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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-of-care 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

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-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.

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 non-randomised 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 I^2 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 non-randomised 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

Study	Country	Design	Device (Manufacturer)	Patient characteristics	Total sample size (CRP/no CRP)
1. randomised controlled trials					
a) patients presenting with signs of respiratory tract infection					
Andreeva 2014[41]	Russia	cluster	Afinion (Axis Shield)	adults with lower respiratory tract infection/acute cough for less than 28 days	179 (101/78)
Cals 2009[19]	the Netherlands	cluster	Nycocard II (Axis Shield)	adults with suspected lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	431 (227/204)
Cals 2010[20]	the Netherlands	individual	Nycocard II (Axis Shield)	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	258 (129/129)
Cals 2013[42]	the Netherlands	cluster	Nycocard II (Axis Shield)	adults with suspected lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	379 (203/176)
Diederichsen 2000[43]	Denmark	individual	Nycocard II (Axis Shield)	children and adults with respiratory tract infection	812 (414/398)
Do 2016[44]	Vietnam	individual	Nycocard II (Axis Shield)	children and adults with at least one focal and one systemic symptom of acute respiratory tract infection	2037 (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[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 presenting with signs of any acute 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)
2. non-randomised trials					
a) patients presenting with signs of respiratory tract infection					
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 presenting with signs of any acute 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)

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] re-consultation 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

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 (I^2 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 (I^2 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, I^2=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, I^2=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]

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 (I^2 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%CI 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%CI) when POC CRP was used with a RR of 1.24 (95%CI 0.64-2.43, I^2=18%).[9, 44]

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, I^2=0% in each subgroup, I^2 for subgroup differences

(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]

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 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.[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

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 www.icmje.org/coi_disclosure.pdf 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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DATA SHARING STATEMENT

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

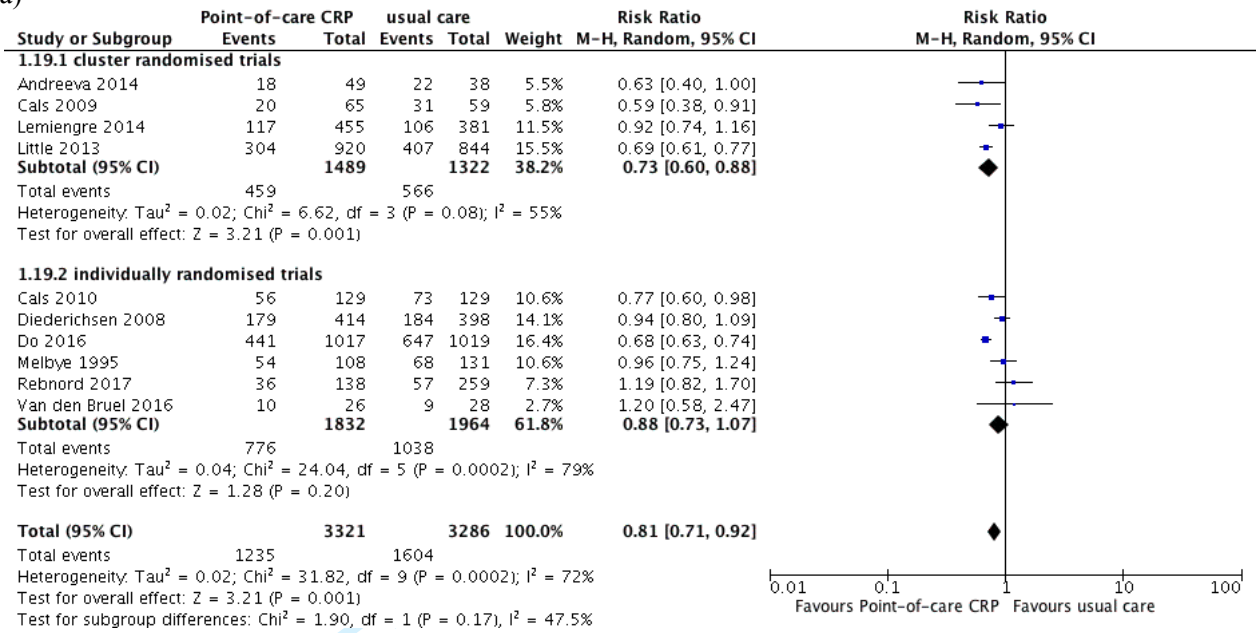
Supplementary file 7: point-of-care CRP versus usual care: referral and admission to hospital

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

(a)



(b)

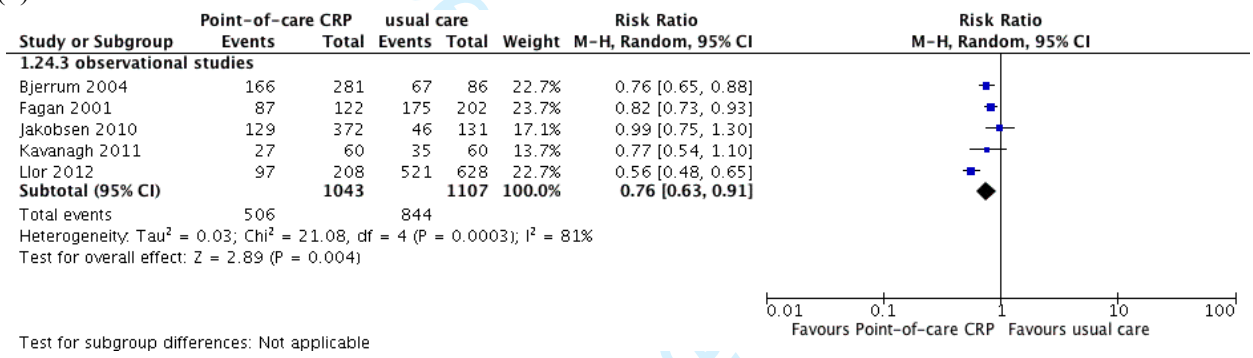
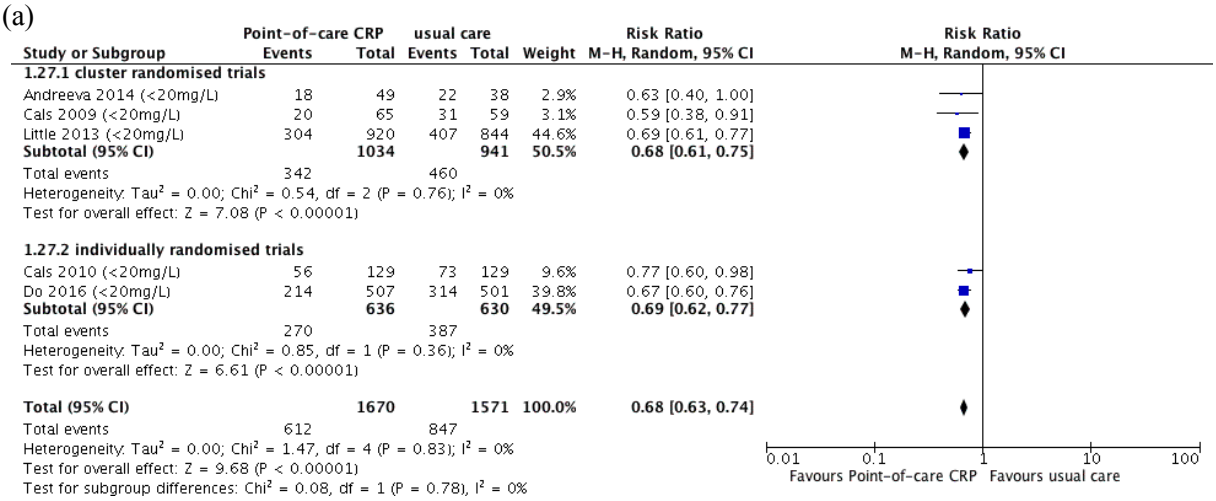


Figure 1: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) all patients, RCTs; (b) all patients, non-randomised studies.

(a)



(b)

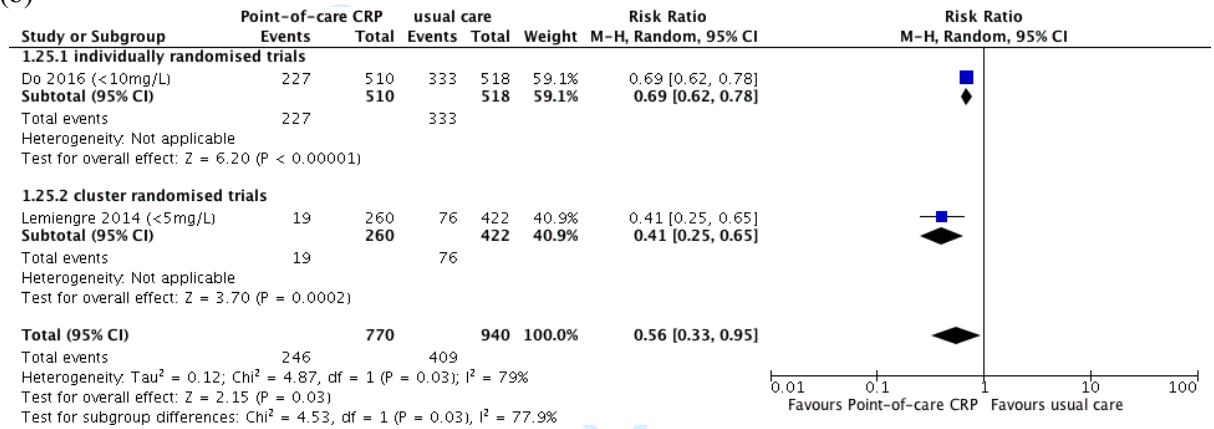


Figure 2: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) RCTs, adults only, if cut-off guidance applied; (b) RCTs, children only, if cut-off guidance applied.
CRP cut-off used to withhold antibiotic treatment between brackets.

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

Medline

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.
30	24 or 25 or 26 or 27 or 28 or 29
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

Embase

1	ambulatory care/
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.
22	((health* or medical) adj2 (facility or facilities)).ti,ab.
23	17 or 18 or 19 or 20 or 21 or 22
24	"point of care testing"/
25	(("point of care" or POC) adj5 (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") adj5 (test* or diagnos*)).ti,ab.
29	((rapid or bedside or bed-side or "near patient") and (test* or diagnos*)).ti.
30	24 or 25 or 26 or 27 or 28 or 29
31	(istat or i-stat or afinion).ti,ab.
32	30 or 31
33	16 and 32
34	23 and 32
35	34 not 33

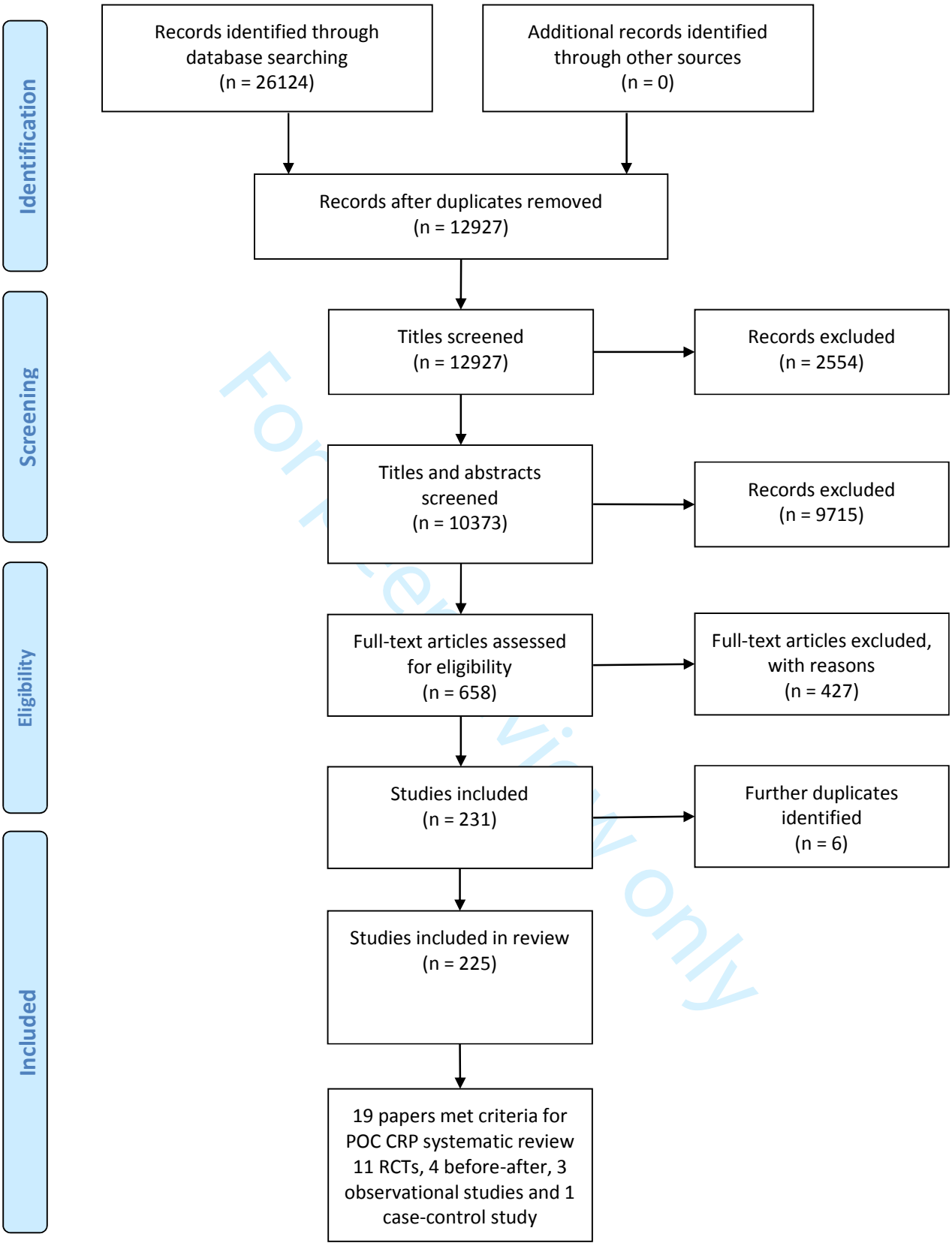
Cochrane

ID	Search
#1	MeSH descriptor: [Ambulatory Care] this term only
#2	MeSH descriptor: [Ambulatory Care Facilities] explode all trees
#3	MeSH descriptor: [General Practice] explode all trees
#4	MeSH descriptor: [General Practitioners] explode all trees
#5	MeSH descriptor: [Physicians, Family] explode all trees
#6	MeSH descriptor: [Physicians, Primary Care] explode all trees
#7	MeSH descriptor: [Primary Health Care] this term only
#8	MeSH descriptor: [Office Visits] explode all trees
#9	MeSH descriptor: [Emergency Service, Hospital] explode all trees
#10	MeSH descriptor: [Emergency Medical Services] this term only
#11	(ambulatory near/3 (care or setting? or facilit* or ward? or department? or service?)):ti,ab,kw (Word variations have been searched)
#12	((general or family) near/2 (practi* or physician? or doctor?)):ti,ab,kw (Word variations have been searched)
#13	(emergency near/3 (care or setting? or facilit* or ward? or department? or service?)):ti,ab,kw (Word variations have been searched)
#14	after hour? or afterhour? or "out of hour?" or ooh:ti,ab,kw (Word variations have been searched)
#15	clinic or clinics or visit or visits:ti,ab,kw (Word variations have been searched)
#16	((health* or medical) near/2 (center? or centre?)):ti,ab,kw (Word variations have been searched)
#17	MeSH descriptor: [Community Health Services] this term only
#18	MeSH descriptor: [Community Health Nursing] explode all trees
#19	MeSH descriptor: [Community Health Workers] explode all trees
#20	(community near/2 (health or health care or service? or program*)):ti,ab,kw
#21	(community near/2 (worker? or aide? or volunteer? or assistant? or visitor?)):ti,ab,kw
#22	((lay or volunteer) near/2 (health worker? or health aide? or health assistant?)):ti,ab,kw
#23	((health* or medical) near/2 (facility or facilities)):ti,ab,kw
#24	#17 or #18 or #19 or #20 or #21 or #22 or #23

#25	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#26	MeSH descriptor: [Point-of-Care Systems] explode all trees
#27	(("point of care" or POC) near/3 (test* or diagnos*)):ti,ab,kw (Word variations have been searched)
#28	(("point of care" or POC) and (test* or diagnos*)):ti (Word variations have been searched)
#29	poct:ti,ab,kw (Word variations have been searched)
#30	((rapid or bedside or bed-side or "near patient") near/3 (test* or diagnos*)):ti,ab,kw (Word variations have been searched)
#31	((rapid or bedside or bed-side or "near patient") and (test* or diagnos*)):ti (Word variations have been searched)
#32	istat or i-stat or afinion:ti,ab,kw (Word variations have been searched)
#33	#26 or #27 or #28 or #29 or #30 or #31 or #32
#34	#25 and #33
#35	#24 and #33
#36	#35 not #34

Web of Science Core Collection

# 3	#2 AND #1
# 2	TS=((("point of care" or POC) NEAR/3 (test* or diagnos*))) OR TI=((("point of care" or POC) and (test* or diagnos*))) OR TS=(poct) OR TS=(((rapid or bedside or bed-side or "near patient") 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))
# 1	TS=((ambulatory NEAR/3 (care or setting? or facilit* or ward? or department? or service?))) OR TS=(((general or family) NEAR/2 (practi* or physician? or doctor?))) OR TS=((primary care or 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 hour?" or ooh)) OR TS=(clinic OR clinics OR visit OR visits) OR TS=(((health* or medical) NEAR/2 (center? or centre?))) Indexes=SCI-EXPANDED Timespan=All years



Supplementary file 2: PRISMA flowchart[67]

Supplementary file 3: characteristics of included & excluded studies

Excluded studies: 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

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 testing 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 index 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**

				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 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 intervention failure), and prescriptions on the second visit in patients without an immediate 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 of 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% CI 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% CI 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% CI 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**

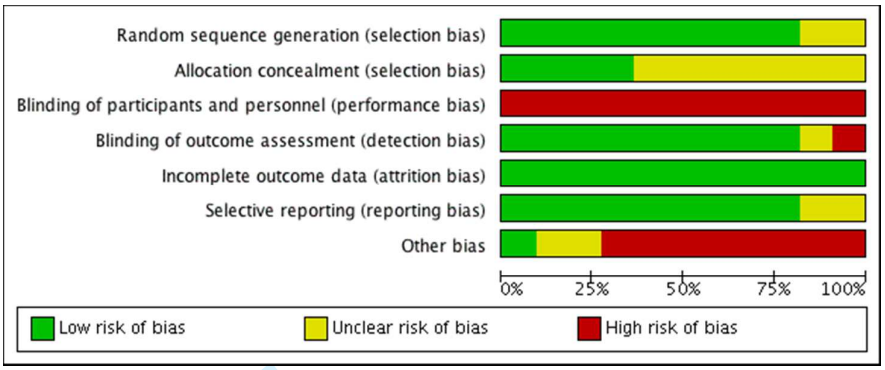
				received antibiotics. The difference from period 1 was not statistically significant (p = 0.34). There were no significant changes in which antibiotics were prescribed, except for a decrease in the use of other antibiotics from 21% to 7% in Tønsberg (p <0.05).
Hughes 2016	adults with symptoms of respiratory 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 GP 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' 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 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 % CI, 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 for rehydration). However, of the 80 children referred to hospital to rule out serious infection, 24 (30.7 %, 95 % CI, 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. 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 combined intervention was associated with the greatest reduction in prescribing rate (CRP risk ratio 0·53, 95%**

		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		**CI 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 good 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, CI 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**

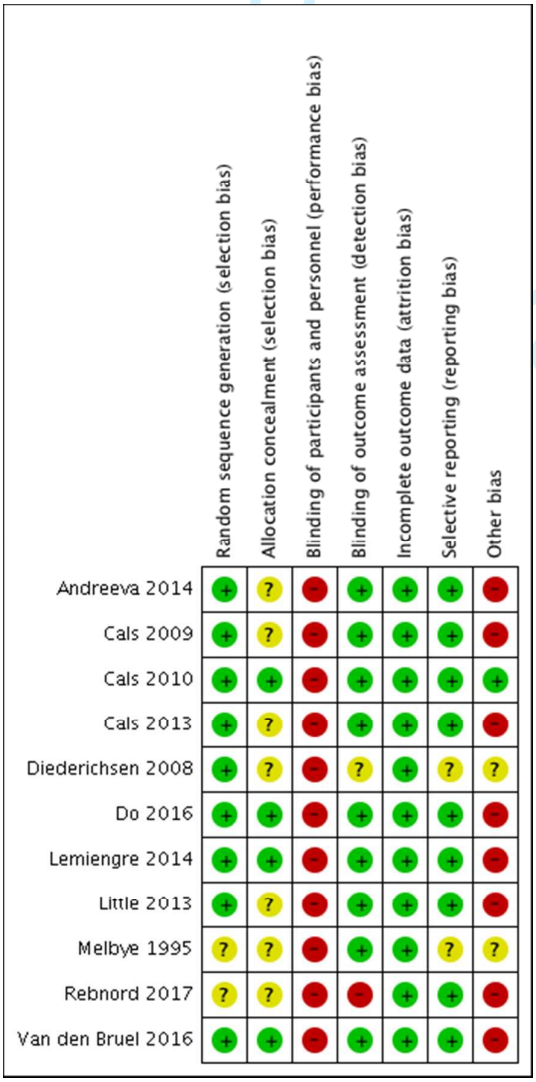
Rebnord 2017	children with fever and/or respiratory symptoms	none stated	usual care	antibiotic prescription and referral to hospital **In the group pretested with CRP, the antibiotic prescription rate was 26%, compared with 22% in the control group. In the group pretested with CRP, 5% were admitted to hospital, compared with 9% in the control group. These differences were not statistically significant**
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 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% CI 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 follow-up period, children randomised to CRP testing received significantly more antibiotic prescriptions (6 versus 1 patient). Five children were admit- ted to hospital, three with infection (pneumonia, appendicitis and a non-specified viral illness)**

Supplementary file 3b: characteristics of included studies

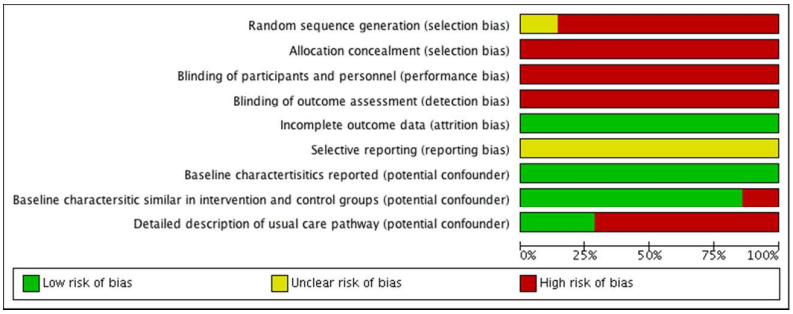
Supplementary file 4: Risk of bias assessment (QUADAS 2)



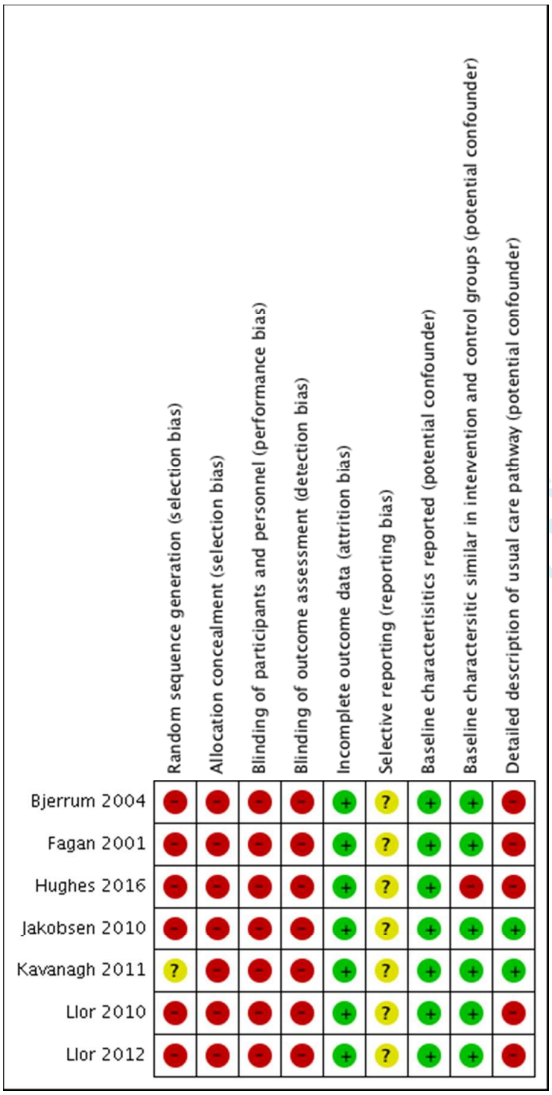
Supplementary file 4a: Risk of bias graph (RCTs): review authors' judgements about each risk of bias item presented as percentages across all included studies



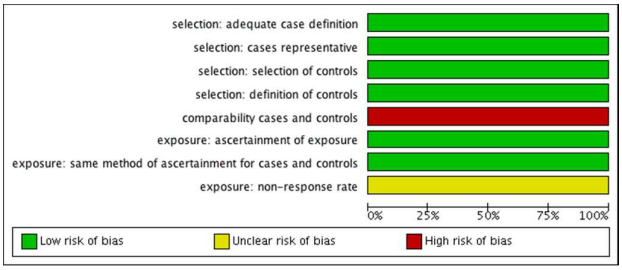
Supplementary file 4b: Risk of bias summary (RCTs): review authors' judgements about each risk of bias item for each included study.



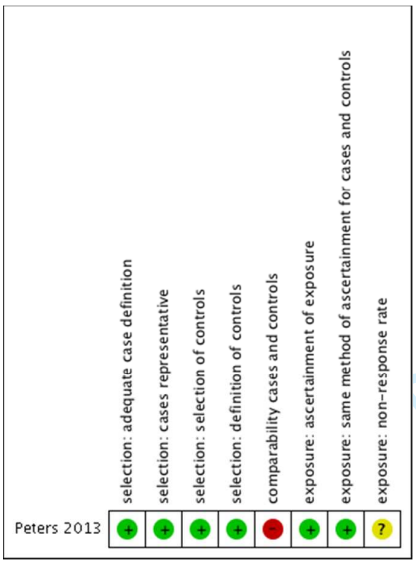
Supplementary file 4c: Risk of bias graph (non-randomised studies).



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

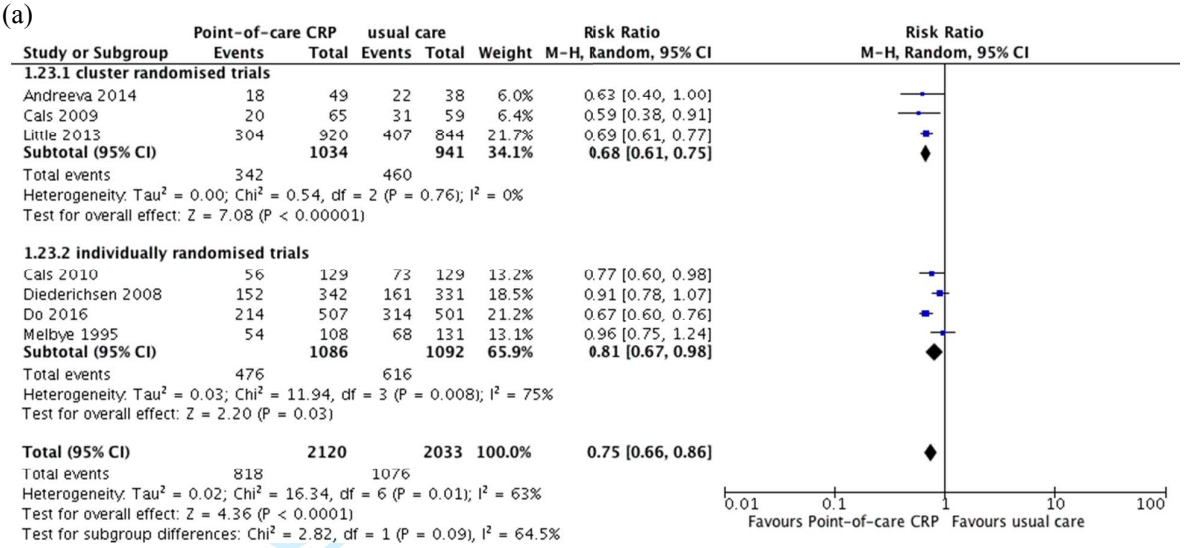


Supplementary file 4e: Risk of bias graph (case-control studies).

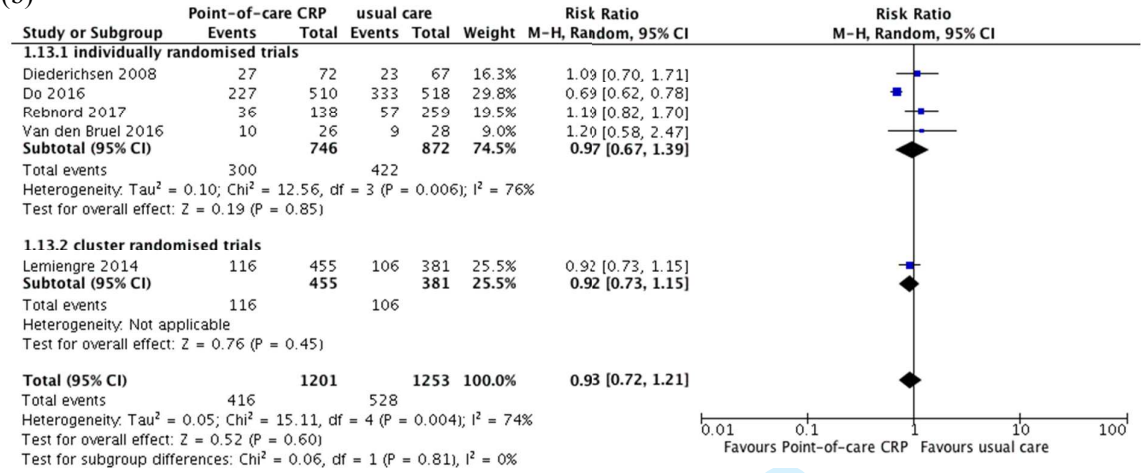


Supplementary file 4f: Risk of bias summary (case-control studies).

(a)

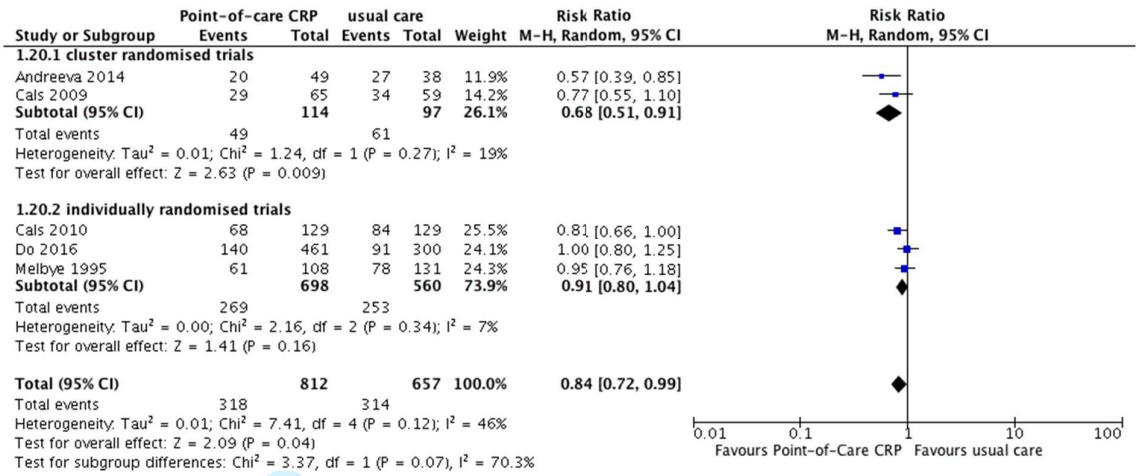


(b)

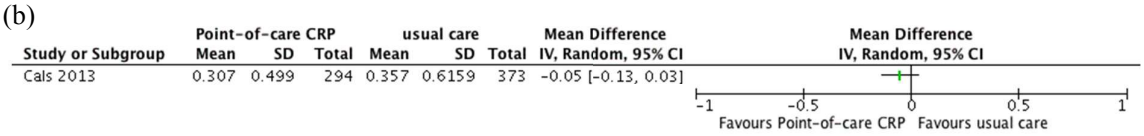


Supplementary file 5: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) RCTs, adults only; (b) RCTs, children only.

(a)



(b)



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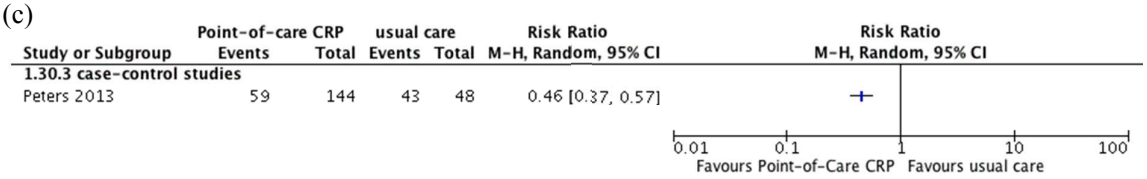
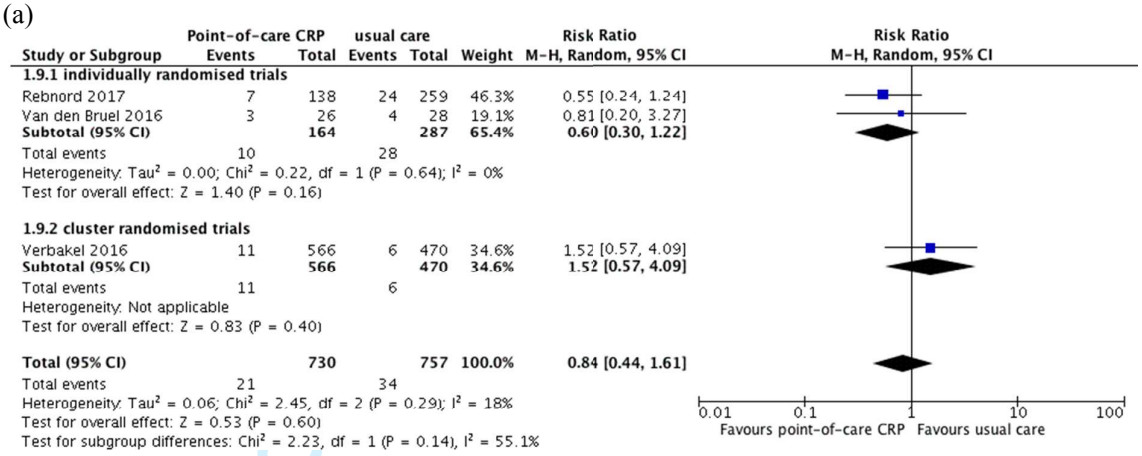
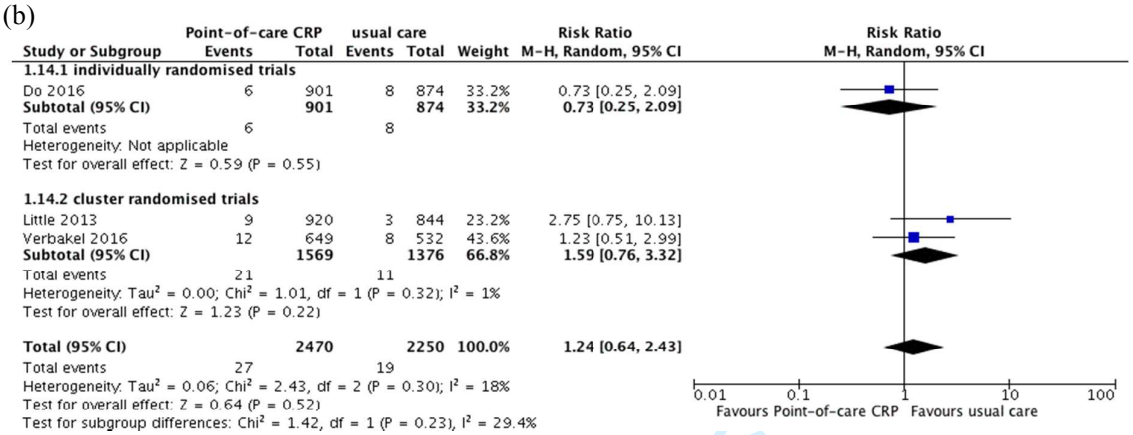


Supplementary file 6: Forest plot of comparison: point-of-care CRP versus usual care, outcome: (a) antibiotic prescribing within 28 days (all patients, RCTs); (b) antibiotic treatment for respiratory tract infection during follow-up (RCT); (c) antibiotic prescribing within 28 days (all patients, non-randomised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

(a)

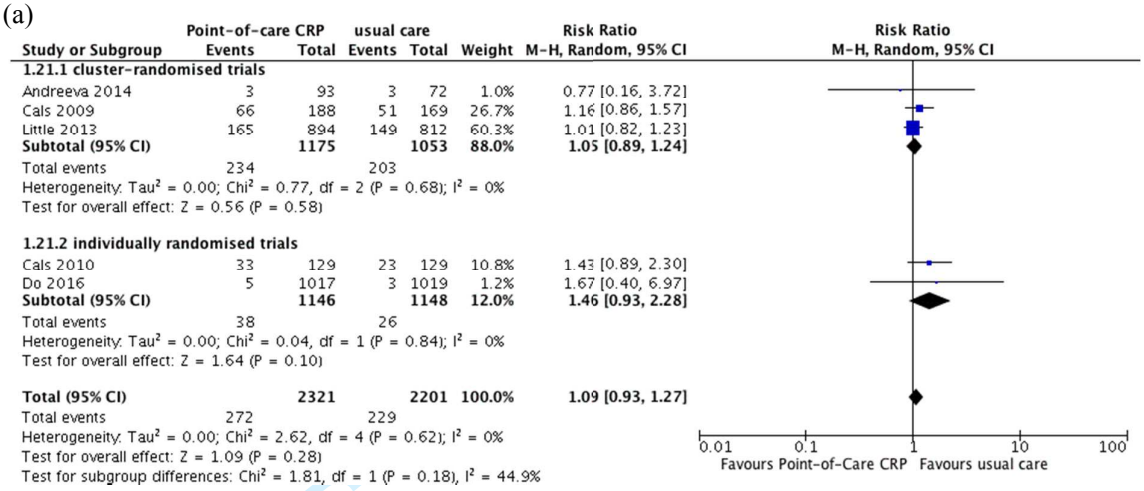


(b)

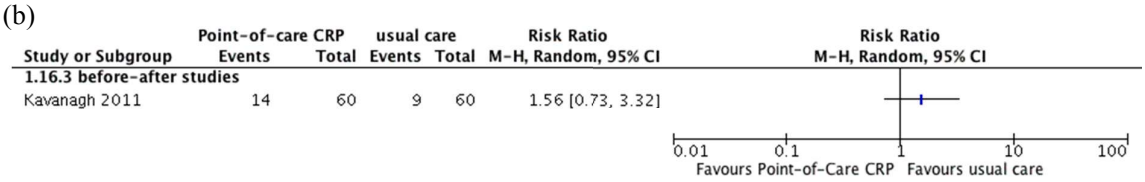


Supplementary file 7: Forest plot of comparison: point-of-care CRP versus usual care, outcome: (a) referral to hospital (RCTs); (b) hospital admission (RCTs).

(a)

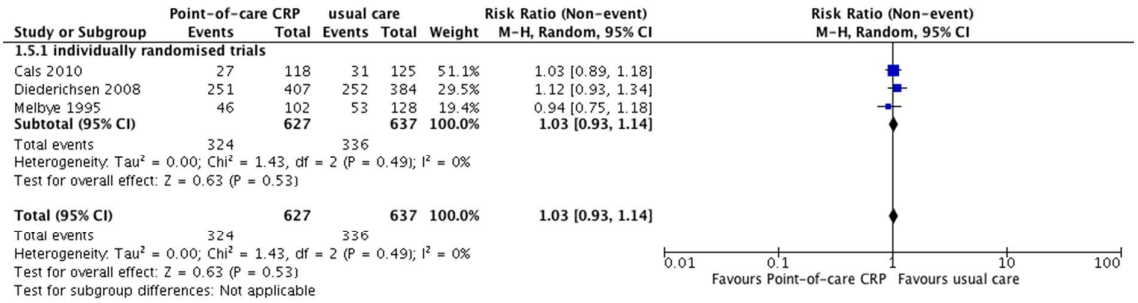


(b)

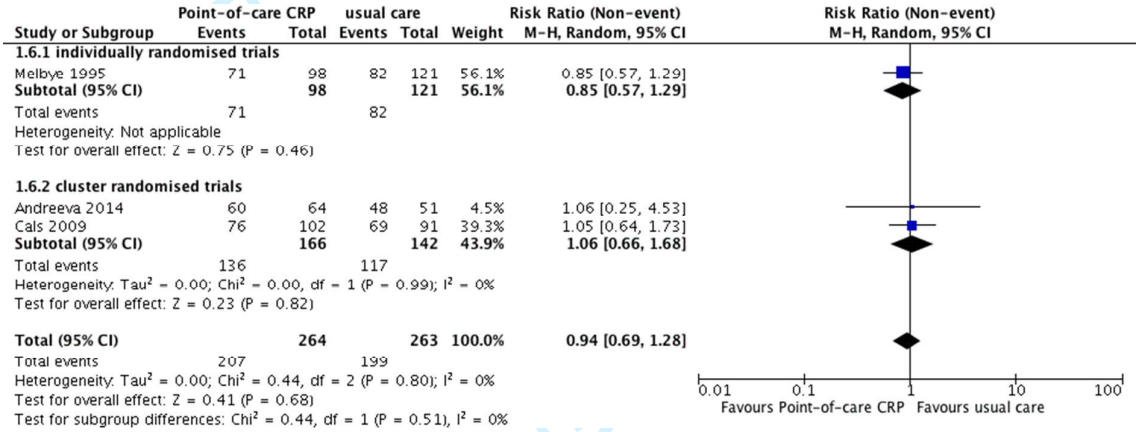


Supplementary file 8: Forest plot of comparison: 1 POC CRP versus usual care, outcome: re-consultations within 28 days.: (a) all patients, RCTs; (b) all patients, non-randomised study.

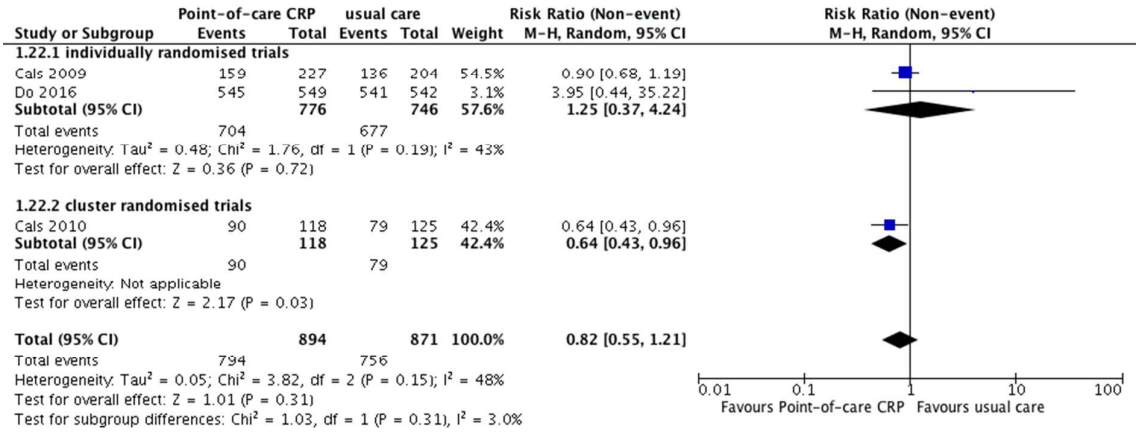
Supplementary file 9: Forest plots secondary outcomes (Figure a-j)



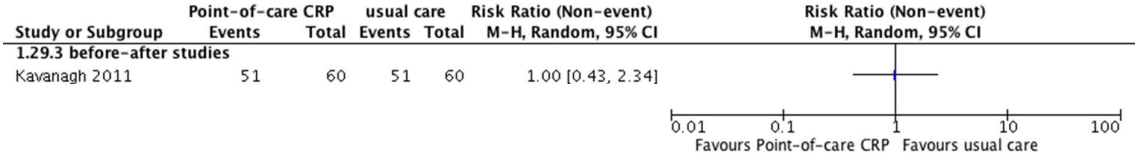
Supplementary file 9a: Forest plot of comparison: 1 POC CRP versus usual care, outcome: clinical recovery day 7 (all studies).



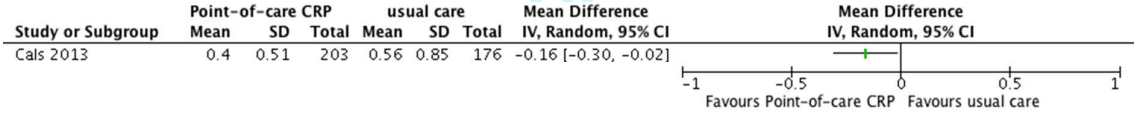
Supplementary file 9b: Forest plot of comparison: 1 POC CRP versus usual care, outcome: clinical recovery day 28 (all studies).



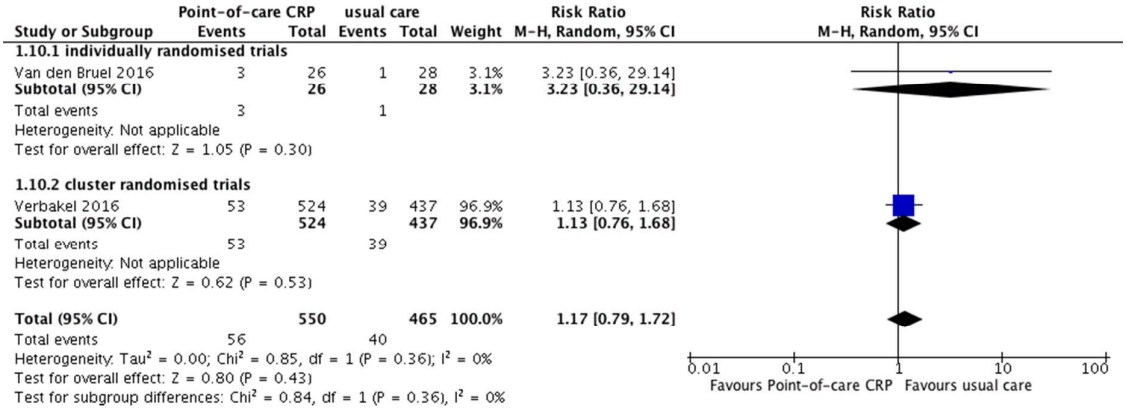
Supplementary file 9c: Forest plot of comparison: 1 POC CRP versus usual care, outcome: patient satisfaction (RCTs).



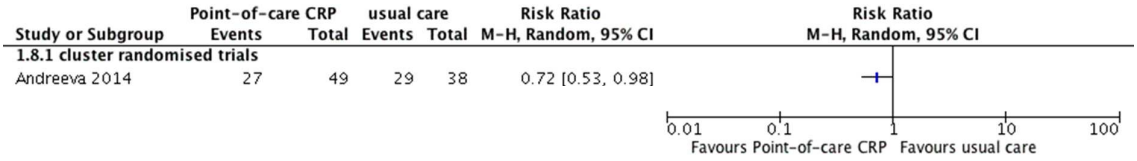
Supplementary file 9d: Forest plot of comparison: 1 POC CRP versus usual care, outcome: patient satisfaction (non-randomised study).



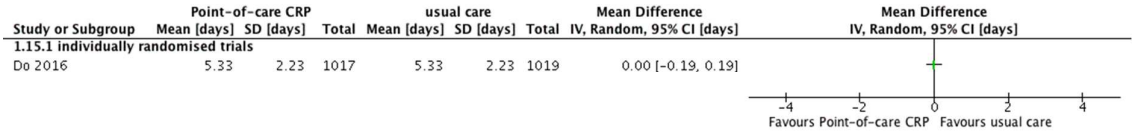
Supplementary file 9e: Forest plot of comparison: 1 POC CRP versus usual care, outcome: respiratory tract infection during follow-up. (RCT)



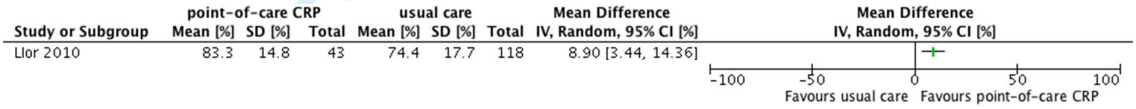
Supplementary file 9f: Forest plot of comparison: 1 POC CRP versus usual care, outcome: additional tests performed (RCTs).



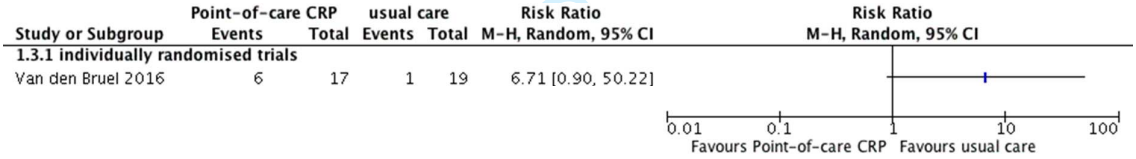
Supplementary file 9g: Forest plot of comparison: 1 POC CRP versus usual care, outcome: referral for chest X-Ray (RCT).



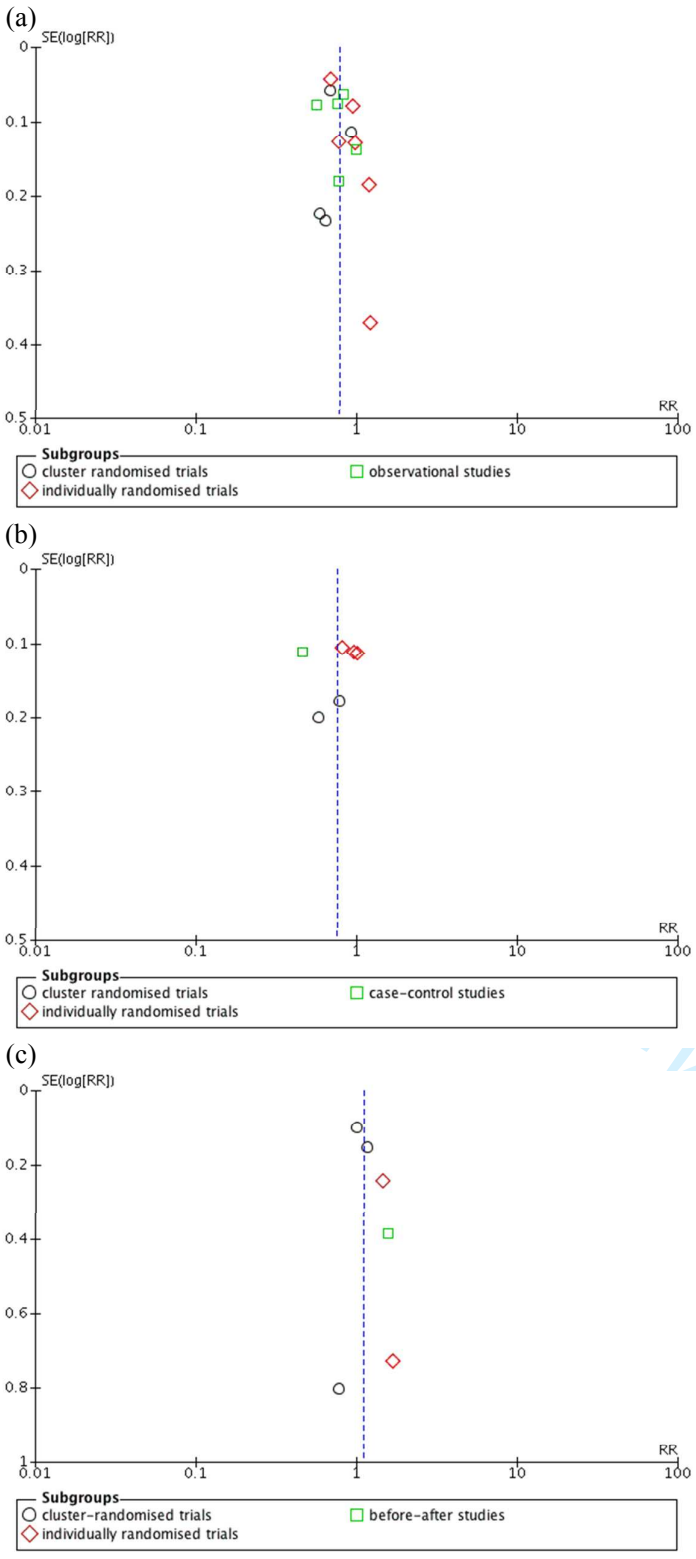
Supplementary file 9h: Forest plot of comparison: 1 POC CRP versus usual care, outcome: time to symptom resolution (RCT).



Supplementary file 9i: Forest plot of comparison: 1 POC CRP versus usual care, outcome: antibiotic treatment adherence (number of containers opened)(RCT).



Supplementary file 9j: Forest plot of comparison: 1 POC CRP versus usual care, outcome: antibiotic prescribing within 10 days. (RCT)



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)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported 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 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

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

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. doi:10.1371/journal.pmed1000097

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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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Keywords:	point-of-care testing, C-reactive protein, antibiotic prescribing rate, PRIMARY CARE, diagnostics, additional testing

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-of-care 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 (I^2 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, 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

- 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

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.

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 non-randomised 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 random-effects models were used for mean difference estimates. Study-to-study heterogeneity was assessed using the I^2 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 non-randomised 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 size (CRP/no CRP)
1. randomised controlled trials					
a) patients presenting with signs of respiratory tract infection					
Andreeva 2014[42]	Russia	cluster	Afinion (Axis Shield)	adults with lower respiratory tract infection/acute cough for less than 28 days	179 (101/78)
Cals 2009[19]	the Netherlands	cluster	Nycocard II (Axis Shield)	adults with suspected lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	431 (227/204)
Cals 2010[20]	the Netherlands	individual	Nycocard II (Axis Shield)	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	258 (129/129)
Cals 2013[43]	the Netherlands	cluster	Nycocard II (Axis Shield)	adults with suspected lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign)	379 (203/176)
Diederichsen 2000[44]	Denmark	individual	Nycocard II (Axis Shield)	children and adults with respiratory tract infection	812 (414/398)
Do 2016[45]	Vietnam	individual	Nycocard II (Axis Shield)	children and adults with at least one focal and one systemic symptom of acute respiratory tract infection	2037 (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 signs of any acute 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)
2. non-randomised trials					
a) patients presenting with signs of respiratory tract infection					
Bjerrum 2004[50]	Denmark	cohort	not specified	children and adults with acute sinusitis, acute tonsillitis, and acute otitis	367 (281/86)
Fagan 2001[51]	Norway	cohort	not specified	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 signs of any acute illness					
Jakobsen 2010[58]	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)

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] re-consultation 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 (I^2 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 (I^2 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, I^2=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, I^2=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, 42, 45] 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**).[44, 46]

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),[45, 47] 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%).[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%CI -28.0 to -14.8%).[52]

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 (I^2 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%CI 0.44-1.61) with low heterogeneity (I^2 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%CI 0.64-2.43, I^2=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, I^2=0% in each subgroup, I^2 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)**

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.[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 (registered by the GP)	[43]	-16%	-30% to -2%	NA
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)**

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.[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

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 prescribing 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

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 www.icmje.org/coi_disclosure.pdf 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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DATA SHARING STATEMENT

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

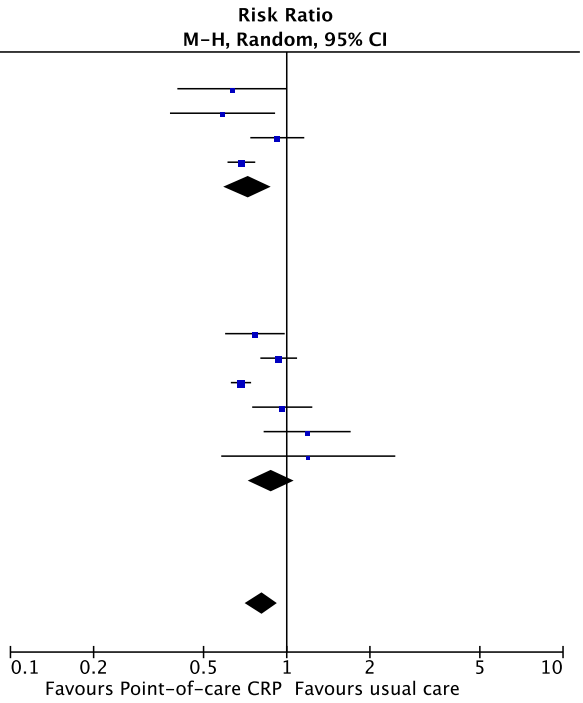
Supplementary file 8: point-of-care CRP versus usual care: re-consultation within 28 days

Supplementary file 9: forest plots of secondary outcomes

Supplementary file 10: funnel plots to assess publication bias

(a)

Study or Subgroup	Point-of-care CRP Events	Total	usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
cluster randomised trials						
Andreeva 2014	18	49	22	38	5.5%	0.63 [0.40, 1.00]
Cals 2009	20	65	31	59	5.8%	0.59 [0.38, 0.91]
Lemiengre 2014	117	455	106	381	11.5%	0.92 [0.74, 1.16]
Little 2013	304	920	407	844	15.5%	0.69 [0.61, 0.77]
Subtotal (95% CI)		**1489**		**1322**	**38.2%**	**0.73 [0.60, 0.88]**
Total events	459		566			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.62$, df = 3 (P = 0.08); $I^2 = 55\%$						
Test for overall effect: Z = 3.21 (P = 0.001)						
individually randomised trials						
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]
Do 2016	441	1017	647	1019	16.4%	0.68 [0.63, 0.74]
Melbye 1995	54	108	68	131	10.6%	0.96 [0.75, 1.24]
Rebnord 2017	36	138	57	259	7.3%	1.19 [0.82, 1.70]
Van den Bruel 2016	10	26	9	28	2.7%	1.20 [0.58, 2.47]
Subtotal (95% CI)		**1832**		**1964**	**61.8%**	**0.88 [0.73, 1.07]**
Total events	776		1038			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 24.04$, df = 5 (P = 0.0002); $I^2 = 79\%$						
Test for overall effect: Z = 1.28 (P = 0.20)						
Total (95% CI)		**3321**		**3286**	**100.0%**	**0.81 [0.71, 0.92]**
Total events	1235		1604			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 31.82$, df = 9 (P = 0.0002); $I^2 = 72\%$						
Test for overall effect: Z = 3.21 (P = 0.001)						
Test for subgroup differences: $Chi^2 = 1.90$, df = 1 (P = 0.17), $I^2 = 47.5\%$						



(b)

Study or Subgroup	Point-of-care CRP Events	Total	usual care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
observational studies						
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]
Jakobsen 2010	129	372	46	131	17.1%	0.99 [0.75, 1.30]
Kavanagh 2011	27	60	35	60	13.7%	0.77 [0.54, 1.10]
Llor 2012	97	208	521	628	22.7%	0.56 [0.48, 0.65]
Subtotal (95% CI)		**1043**		**1107**	**100.0%**	**0.76 [0.63, 0.91]**
Total events	506		844			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 21.08$, df = 4 (P = 0.0003); $I^2 = 81\%$						
Test for overall effect: Z = 2.89 (P = 0.004)						
Test for subgroup differences: Not applicable						

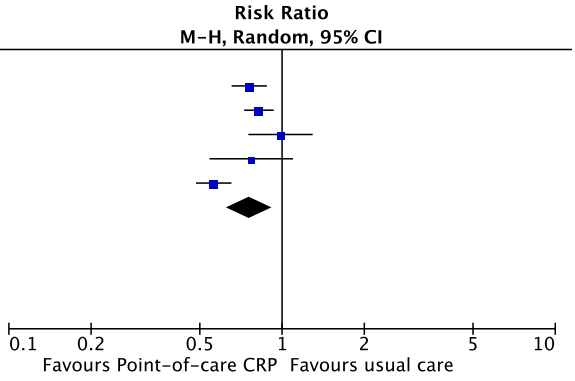
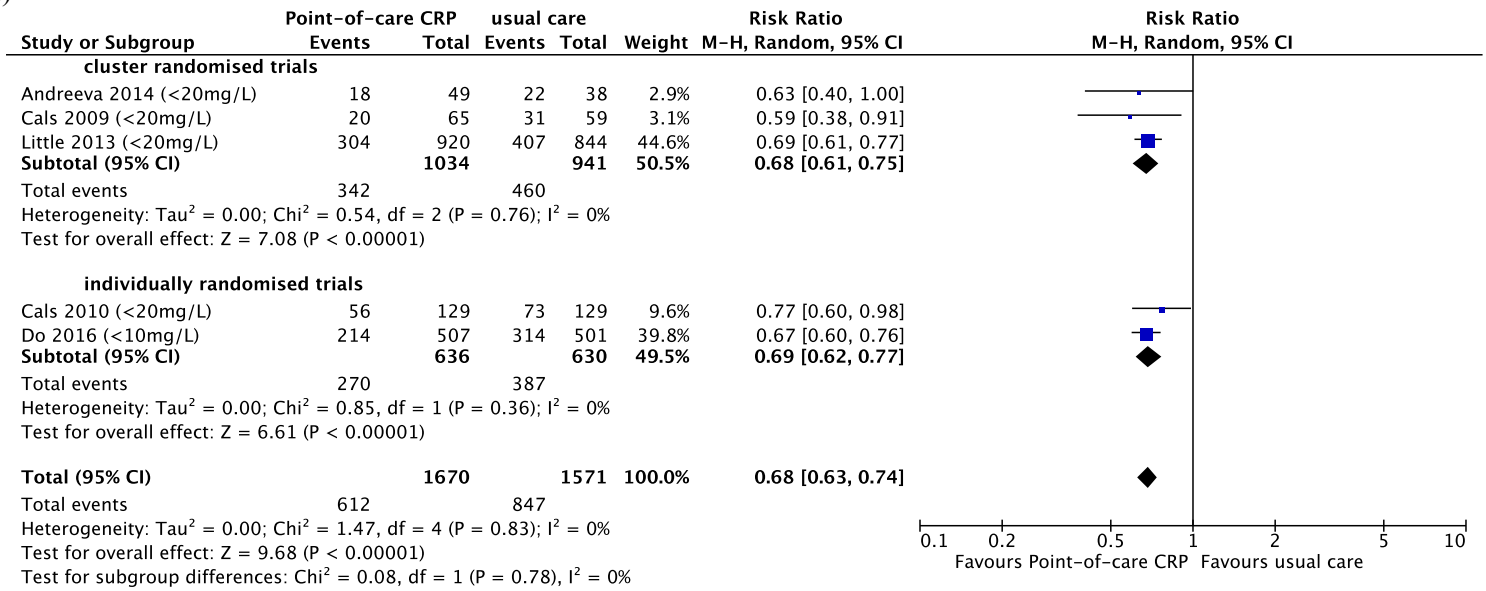


Figure 1: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) all patients, RCTs; (b) all patients, non-randomised studies.

(a)



(b)

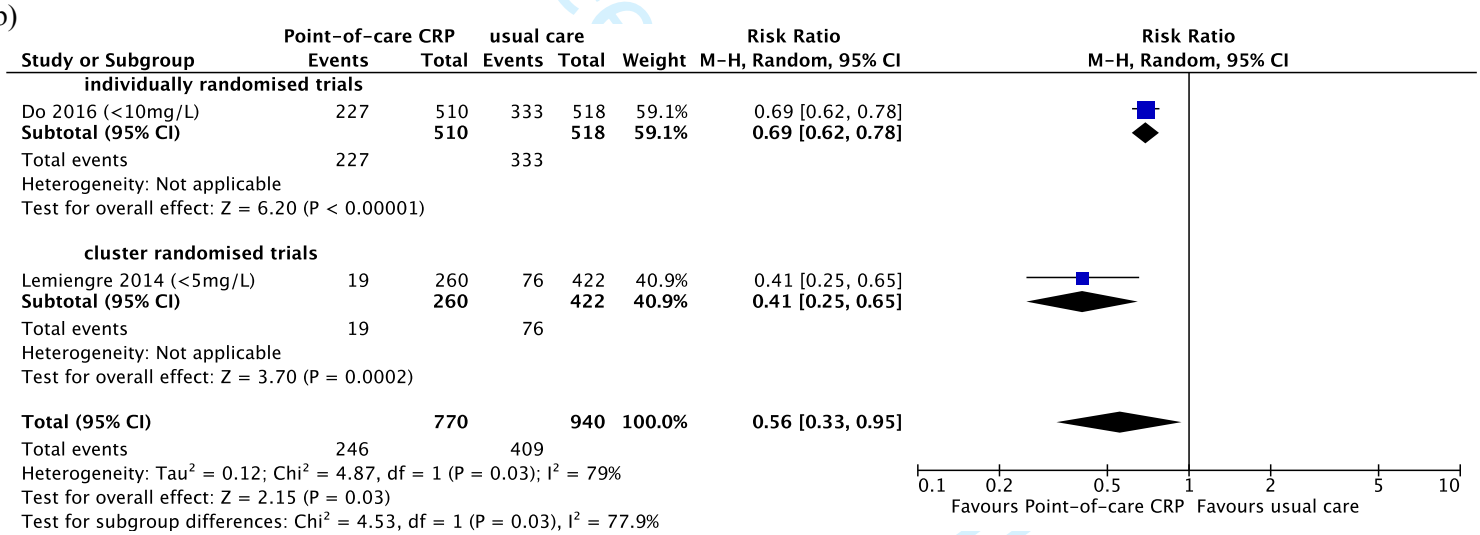


Figure 2: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) RCTs, adults only, if cut-off guidance applied; (b) RCTs, children only, if cut-off guidance applied.
CRP cut-off used to withhold antibiotic treatment between brackets.

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

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

Supplementary file 1: Search strategy

Medline

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.
30	24 or 25 or 26 or 27 or 28 or 29
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

Embase

1	ambulatory care/
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.
22	((health* or medical) adj2 (facility or facilities)).ti,ab.
23	17 or 18 or 19 or 20 or 21 or 22
24	"point of care testing"/
25	(("point of care" or POC) adj5 (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") adj5 (test* or diagnos*)).ti,ab.
29	((rapid or bedside or bed-side or "near patient") and (test* or diagnos*)).ti.
30	24 or 25 or 26 or 27 or 28 or 29
31	(istat or i-stat or afinion).ti,ab.
32	30 or 31
33	16 and 32
34	23 and 32
35	34 not 33

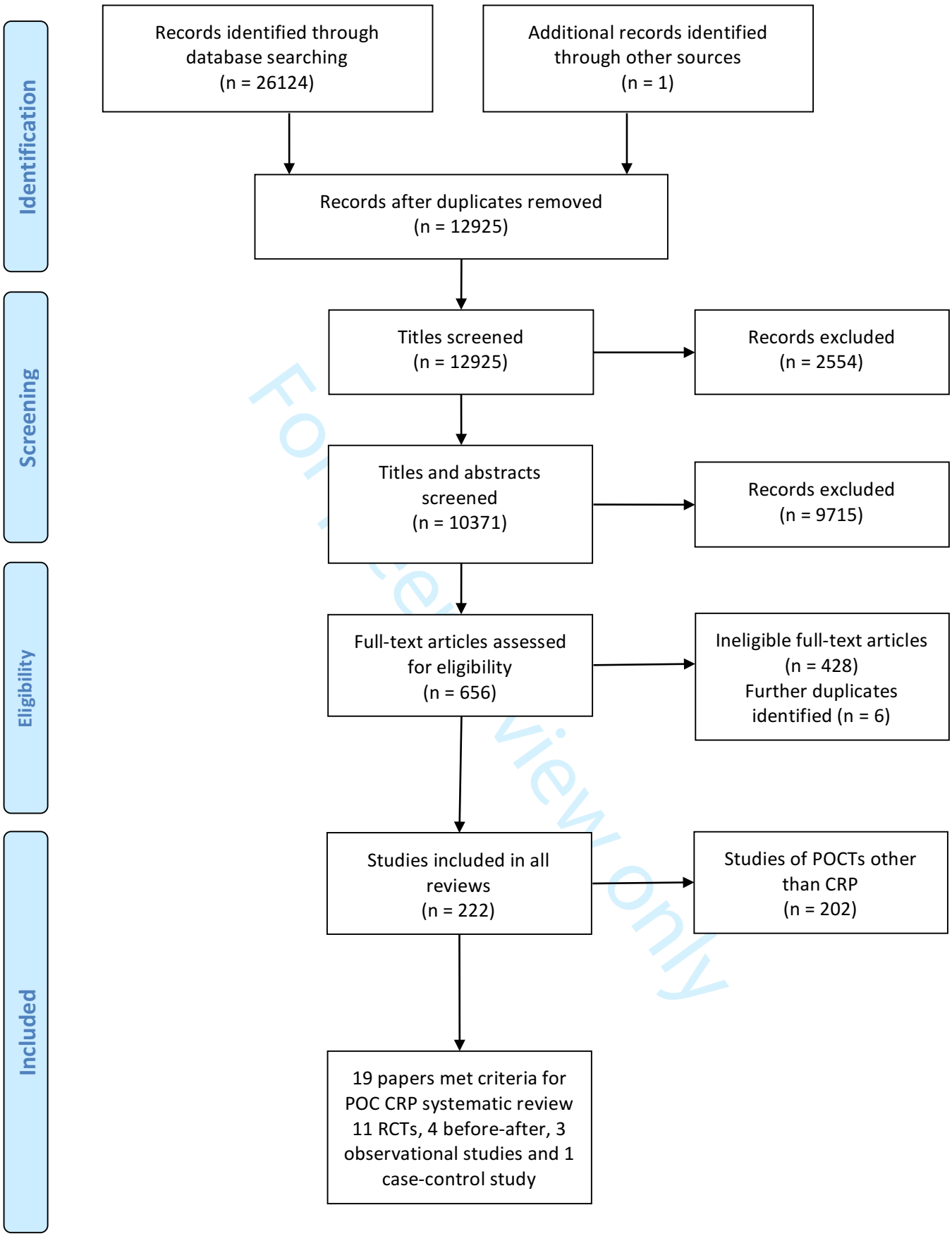
Cochrane

ID	Search
#1	MeSH descriptor: [Ambulatory Care] this term only
#2	MeSH descriptor: [Ambulatory Care Facilities] explode all trees
#3	MeSH descriptor: [General Practice] explode all trees
#4	MeSH descriptor: [General Practitioners] explode all trees
#5	MeSH descriptor: [Physicians, Family] explode all trees
#6	MeSH descriptor: [Physicians, Primary Care] explode all trees
#7	MeSH descriptor: [Primary Health Care] this term only
#8	MeSH descriptor: [Office Visits] explode all trees
#9	MeSH descriptor: [Emergency Service, Hospital] explode all trees
#10	MeSH descriptor: [Emergency Medical Services] this term only
#11	(ambulatory near/3 (care or setting? or facilit* or ward? or department? or service?)):ti,ab,kw (Word variations have been searched)
#12	((general or family) near/2 (practi* or physician? or doctor?)):ti,ab,kw (Word variations have been searched)
#13	(emergency near/3 (care or setting? or facilit* or ward? or department? or service?)):ti,ab,kw (Word variations have been searched)
#14	after hour? or afterhour? or "out of hour?" or ooh:ti,ab,kw (Word variations have been searched)
#15	clinic or clinics or visit or visits:ti,ab,kw (Word variations have been searched)
#16	((health* or medical) near/2 (center? or centre?)):ti,ab,kw (Word variations have been searched)
#17	MeSH descriptor: [Community Health Services] this term only
#18	MeSH descriptor: [Community Health Nursing] explode all trees
#19	MeSH descriptor: [Community Health Workers] explode all trees
#20	(community near/2 (health or health care or service? or program*)):ti,ab,kw
#21	(community near/2 (worker? or aide? or volunteer? or assistant? or visitor?)):ti,ab,kw
#22	((lay or volunteer) near/2 (health worker? or health aide? or health assistant?)):ti,ab,kw
#23	((health* or medical) near/2 (facility or facilities)):ti,ab,kw
#24	#17 or #18 or #19 or #20 or #21 or #22 or #23

#25	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#24	MeSH descriptor: [Point-of-Care Systems] explode all trees
#23	(("point of care" or POC) near/3 (test* or diagnos*)):ti,ab,kw (Word variations have been searched)
#22	(("point of care" or POC) and (test* or diagnos*)):ti (Word variations have been searched)
#21	poct:ti,ab,kw (Word variations have been searched)
#20	((rapid or bedside or bed-side or "near patient") near/3 (test* or diagnos*)):ti,ab,kw (Word variations have been searched)
#19	((rapid or bedside or bed-side or "near patient") and (test* or diagnos*)):ti (Word variations have been searched)
#18	istat or i-stat or afinion:ti,ab,kw (Word variations have been searched)
#17	#26 or #27 or #28 or #29 or #30 or #31 or #32
#16	#25 and #33
#15	#24 and #33
#14	#35 not #34

Web of Science Core Collection

# 3	#2 AND #1
# 2	TS=((("point of care" or POC) NEAR/3 (test* or diagnos*))) OR TI=((("point of care" or POC) and (test* or diagnos*))) OR TS=(poct) OR TS=(((rapid or bedside or bed-side or "near patient") 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))
# 1	TS=((ambulatory NEAR/3 (care or setting? or facilit* or ward? or department? or service?))) OR TS=(((general or family) NEAR/2 (practi* or physician? or doctor?))) OR TS=((primary care or 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 hour?" or ooh)) OR TS=(clinic OR clinics OR visit OR visits) OR TS=(((health* or medical) NEAR/2 (center? or centre?))) Indexes=SCI-EXPANDED Timespan=All years



Supplementary file 2: PRISMA flowchart[67]

Supplementary file 3: characteristics of included & excluded studies

Excluded studies: 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

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 testing was 59% (95%CI=56 to 62) compared with78%(95%CI=73 to 82) 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 index consultation (relative risk [RR] = 0.77; 95% confidence interval [CI], 0.56-0.98). This difference remained significant during follow-up (52.7% vs 65.1%; RR=0.81; 95% CI, 0.62-0.99). Delayed prescriptions in the CRP-**

				assisted group were filled only in a minority of cases (23% vs 22% in control group, P <.001). Recovery was 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 training 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 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 intervention failure), and prescriptions on the second visit in patients without an immediate 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 of re-consultations, 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% CI 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% CI 68–96). 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% CI 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. Doxycycline 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**

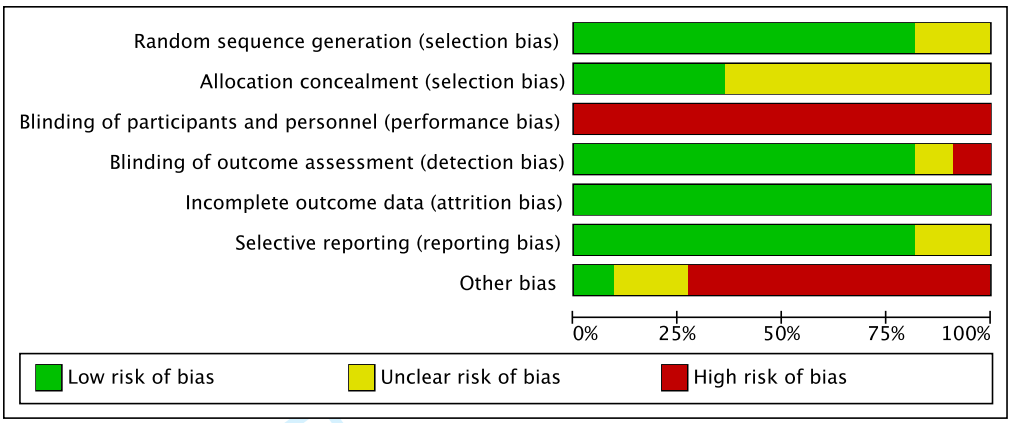
				prescribing from period 1 was statically significant (p <0.001). In Tønsberg, 74% of patients in period 2 received antibiotics. The difference from period 1 was not statistically significant (p = 0.34). There were no significant changes in which antibiotics were prescribed, except for a decrease in the 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 GP 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 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 % CI, 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 for rehydration). However, of the 80 children referred to hospital to rule out serious infection, 24 (30.7 %, 95 % CI, 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 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. 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**

		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 in prescribing rate (CRP risk ratio 0·53, 95% CI 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 only significant among physicians assigned to FIG. In comparison with the control group, the OR for antibiotic 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 good 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, CI 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	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,**

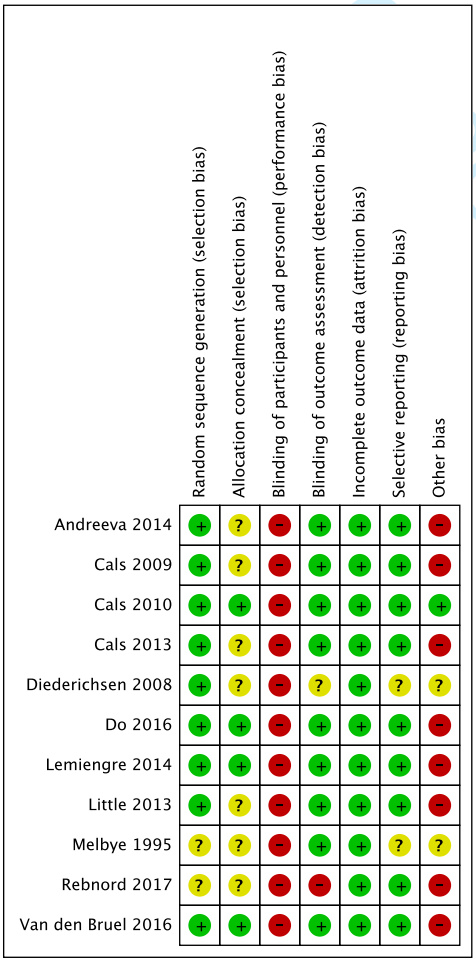
	respiratory tract infection			**compared with 59 out of the 144 patients (41%) in the case group (OR = 12.0; 95% CI = 4.1–35.3). There were no significant differences between the case and control groups regarding changes in antibiotic prescriptions during follow-up**
Rebnord 2017	children with fever and/or respiratory symptoms	none stated	usual care	antibiotic prescription and referral to hospital **In the group pretested with CRP, the antibiotic prescription 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**
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 referral or admission, additional testing in primary care, or re-consultation in primary or secondary care **Antibiotics were prescribed to 60 children (30%, 95% CI 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 follow-up period, children randomised to CRP testing received significantly more antibiotic prescriptions (6 versus 1 patient). Five children were admitted to hospital, three with infection (pneumonia, appendicitis and a non-specified viral illness)**

Supplementary file 3b: characteristics of included studies

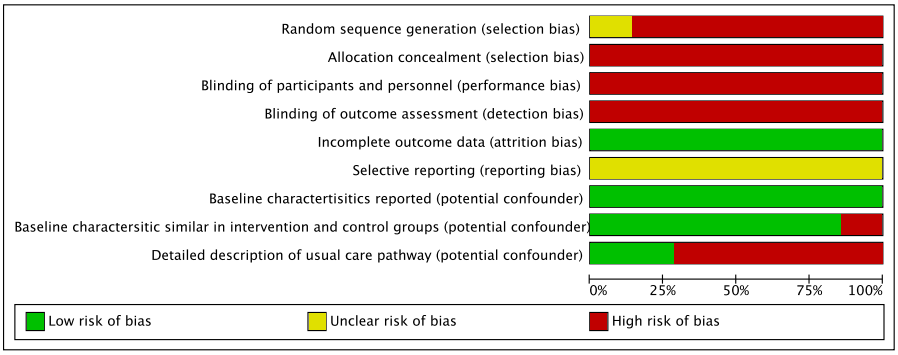
Supplementary file 4: Risk of bias assessment (QUADAS 2)



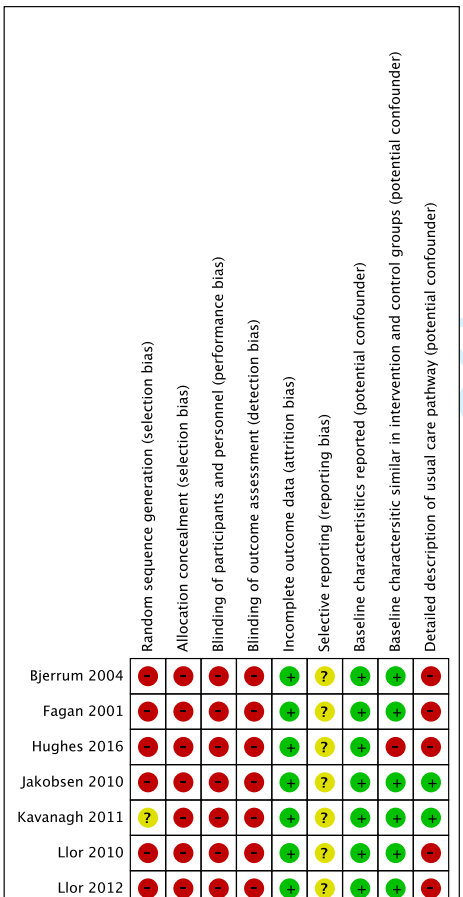
Supplementary file 4a: Risk of bias graph (RCTs): review authors' judgements about each risk of bias item presented as percentages across all included studies



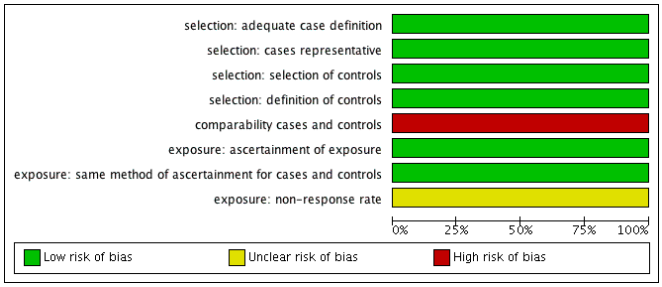
Supplementary file 4b: Risk of bias summary (RCTs): review authors' judgements about each risk of bias item for each included study.



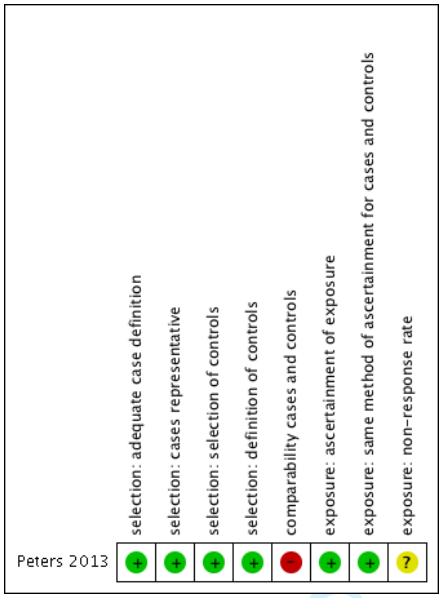
Supplementary file 4c: Risk of bias graph (non-randomised studies).



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

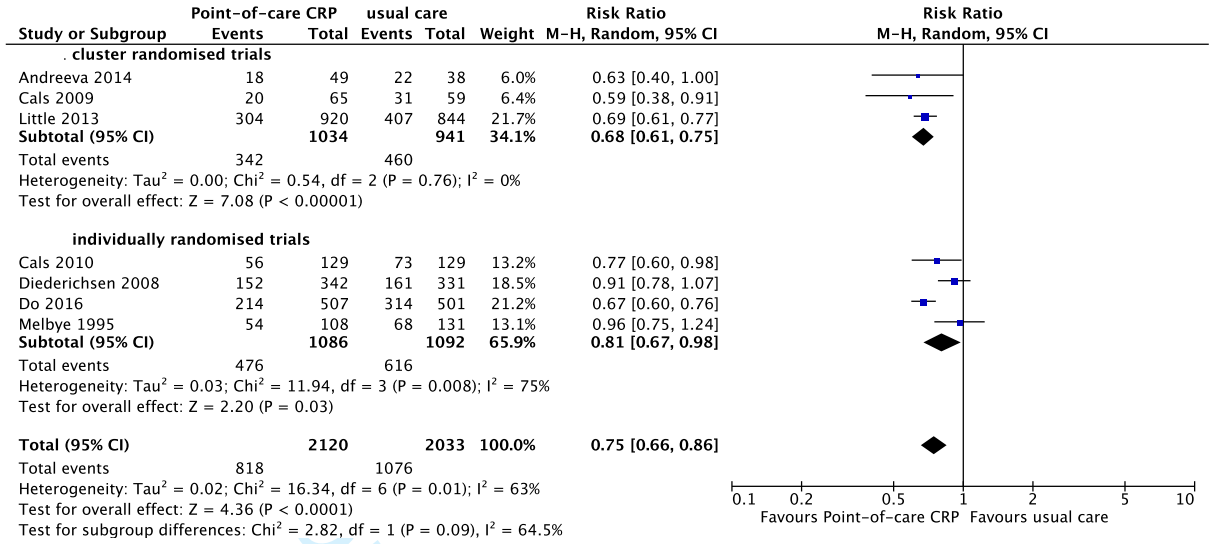


Supplementary file 4e: Risk of bias graph (case-control studies).

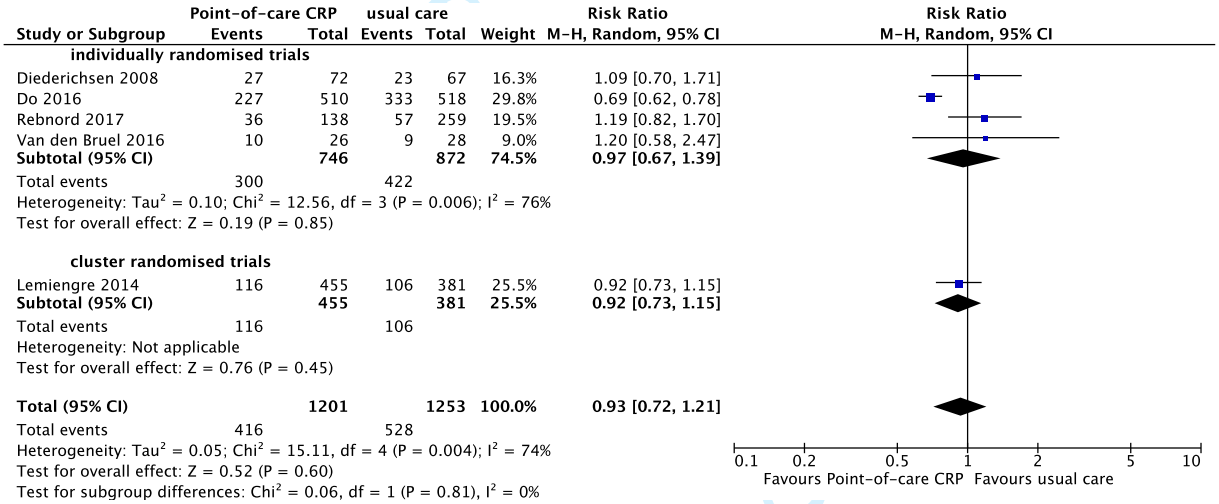


Supplementary file 4f: Risk of bias summary (case-control studies).

(a)



(b)



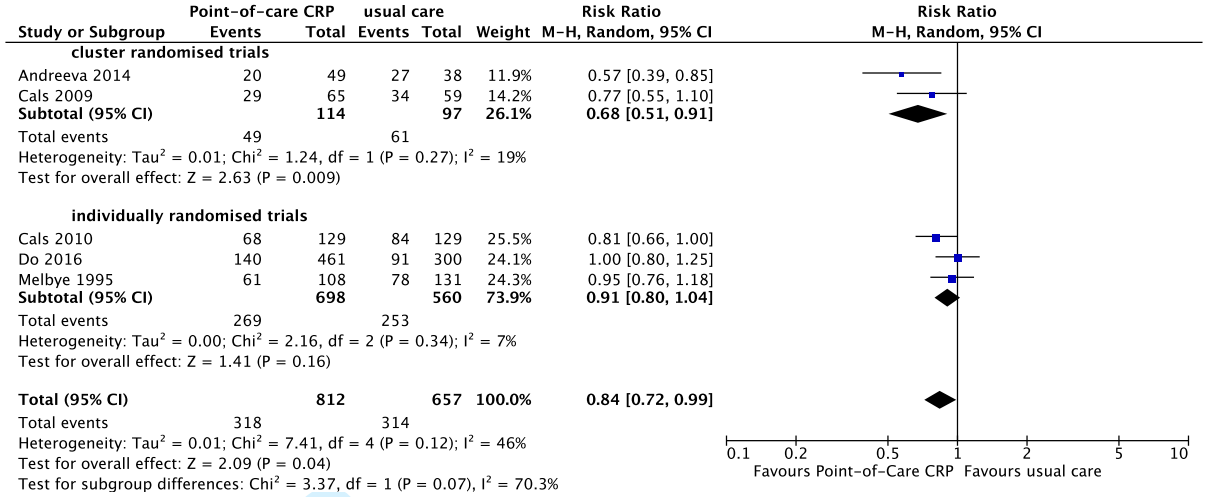
Supplementary file 5: Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (a) RCTs, adults only; (b) RCTs, children only.

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.

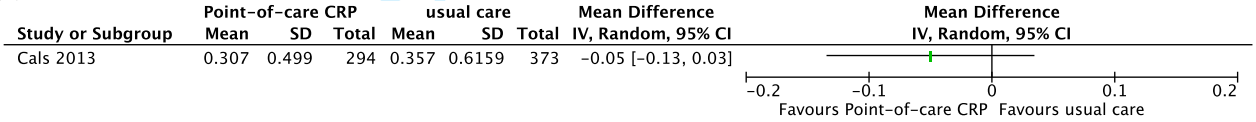
Outcome	Comparing subgroup of RCTs	Overall heterogeneity I^2 (%)	% between-study heterogeneity explained via meta-regression	% residual between-study heterogeneity
Antibiotic prescribing at index consultation	All patients	72%	/	/
	Adults versus children	63% (adults) versus 74% (children)	100%	0%
	CRP 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, I^2: I-squared

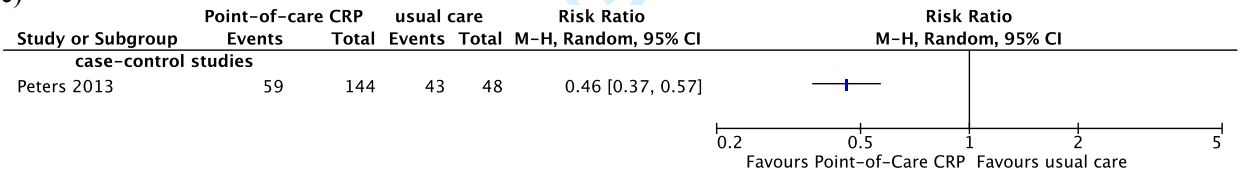
(a)



(b)

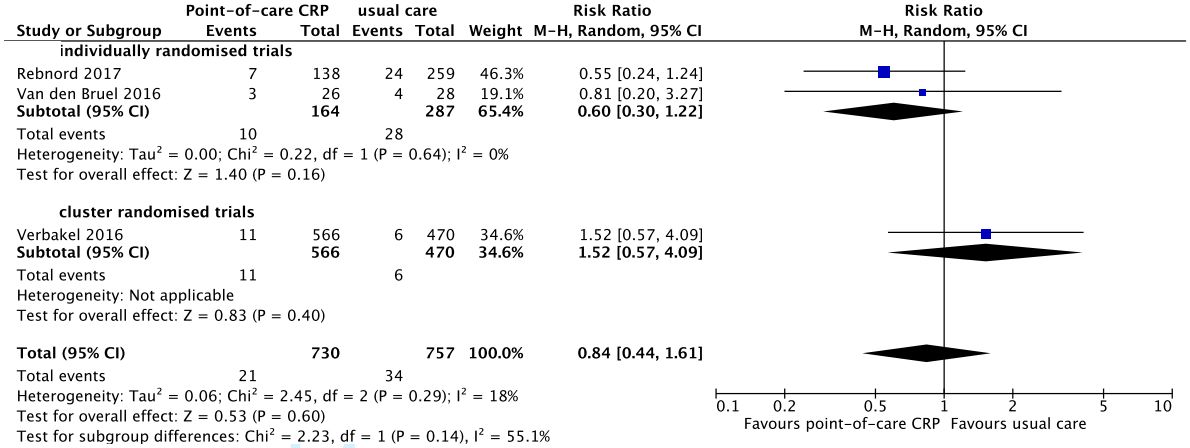


(c)

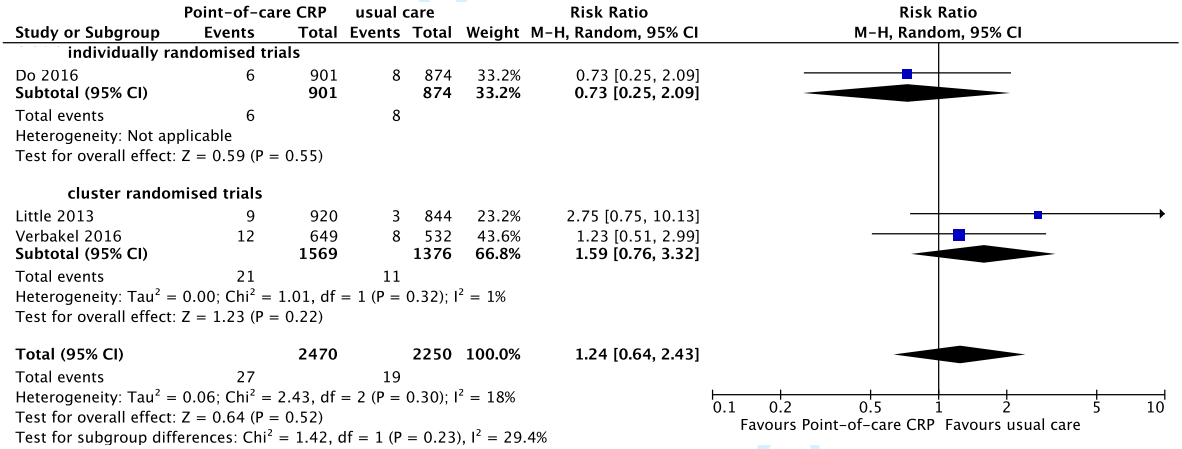


Supplementary file 7: Forest plot of comparison: point-of-care CRP versus usual care, outcome: (a) antibiotic prescribing within 28 days (all patients, RCTs); (b) antibiotic treatment for respiratory tract infection during follow-up (RCT); (c) antibiotic prescribing within 28 days (all patients, non-randomised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

(a)

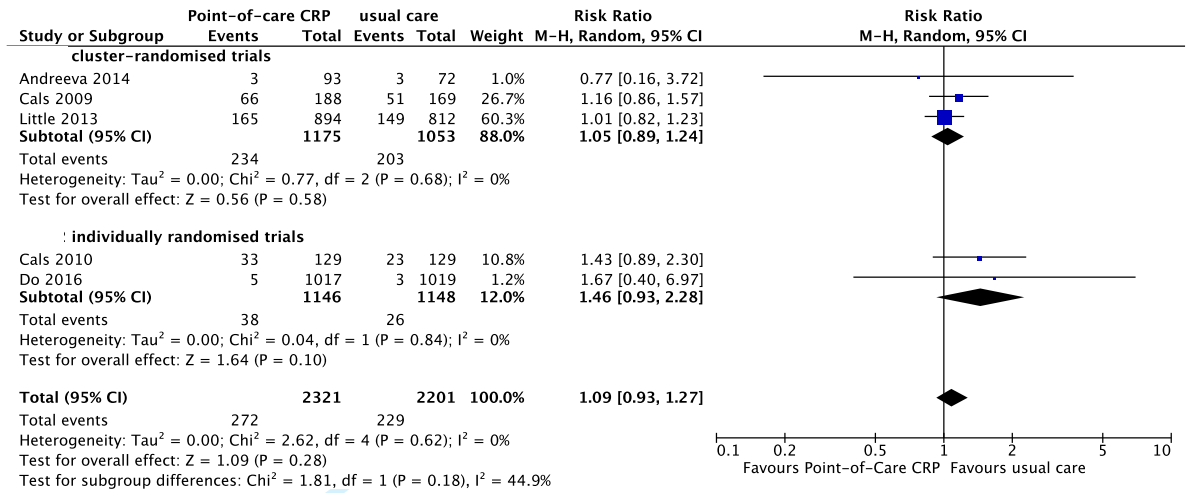


(b)

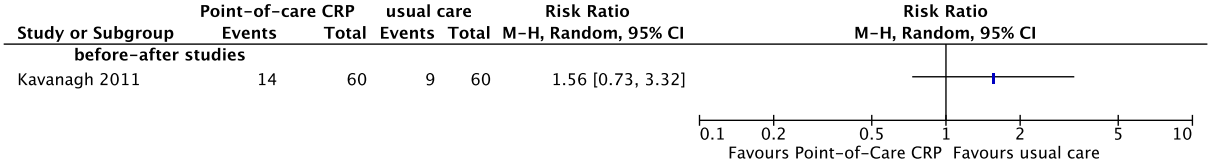


Supplementary file 8: Forest plot of comparison: point-of-care CRP versus usual care, outcome: (a) referral to hospital (RCTs); (b) hospital admission (RCTs).

(a)

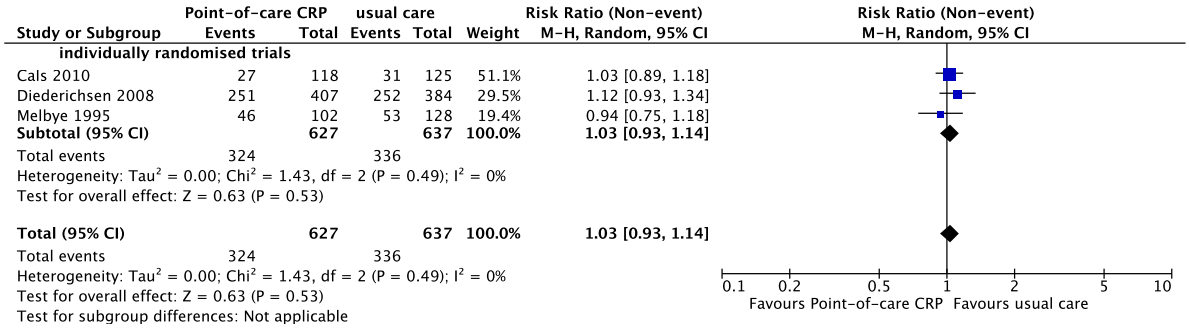


(b)

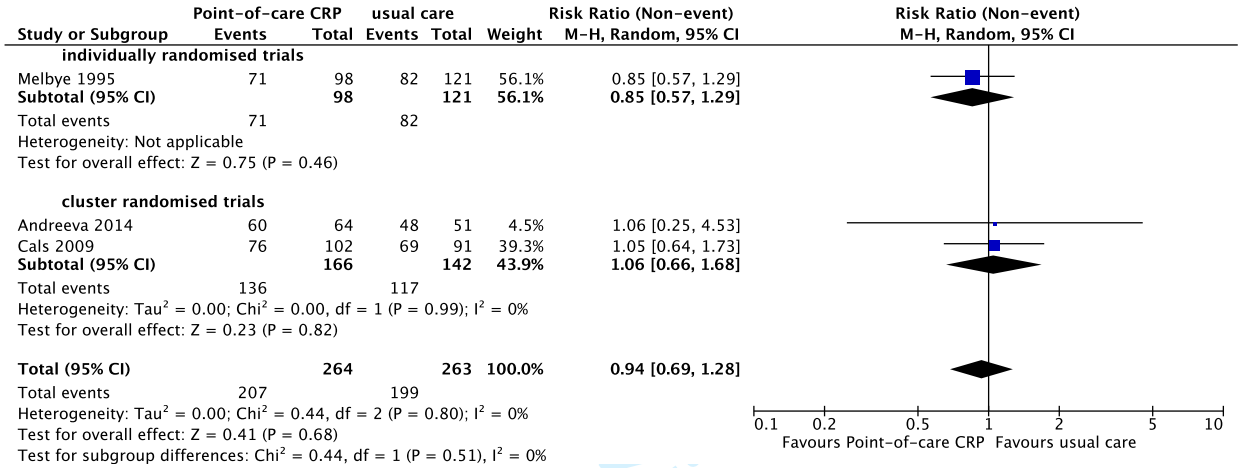


Supplementary file 9: Forest plot of comparison: 1 POC CRP versus usual care, outcome: re-consultations within 28 days.: (a) all patients, RCTs; (b) all patients, non-randomised study.

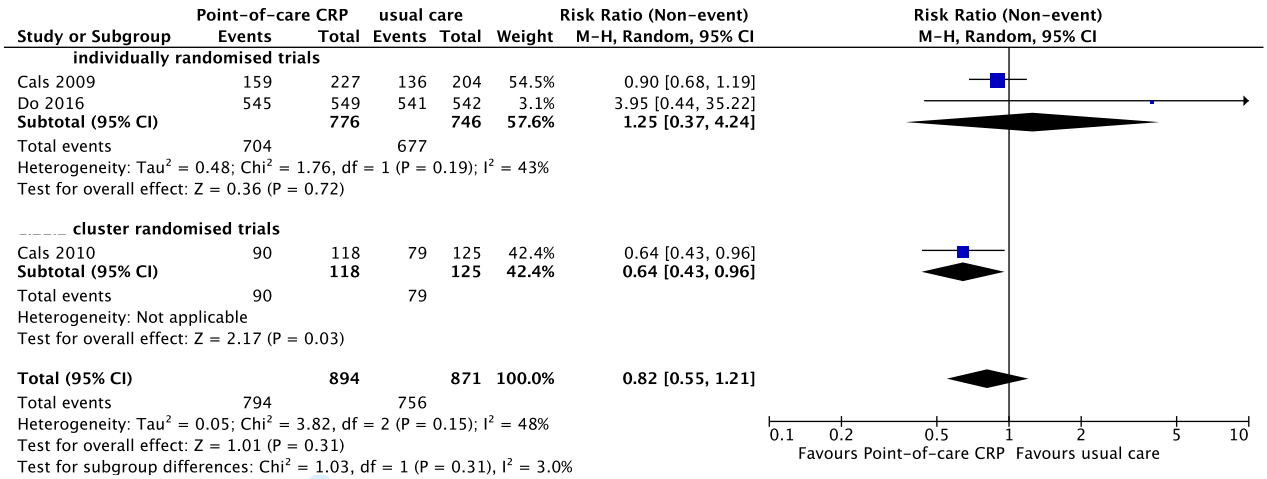
Supplementary file 10: Forest plots secondary outcomes (Figure a-j)



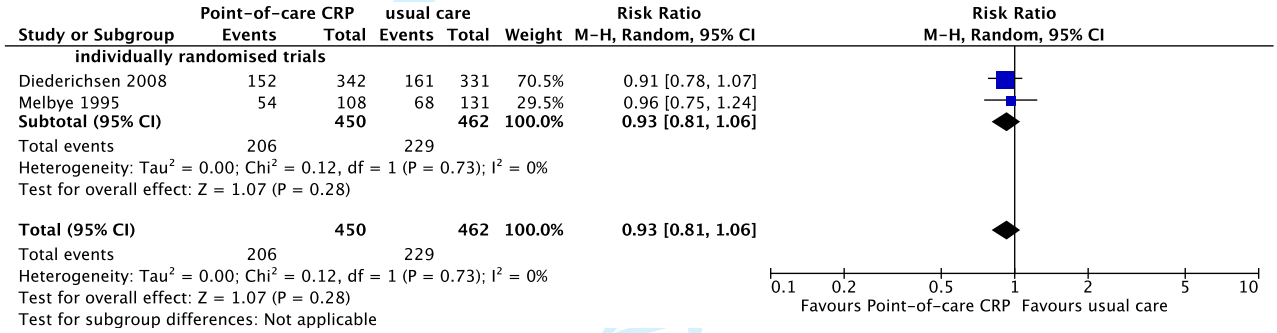
Supplementary file 10a: Forest plot of comparison: 1 POC CRP versus usual care, outcome: clinical recovery day 7 (all studies).



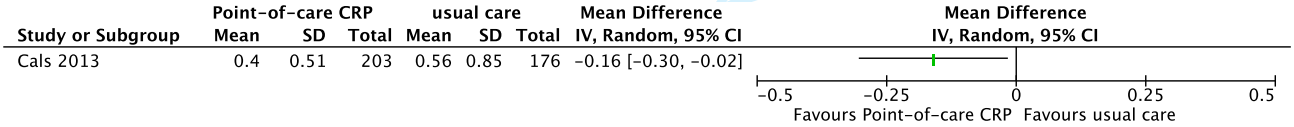
Supplementary file 10b: Forest plot of comparison: 1 POC CRP versus usual care, outcome: clinical recovery day 28 (all studies).



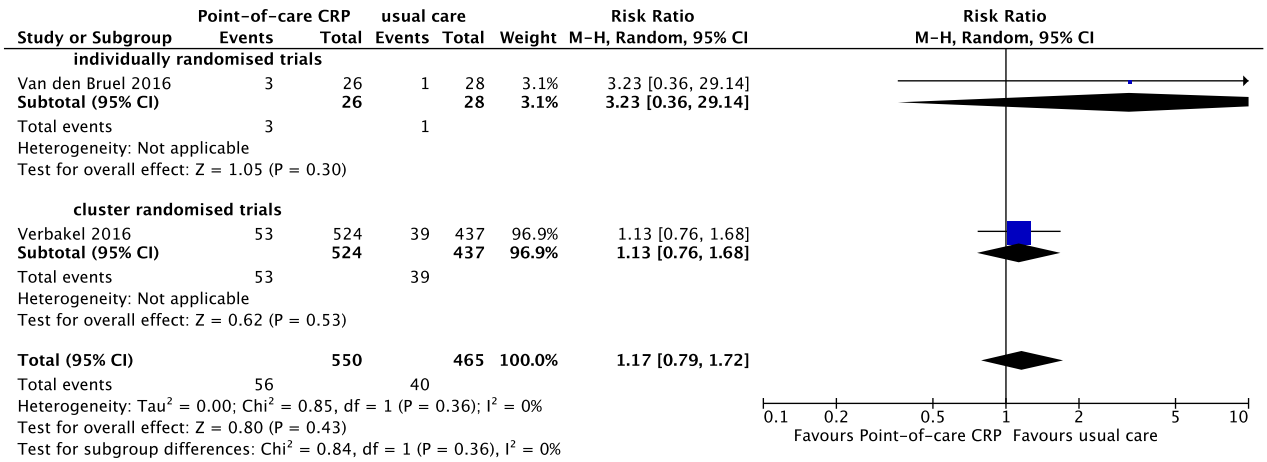
Supplementary file 10c: Forest plot of comparison: 1 POC CRP versus usual care, outcome: patient satisfaction (RCTs).



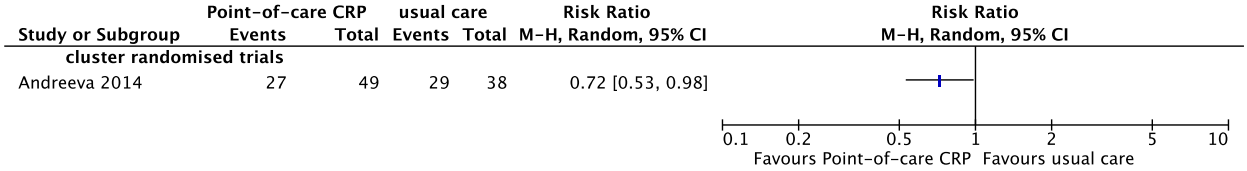
Supplementary file 10d: Forest plot of comparison: 1 POC CRP versus usual care, outcome: patient satisfaction (non-randomised study).



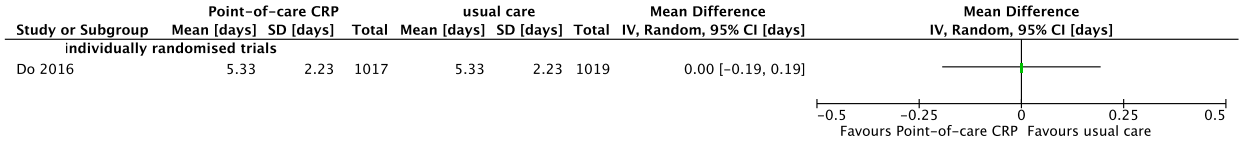
Supplementary file 10e: Forest plot of comparison: 1 POC CRP versus usual care, outcome: respiratory tract infection during follow-up. (RCT)



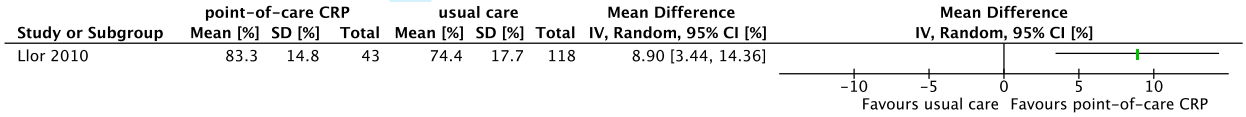
Supplementary file 10f: Forest plot of comparison: 1 POC CRP versus usual care, outcome: additional tests performed (RCTs).



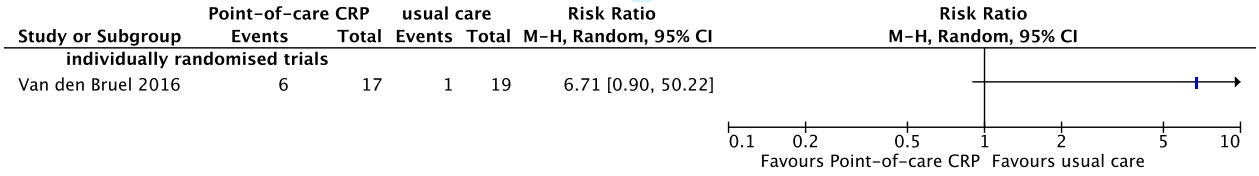
Supplementary file 10g: Forest plot of comparison: 1 POC CRP versus usual care, outcome: referral for chest X-Ray (RCT).



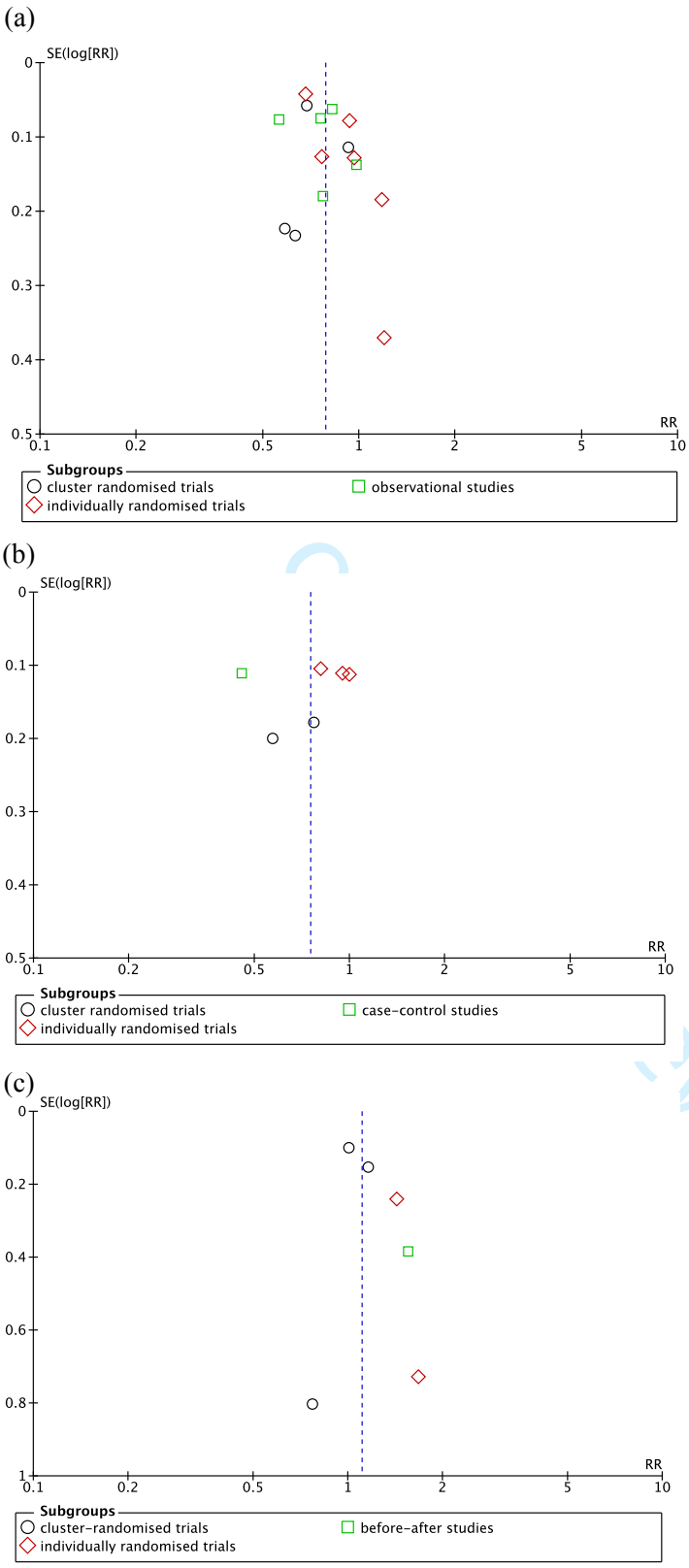
Supplementary file 10h: Forest plot of comparison: 1 POC CRP versus usual care, outcome: time to symptom resolution (RCT).



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



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	Reported 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 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

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

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. doi:10.1371/journal.pmed1000097

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