Primary outcome • Antibiotic use at index consultation Secondary outcomes • Antibiotic use (any use for current infection) in 21 days • Clinical recovery: no. of patients recovered on day 7 and day 21 No significant difference was found in the number of antibiotic po 0.75 to 1.24). No difference in patient recovery rate on rate of imp 0.75 to 1.18) or day 21 (RR 0.85, Cl 0.57 to 1.29). Management dec testing in 10% (11/108) of the cases; estimated algorithm adherent	prescriptions between the groups (RR 0.96, CI provement was observed on day 7 (RR 0.94, CI cisions were changed by C-reactive protein
Peters 2013	children and adults with an intellectual disability suspected of lower	none stated	usual care	antibiotic prescriptions for LRTIs by physicians specialising in the Gree Of the 48 patients in the control group who were diagnosed as a g	e of individuals with intellectual disabilities
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	respiratory tract infection			compared with 59 out of the 144 patients (41%) in the case g no significant differences between the case and contr antibiotic prescriptions during follow-up	roup (OR = 12.0; 95% CI = 4.1–35.3). There were
Rebnord 2017	children with fever and/or respiratory symptoms	none stated	usual care	antibiotic prescription and referral to hospital In the group pretested with CRP, the antibiotic prescription r group. In the group pretested with CRP, 5% were admitted to These differences were not statistically significant	
Van den Bruel 2016	children with an acute illness less than 5 days	Children were excluded if they had consulted for acute trauma, were clinically unstable warranting immediate care, or had been included in this study before	usual care	Secondary outcomes included antibiotic prescribing, hospital refere- re-consultation in primary or secondary care Antibiotics were prescribed to 60 children (30%, 95% CI 23.66 received explicit safety-netting advice and 11 (5.5%) were ref significant difference in any outcome between those tested of follow-up period, children randomised to CRP testing received versus 1 patient). Five children were admitted to hospital, thr non-specified viral illness)	20 36.4%) at the index consultation, 70 (35%) effed to hospital. There was no statistically root tested with CRP point-of-care. In the 10-day efficiently more antibiotic prescriptions (6 South for the fortune of the state
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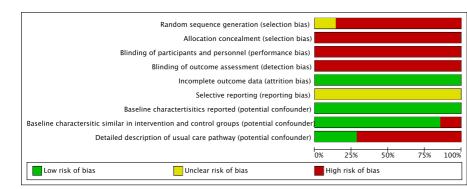
Supplementary file 4: Risk of bias assessment (QUADAS 2)

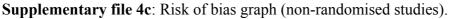


Supplementary file 4a: Risk of bias graph (RCTs): review authors' judgements about each risk of bias item presented as percentages across all included studies



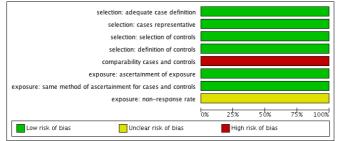
Supplementary file 4b: Risk of bias summary (RCTs): review authors' judgements about each risk of bias item for each included study.





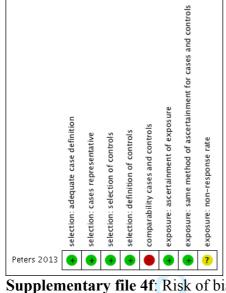


Supplementary file 4d: Risk of bias summary (non-randomised studies).



Supplementary file 4e: Risk of bias graph (case-control studies).

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$\begin{array}{c} 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 9\\ 50\\ 51\\ 52\\ 53\\ 56\\ 57\end{array}$		
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$\begin{array}{c} 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 9\\ 50\\ 51\\ 52\\ 53\\ 55\\ 56\\ 57\end{array}$	22	
$\begin{array}{c} 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\end{array}$		
$\begin{array}{c} 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\end{array}$		
$\begin{array}{c} 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\end{array}$		
$\begin{array}{c} 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\end{array}$		
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Supplementary file 4f: Risk of bias summary (case-control studies).

i bias summa.

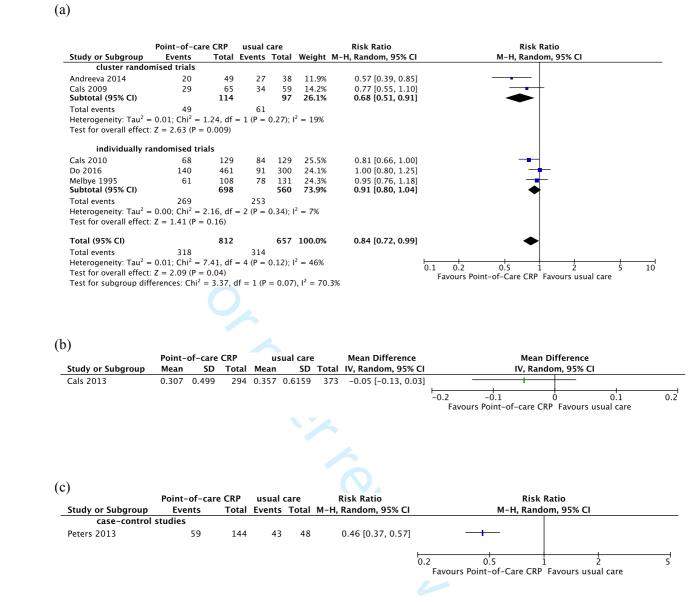
6. I I	Point-of-c		usual			Risk Ratio	Risk Ratio
Study or Subgroup	Events mised trials	Total	Events	Total	Weight M	-H, Random, 95% CI	M-H, Random, 95% CI
Andreeva 2014	18	49	22	38	6.0%	0.63 [0.40, 1.00]	
Cals 2009	20	65	31	59	6.4%	0.59 [0.38, 0.91]	
Little 2013	304	920	407	844	21.7%	0.69 [0.61, 0.77]	
Subtotal (95% CI)	2.42	1034		941	34.1%	0.68 [0.61, 0.75]	•
Total events Heterogeneity: Tau ² Test for overall effect				0.76);	$1^2 = 0\%$		
individually r	andomised t	rials					
, Cals 2010	56	129	73	129	13.2%	0.77 [0.60, 0.98]	_ _
Diederichsen 2008	152	342	161	331	18.5%	0.91 [0.78, 1.07]	
Do 2016	214	507	314	501	21.2%	0.67 [0.60, 0.76]	
Melbye 1995 Subtotal (95% CI)	54	108 1086	68	131 1092	13.1% 65.9%	0.96 [0.75, 1.24]	
Total events	476	1090	616	1092	03.9%	0.81 [0.67, 0.98]	
Heterogeneity: Tau ² Test for overall effect	= 0.03; Chi ² =			= 0.008	3); $I^2 = 75\%$		
Total (95% CI)		2120		2033	100.0%	0.75 [0.66, 0.86]	•
Total events	818		1076				•
Heterogeneity: Tau ²				= 0.01)	$I^2 = 63\%$		0.1 0.2 0.5 1 2
Test for overall effect							Favours Point-of-care CRP Favours usua
Test for subgroup dii	ferences: Chi	2 = 2.82, 0	df = 1 (P	= 0.09), I ² = 64.5%		
b)	Point-of-ca	are CRP	usual o	are		Risk Ratio	Risk Ratio
b) Study or Subgroup	Point-of-ca Events	are CRP Total	usual o	are			Risk Ratio
b)	Point-of-ca Events	are CRP Total	usual o	are		Risk Ratio	Risk Ratio M-H, Random, 95% Cl
b) 	Point-of-ca Events andomised ti	are CRP Total rials	usual o Events	care Total	Weight M	Risk Ratio -H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
D) <u>Study or Subgroup</u> individually r Diederichsen 2008 Do 2016 Rebnord 2017	Point-of-ca Events andomised tr 27 227 36	are CRP Total rials 72 510 138	usual c Events 23 333 57	care Total 67 518 259	Weight M 16.3% 29.8% 19.5%	Risk Ratio - H, Random, 95% Cl 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70]	Risk Ratio M-H, Random, 95% CI
Study or Subgroup individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016	Point-of-ca Events andomised tu 27 227	are CRP Total rials 72 510 138 26	usual o Events 23 333	care Total 67 518 259 28	Weight M 16.3% 29.8% 19.5% 9.0%	Risk Ratio - H, Random, 95% CI 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70] 1.20 [0.58, 2.47]	Risk Ratio M-H, Random, 95% Cl
Study or Subgroup individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016 Subtotal (95% CI)	Point-of-ca Events andomised to 27 227 36 10	are CRP Total rials 72 510 138	usual o Events 23 333 57 9	care Total 67 518 259	Weight M 16.3% 29.8% 19.5%	Risk Ratio - H, Random, 95% Cl 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70]	Risk Ratio M-H, Random, 95% Cl
Study or Subgroup individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016	Point-of-ca Events andomised ti 27 227 36 10 300 e 0.10; Chi ² =	are CRP Total rials 72 510 138 26 746 : 12.56, df	usual c Events 23 333 57 9 422	care Total 67 518 259 28 872	Weight M 16.3% 29.8% 19.5% 9.0% 74.5%	Risk Ratio - H, Random, 95% CI 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70] 1.20 [0.58, 2.47]	Risk Ratio M-H, Random, 95% CI
Study or Subgroup individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016 Subtotal (95% Cl) Total events Heterogeneity: Tau ² =	Point-of-ca Events andomised ta 27 227 36 10 300 \$0.10; Chi ² = ; Z = 0.19 (P	are CRP Total rials 72 510 138 26 746 : 12.56, df	usual c Events 23 333 57 9 422	care Total 67 518 259 28 872	Weight M 16.3% 29.8% 19.5% 9.0% 74.5%	Risk Ratio - H, Random, 95% CI 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70] 1.20 [0.58, 2.47]	Risk Ratio M-H, Random, 95% CI
5tudy or Subgroup individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect	Point-of-ca Events andomised ta 27 227 36 10 300 \$0.10; Chi ² = ; Z = 0.19 (P	are CRP Total rials 72 510 138 26 746 : 12.56, df	usual c Events 23 333 57 9 422 = 3 (P = 106	care Total 67 518 259 28 872	Weight M 16.3% 29.8% 19.5% 9.0% 74.5%	Risk Ratio - H, Random, 95% CI 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70] 1.20 [0.58, 2.47]	Risk Ratio M-H, Random, 95% Cl
D) Study or Subgroup individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect cluster rando Lemiengre 2014	Point-of-ca Events andomised tri 27 36 10 300 e 0.10; Chi² = z = 0.19 (P + mised trials 116 116 116	are CRP Total rials 72 510 138 26 746 • 12.56, df = 0.85) 455 455	usual o Events 23 333 57 9 422 = 3 (P =	care Total 67 518 259 28 872 • 0.006	<u>Weight M</u> 16.3% 29.8% 19.5% 9.0% 74.5% $;;$ $ ^2 = 76\%$ 25.5%	Risk Ratio -H, Random, 95% Cl 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70] 1.20 [0.58, 2.47] 0.97 [0.67, 1.39] 0.92 [0.73, 1.15]	Risk Ratio M-H, Random, 95% CI
Study or Subgroup individually r individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect cluster rando Lemiengre 2014 Subtotal (95% Cl) Total events	Point-of-ca Events andomised tri 27 36 10 300 e 0.10; Chi² = z = 0.19 (P + mised trials 116 116 116	are CRP Total rials 72 510 138 26 746 • 12.56, df = 0.85) 455 455	usual c Events 23 333 57 9 422 = 3 (P = 106	care Total 67 518 259 28 872 6 0.006 381 381	<u>Weight M</u> 16.3% 29.8% 19.5% 9.0% 74.5% $;;$ $ ^2 = 76\%$ 25.5%	Risk Ratio -H, Random, 95% Cl 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70] 1.20 [0.58, 2.47] 0.97 [0.67, 1.39] 0.92 [0.73, 1.15]	Risk Ratio M-H, Random, 95% Cl
D) Study or Subgroup individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect cluster rando Lemiengre 2014 Subtotal (95% Cl) Total events Heterogeneity: Not ag Test for overall effect	Point-of-ca Events andomised tri 27 36 10 300 e 0.10; Chi² = z = 0.19 (P + mised trials 116 116 116	are CRP Total rials 72 510 138 26 746 : 12.56, df = 0.85) 455 455 = 0.45)	usual c Events 23 333 57 9 422 = 3 (P = 106	care Total 67 518 259 28 872 6 0.006 381 381	Weight M 16.3% 29.8% 19.5% 9.0% 74.5%	Risk Ratio -H, Random, 95% Cl 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70] 1.20 [0.58, 2.47] 0.97 [0.67, 1.39] 0.97 [0.67, 1.39] 0.92 [0.73, 1.15] 0.92 [0.73, 1.15]	Risk Ratio M-H, Random, 95% Cl
D) Study or Subgroup individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect cluster rando Lemiengre 2014 Subtotal (95% CI) Total events Heterogeneity: Not ag Test for overall effect Total events Heterogeneity: Not ag Heterogeneity: Not ag Heterogeneity: Not ag Heterogeneity: Tau ² =	Point-of-ca Events andomised tu 27 227 36 10 300 c 0.10; Chi ² = Z = 0.19 (P mised trials 116 116 cplicable c Z = 0.76 (P 416 c 0.05; Chi ² =	are CRP Total rials 72 510 138 26 746 • 12.56, df = 0.85) 455 455 455 = 0.45) 1201 • 15.11, df	usual c Events 23 333 57 9 422 = 3 (P = 106 106	care Total 67 518 259 28 872 € 0.0066 381 381 1253	Weight M 16.3% 29.8% 19.5% 9.0% 74.5% 9.0% 25.5% 25.5% 100.0% 100.0%	Risk Ratio -H, Random, 95% Cl 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70] 1.20 [0.58, 2.47] 0.97 [0.67, 1.39] 0.97 [0.67, 1.39] 0.92 [0.73, 1.15] 0.92 [0.73, 1.15]	Risk Ratio M-H, Random, 95% CI
D) Study or Subgroup individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect cluster rando Lemiengre 2014 Subtotal (95% Cl) Total events Heterogeneity: Not ag Test for overall effect Total (95% Cl) Total events Heterogeneity: Tau ² = Total (95% Cl) Total events Heterogeneity: Tau ² = Total openeity: Tau ² = Total events Heterogeneity: Tau ² = Test for overall effect	Point-of-ca Events andomised tr 27 227 36 10 300 c 0.10; Chi ² = : Z = 0.19 (P mised trials 116 116 pplicable : Z = 0.76 (P 416 c 0.05; Chi ² = : Z = 0.52 (P	are CRP Total rials 72 510 138 26 746 = 12.56, df = 0.85) 455 455 455 = 0.45) 1201 = 15.11, df = 0.60)	usual c Events 23 333 57 9 422 = 3 (P = 106 106 106 528 = 4 (P =	care Total 67 518 259 28 872 € 0.0006 381 381 1253 € 0.004	Weight M 16.3% 29.8% 19.5% 9.0% 74.5% 3.0% 74.5% 3.0% 25.5% 25.5% 100.0% 3.0% $12 = 74\%$ 3.0%	Risk Ratio -H, Random, 95% Cl 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70] 1.20 [0.58, 2.47] 0.97 [0.67, 1.39] 0.97 [0.67, 1.39] 0.92 [0.73, 1.15] 0.92 [0.73, 1.15]	Risk Ratio M-H, Random, 95% CI
D) Study or Subgroup individually r Diederichsen 2008 Do 2016 Rebnord 2017 Van den Bruel 2016 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect cluster rando Lemiengre 2014 Subtotal (95% CI) Total events Heterogeneity: Not ag Test for overall effect Total events Heterogeneity: Not ag Heterogeneity: Not ag Heterogeneity: Not ag Heterogeneity: Tau ² =	Point-of-ca Events andomised tr 27 227 36 10 300 c 0.10; Chi ² = : Z = 0.19 (P mised trials 116 116 pplicable : Z = 0.76 (P 416 c 0.05; Chi ² = : Z = 0.52 (P	are CRP Total rials 72 510 138 26 746 = 12.56, df = 0.85) 455 455 455 = 0.45) 1201 = 15.11, df = 0.60)	usual c Events 23 333 57 9 422 = 3 (P = 106 106 106 528 = 4 (P =	care Total 67 518 259 28 872 € 0.0006 381 381 1253 € 0.004	Weight M 16.3% 29.8% 19.5% 9.0% 74.5% $3000000000000000000000000000000000000$	Risk Ratio -H, Random, 95% Cl 1.09 [0.70, 1.71] 0.69 [0.62, 0.78] 1.19 [0.82, 1.70] 1.20 [0.58, 2.47] 0.97 [0.67, 1.39] 0.97 [0.67, 1.39] 0.92 [0.73, 1.15] 0.92 [0.73, 1.15]	Risk Ratio M-H, Random, 95% CI

Supplementary file 5: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) RCTs, adults only; (b) RCTs, children only.

Supplementary file 6: Table: statistical heterogeneity: I-squared estimates for overall results and different subgroups based on meta-regression results for the effect of point-of-care CRP versus usual care on antibiotic prescribing at index consultation in RCTs.

Outcome	Comparing subgroup of RCTs	Overall heterogeneity I ² (%)	% between-study heterogeneity explained via meta- regression	% residual between-study heterogeneity
Antibiotic prescribing at index consultation	All patients	72%	/	/
	Adults versus children	63% (adults) versus 74% (children)	100%	0%
	CRP cutoff guidance versus no-guidance in adults	0% (guidance) versus 0% (no guidance)	100%	0%
	CRP cutoff guidance versus no-guidance in children	79% (guidance) versus 0% (no guidance)	85.6%	6.9%

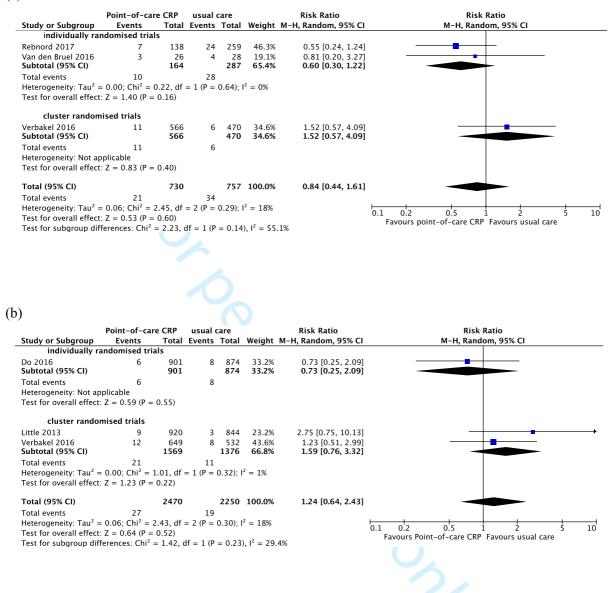
RCTs: randomised controlled trials, I²: I-squared



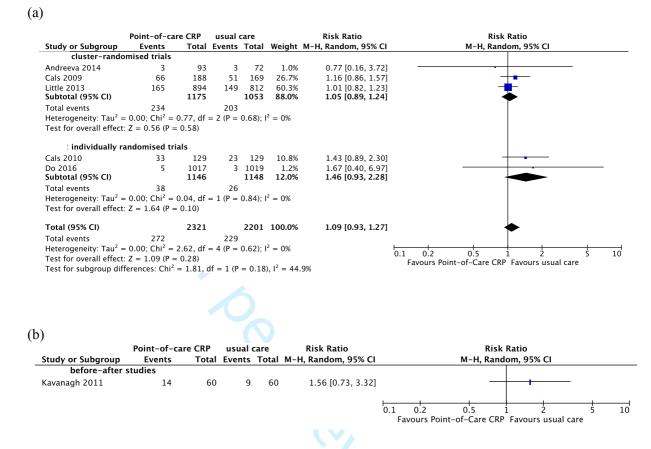
Supplementary file 7: Forest plot of comparison: point-of-care CRP versus usual care, outcome: (a) antibiotic prescribing within 28 days (all patients, RCTs); (b) antibiotic treatment for respiratory tract infection during follow-up (RCT); (c) antibiotic prescribing within 28 days (all patients, non-randomised study).

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(a)	
(a	.)	

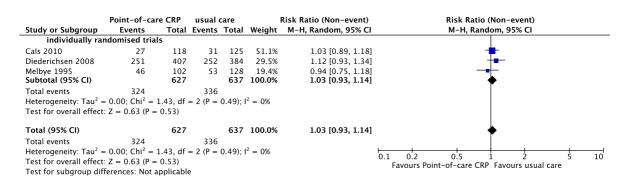


Supplementary file 8: Forest plot of comparison: point-of-care CRP versus usual care, outcome: (a) referral to hospital (RCTs); (b) hospital admission (RCTs).



Supplementary file 9: Forest plot of comparison: 1 POC CRP versus usual care, outcome: re-consultations within 28 days.: (a) all patients, RCTs; (b) all patients, non-randomised study.

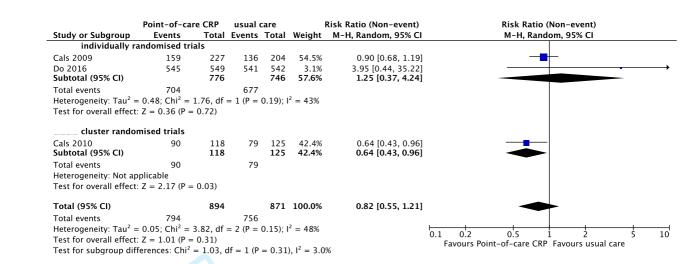
Supplementary file 10: Forest plots secondary outcomes (Figure a-j)



Supplementary file 10a: Forest plot of comparison: 1 POC CRP versus usual care, outcome: clinical recovery day 7 (all studies).

	Point-of-car	e CRP	usual o	are	1	Risk Ratio (Non-event)	Risk Ratio (Non-event)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
individually ra	ndomised trial	s					
Melbye 1995 Subtotal (95% CI)	71	98 98	82	121 121	56.1% 56.1%	0.85 [0.57, 1.29] 0.85 [0.57, 1.29]	
Total events	71		82				
Heterogeneity: Not a	pplicable						
Test for overall effect	t: Z = 0.75 (P =	0.46)					
cluster randon	nised trials						
Andreeva 2014	60	64	48	51	4.5%	1.06 [0.25, 4.53]	
Cals 2009	76	102	69	91	39.3%	1.05 [0.64, 1.73]	
Subtotal (95% CI)		166		142	43.9%	1.06 [0.66, 1.68]	
Total events	136		117				
Heterogeneity: Tau ² :	= 0.00; Chi ² = 0).00, df =	= 1 (P =	0.99); I	$^{2} = 0\%$		
Test for overall effect	t: $Z = 0.23 (P =$	0.82)					
Total (95% CI)		264		263	100.0%	0.94 [0.69, 1.28]	•
Total events	207		199				
Heterogeneity: Tau ² :	= 0.00; Chi ² = 0	.44, df =	= 2 (P =	0.80); I	$^{2} = 0\%$		0.1 0.2 0.5 1 2 5 10
Test for overall effect	t: $Z = 0.41 (P =$	0.68)					0.1 0.2 0.5 1 2 5 10 Favours Point-of-care CRP Favours usual care
Test for subgroup dif	fferences: Chi ² =	= 0.44, d	f = 1 (P	= 0.51), $I^2 = 0\%$		ravours rome-or-care cive Favours usual care

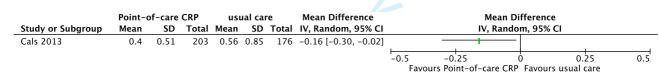
Supplementary file 10b: Forest plot of comparison: 1 POC CRP versus usual care, outcome: clinical recovery day 28 (all studies).



Supplementary file 10c: Forest plot of comparison: 1 POC CRP versus usual care, outcome: patient satisfaction (RCTs).

	Point-of-ca	re CRP	usual	care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M–H, Random, 95% CI
individually r	andomised tri	als					
Diederichsen 2008	152	342	161	331	70.5%	0.91 [0.78, 1.07]	
Melbye 1995 Subtotal (95% CI)	54	108 450	68	131 462	29.5% 100.0%		
Total events Heterogeneity: Tau ² = Test for overall effect			229 = 1 (P =	0.73);	² = 0%		
Total (95% CI)		450		462	100.0%	0.93 [0.81, 1.06]	•
Total events Heterogeneity: Tau ² = Test for overall effect Test for subgroup dif	z = 1.07 (P = 1.07)	0.28)		0.73);	² = 0%		0.1 0.2 0.5 1 2 5 10 Favours Point-of-care CRP Favours usual care

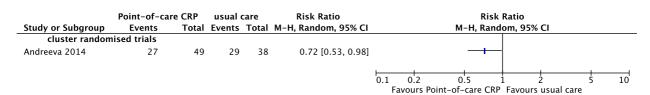
Supplementary file 10d: Forest plot of comparison: 1 POC CRP versus usual care, outcome: patient satisfaction (non-randomised study).



Supplementary file 10e: Forest plot of comparison: 1 POC CRP versus usual care, outcome: respiratory tract infection during follow-up. (RCT)

	Point-of-car	e CRP	usual	care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
individually ra	andomised tria	als					
Van den Bruel 2016 Subtotal (95% CI)	3	26 26		28 28	3.1% 3.1%		
Total events	3		1				
Heterogeneity: Not ap	plicable						
Test for overall effect	Z = 1.05 (P =	0.30)					
cluster rando	mised trials						
Verbakel 2016	53	524	39	437	96.9%	1.13 [0.76, 1.68]	
Subtotal (95% CI)		524		437	96.9%	1.13 [0.76, 1.68]	
Total events	53		39				
Heterogeneity: Not ap	plicable						
Test for overall effect	: Z = 0.62 (P =	0.53)					
Total (95% CI)		550		465	100.0%	1.17 [0.79, 1.72]	-
Total events	56		40				
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0	0.85, df	= 1 (P =	0.36);	$^{2} = 0\%$		
Test for overall effect	Z = 0.80 (P =	0.43)					0.1 0.2 0.5 1 2 5 10 Favours Point-of-care CRP Favours usual care
Test for subgroup diff	ferences: Chi ²	= 0.84,	df = 1 (P	= 0.36), $I^2 = 0\%$		ravours round of care ext Tavours usual care

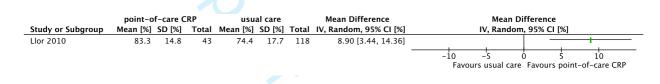
Supplementary file 10f: Forest plot of comparison: 1 POC CRP versus usual care, outcome: additional tests performed (RCTs).



Supplementary file 10g: Forest plot of comparison: 1 POC CRP versus usual care, outcome: referral for chest X-Ray (RCT).

Study or Subaroup	Point-of Mean [days]	-care CRP	Total		al care	Total	Mean Difference IV, Random, 95% CI [days]	Mean Differer IV. Random, 95% C	
	andomised trial		Total	wear [days]	50 [uays]	Total	TV, Kandolii, 55% Ci [days]	1V, Kalidolii, 55% C	i [uays]
Do 2016	5.33	2.23	1017	5.33	2.23	1019	0.00 [-0.19, 0.19]		
								-0.5 -0.25 0 Favours Point-of-care CRP Favor	0.25 0.5 urs usual care
0 1 4	61	101 T	-	. 1 .	c			ND 1	

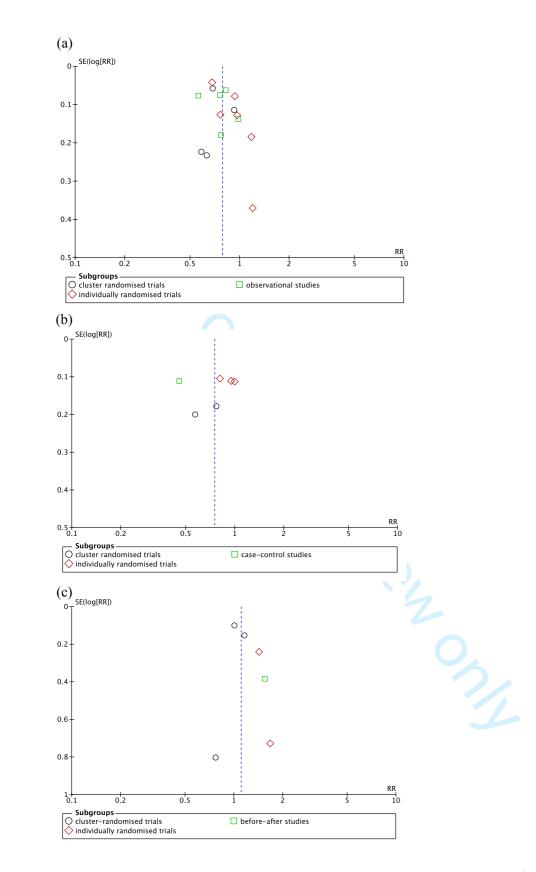
Supplementary file 10h: Forest plot of comparison: 1 POC CRP versus usual care, outcome: time to symptom resolution (RCT).



Supplementary file 10i: Forest plot of comparison: 1 POC CRP versus usual care, outcome: antibiotic treatment adherence (number of containers opened)(RCT).

	Point-of-care	usual care		Risk Ratio	Risk Ratio						
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% Cl		M-H, Random, 95% CI				
individually ra	ndomised trials	5									
Van den Bruel 2016	6	17	1	19	6.71 [0.90, 50.22]					+	
						L L.		+ +			
						0.1 0.2	0.5	1 2	5	10	
						0.1	0.5 Point-of-care CR	P Favours usi	al care		

Supplementary file 10j: Forest plot of comparison: 1 POC CRP versus usual care, outcome: antibiotic prescribing within 10 days. (RCT)



Supplementary file 11: Funnel plots to assess publication bias: Funnel plots (for the following outcomes: (a) antibiotic prescribing at index consultation, (b) antibiotic prescribing within 28 days, (c) re-consultation within 28 days)



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reporte on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criter participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	5 Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	9 State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	1 List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6-7

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PRISMA 2009 Checklist

Section/topic	# Checklist item				
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).			
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.			
RESULTS	<u> </u>				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8		
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.			
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11		
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-11		
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11		
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9		
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11		
DISCUSSION					
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12		
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12		
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14		
FUNDING					
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15		

41 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. 42 doi:10.1371/journal.pmed1000097 For more information, visit: www.prisma-statement.org.

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