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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 C reactive protein (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, reconsultation, 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 8 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 with 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 to 0.74 in adults and 0.56; 95% CI 0.33 to 0.95 in children). We found no significant effect of point-of-care CRP testing on patient satisfaction, clinical recovery, reconsultation, further testing and hospital admission.

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

PROSPERO registration number CRD42016035426; Results.

Strengths and limitations of this study

- ► A systematic review and meta-analysis to assess the impact of point-of-care C reactive protein 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 CIs 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, for example, 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 min.[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] The 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 the clinical failure to subsequent antibiotic treatment.[12] Introducing better diagnostic tests might strengthen the assessment of infections in ambulatory care.[13]General practitioners (GPs) 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 (RTIs) 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 RTIs 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 RTIs.[17 18] Both recommendations are based on the same three randomised controlled trials (RCTs) (two randomised at the practice level and one at patient level), showing a significant reduction in immediate antibiotic prescribing rate when POC CRP was used (risk ratios (RRs) 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 RTIs by 22%,[14] however, the broader impact on other clinically relevant outcomes, such as hospital admissions, missed diagnoses, inducing indication creep,[22] reconsultation, 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, reconsultation, 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 online supplementary file 1.

Selection of studies

Studies were eligible if they reported the impact of POC 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 POC test vs 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, JYV, TA and JJL). Discrepancies between the reviewers were resolved by a third independent reviewer of the team. For this paper, studies on POC CRP testing were identified from the overall selection by two independent researchers (JYV and CG).

Data extraction and assessment of methodological quality

Data were extracted by one reviewer (JYV) and checked by a second reviewer (JJL), 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 (JYV and JJL). Any disagreements were resolved by a 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 prespecified 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 the antibiotic prescribing rate at the index consultation and during follow-up, reconsultation, referral or admission to hospital and mortality. Secondary outcomes included clinical recovery, patient satisfaction, RTIs 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 National Institute for Health Research (NIHR) Diagnostic Evidence Cooperative (DEC) Oxford portfolio, and as such benefits from reflection and advice from the DEC's standing patient and public involvement (PPI) panel. Our panel has shown great interest in the introduction of POC tests in ambulatory care, especially in relation to the assessment of acutely

ill children and the monitoring of anticoagulant therapy. The 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 RCTs 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 CIs accordingly.[25] Individual study estimates were pooled in a meta-analysis using Mantel-Haenszel random-effects models for RR 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% CIs. Whenever data on mean differences were missing, we followed recommendations in the Cochrane Handbook for Systematic Reviews of Interventions to approximate the mean and SD from the reported IQR.[23]

Subgroup analyses were limited to the type of randomisation (at cluster (practice) or patient level), age group (children vs 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 V.5.3, meta-regression with R V.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 11 RCTs and 8 non-randomised studies reporting on 16 064 patients in total (table 1). Details of the search strategy and screening are provided in (online supplementary files 1 and 2).

Sixteen studies on POC CRP testing were excluded at full-text screening because they were not in an 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] (online supplementary file 3).

Included studies

Twelve studies included adult patients only (totalling 7778 patients),[19–21 42–50] three studies included children only (3598 patients)[9 51 52] and four studies both (4688 patients).[53–56] Of the 11 randomised trials, five were randomised at practice level (cluster randomised)[19 21 42 43 57] and six at a patient level only (individually randomised).[20 44 51–54] Most studies included patients with RTIs (16 out of 19 in total), of which eight studies concerned lower respiratory tract only.[19 20 42–45 49 56] Two studies included patients with sinusitis, tonsillitis or otitis media,[48 55] whereas three studies included patients presenting with any acute illness.[50 52 57]

Ten studies tested CRP on the NycoCard Reader II (by Alere),[19 20 43 44 48–50 53 54 56] four studies on the Afinion AS100 Analyzer (Alere),[42 46 52 57] three on the QuikRead,[21 47 50] and one study tested CRP on the QuikRead Go (both by Orion Diagnostica).[51] Antibiotic prescribing rate was reported as the primary outcome in 17 of the 19 studies,[19–21 42 44–47 49–57] reconsultation within 28 days in six studies,[19–21 42 47 54] clinical recovery within 7 and/or 28 days in five studies,[19 20 42 44 53] and referral[9 51 52] or admission to hospital,[9 21 54] both in three studies (online 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 47 54] RTI during follow-up,[43] referral for chest X-ray,[42] additional tests performed,[9 52] time to symptom resolution[54] and adherence to antibiotic treatment.[48]

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),51 53 and two studies with an unclear risk of reporting bias (no study protocol available).44 53 Considering only studies that focused 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 (online 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.[45–50 55] 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 10 RCTs, performing a POC CRP test resulted in a reduction of antibiotic prescriptions issued at the index consultation with a pooled effect estimate RR of 0.81 (95%

Table 1 Baseline characteristics of included studies

Study	Country	Design	Device (manufacturer)	Patient characteristics	Total sample size (C reactive protein (CRP)/no CRP)
1. Randomised controlled trials					
(a) Patients presenting with signs of respiratory tract infection					
Andreeva and Melbye[42]	Russia	Cluster	Afinion (Axis Shield)	Adults with lower respiratory tract infection (LRTI)/acute cough for less than 28 days.	179 (101/78)
Cals *et al*[19]	The Netherlands	Cluster	NycoCard II (Axis Shield)	Adults with suspected LRTI (cough <4 weeks, +1 focal and +1 systemic symptom or sign).	431 (227/204)
Cals *et al*[20]	The Netherlands	Individual	NycoCard II (Axis Shield)	Adult with LRTI (cough <4 weeks, +1 focal and +1 systemic symptom or sign) or rhinosinusitis <4 weeks, +2 symptoms or signs.	258 (129/129)
Cals *et al*[43]	The Netherlands	Cluster	NycoCard II (Axis Shield)	Adults with suspected LRTI (cough <4 weeks, +1 focal and +1 systemic symptom or sign).	379 (203/176)
Diederichsen *et al*[53]	Denmark	Individual	NycoCard II (Axis Shield)	Children and adults with respiratory tract infection.	812 (414/398)
Do *et al*[54]	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 *et al*[21]	Spain, England, Wales (UK), Poland, Belgium, the Netherlands	Cluster	QuikRead (Orion Diagnostica)	Adults with upper or LRTI less than 28 days.	4264 (2224/2040)
Melbye *et al*[44]	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 *et al*[57] (also Verbakel *et al*[9])	Belgium	Cluster	Afinion (Alere)	Children with an acute illness less than 5 days.	3147 (1730/1417)
Rebnord *et al*[51]	Norway	Individual	QuikRead Go (Orion Diagnostica)	Children with fever and/or respiratory symptoms.	397 (138/259)
Van den Bruel *et al*[52]	UK	Individual	Afinion (Alere)	Children with an acute illness less than 5 days.	54 (26/28)
2. Non-randomised trials					

Continued

Table 1 Continued

Study	Country	Design	Device (manufacturer)	Patient characteristics	Total sample size (C reactive protein (CRP)/no CRP)
(a) Patients presenting with signs of respiratory tract infection					
Bjerrum[55]	Denmark	Cohort	Not specified	Children and adults with acute sinusitis, acute tonsillitis, and acute otitis.	367 (281/86)
Fagan[45]	Norway	Cohort	Not specified	Adults treated for acute bronchitis.	324 (122/202)
Hughes[46]	Wales (UK)	Before–after	Afinion (Alere)	Adults with symptoms of respiratory tract infection and other.	94 (not specified)
Kavanagh *et al*[47]	Ireland	Before–after	QuikRead (Orion Diagnostica)	Adults with acute cough and/or sore throat less than 1 month.	120 (60/60)
Llor *et al*[48]	Spain	Before–after	NycoCard II (Axis Shield)	Adults with acute sinusitis, acute tonsillitis, and acute otitis.	161 (43/118)
Llor *et al*[49] (also Llor *et al*[67])	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 *et al*[56]	The Netherlands	Case–control	NycoCard II (Axis Shield)	Children and adults with an intellectual disability suspected of LRTI.	1472 (882/590)
(b) Patients presenting with signs of any acute illness					
Jakobsen *et al*[50]	Norway, Sweden, Wales (UK)	Cohort	NycoCard II (Axis Shield) and QuikRead (Orion Diagnostica)	Adults with an acute illness episode less than 28 days.	503 (372/131)

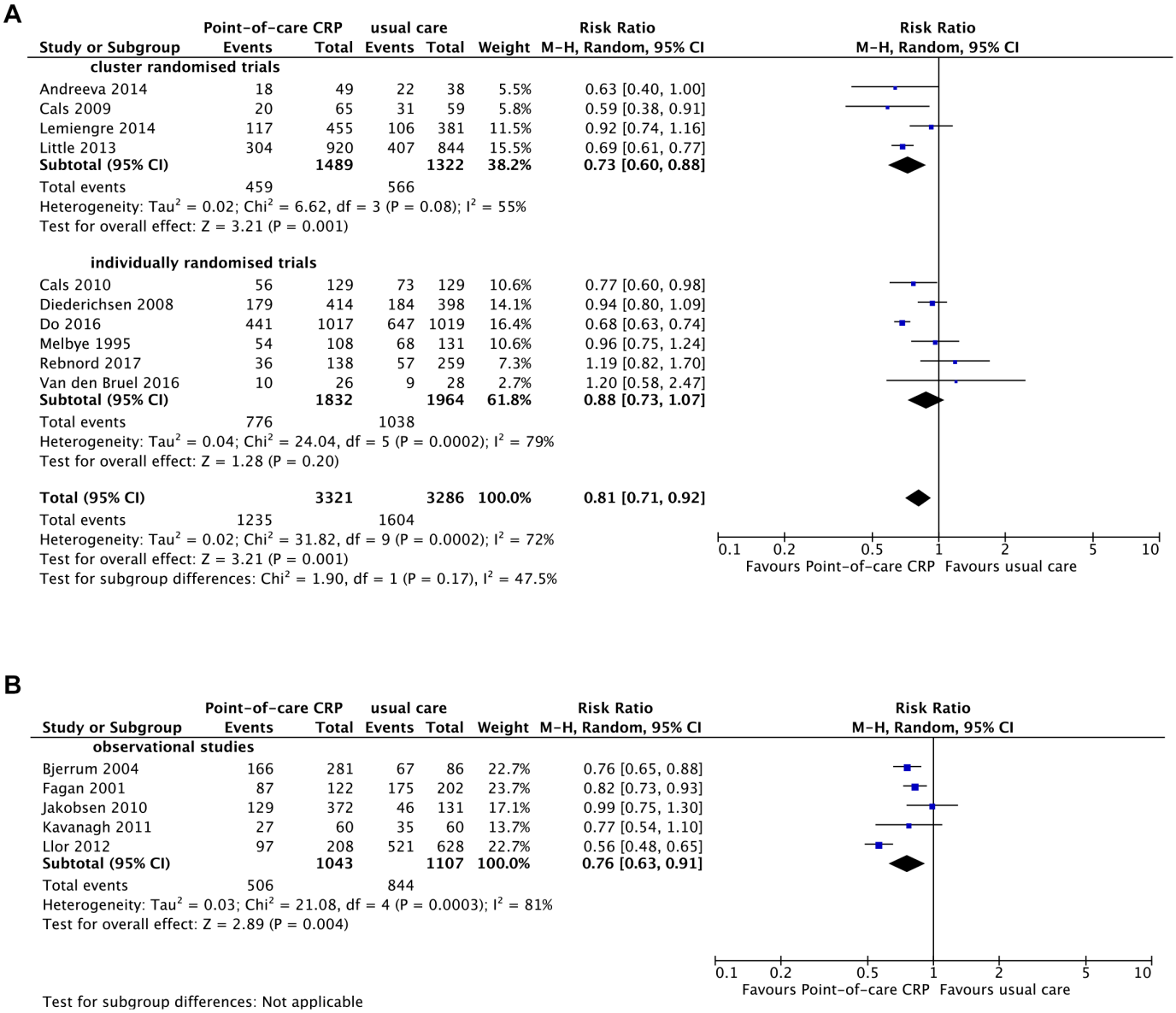

Figure 1 Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (A) all patients, RCTs; (B) all patients, non-randomised studies. CRP, C reactive protein; M-H, Mantel-Haenszel; RCTs, randomised controlled trials.

CI 0.71 to 0.92), but heterogeneity was high (I^2=72%) (figure 1A).[19–21 42 44 51–54 57] The five non-randomised studies (all on adult populations) suggested an even larger reduction with an RR 0.76 (95% CI 0.63 to 0.91), again with high heterogeneity (I^2=81%)[45 47 49 50 55] (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 to 0.86, I^2=63%).[19–21 42 44 53 54] Five RCTs examining antibiotic prescribing in children found a pooled RR 0.93 (95% CI 0.72 to 1.21, I^2=74%) (online supplementary file 5).

Five studies (all in adults) providing guidance on when to initiate antibiotic treatment by CRP level showed an overall RR 0.68 (95% CI 0.63 to 0.74, I^2=0%),[19–21 42 54] whereas two RCTs where no guidance was applied found no effect (RR 0.93; 95% CI 0.81 to 1.06, I^2=0%) (figure 2A).[44 53]

A similar effect was seen in children, where two studies providing guidance resulted in fewer antibiotic prescriptions (RR 0.56; 95% CI 0.33 to 0.95),[54 57] 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 to 1.20, I^2=0%).[51–53 57]

In addition to the 10 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%).[46]

Using meta-regression, heterogeneity could be explained by both the age group (adults vs 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) (online supplementary file 6).

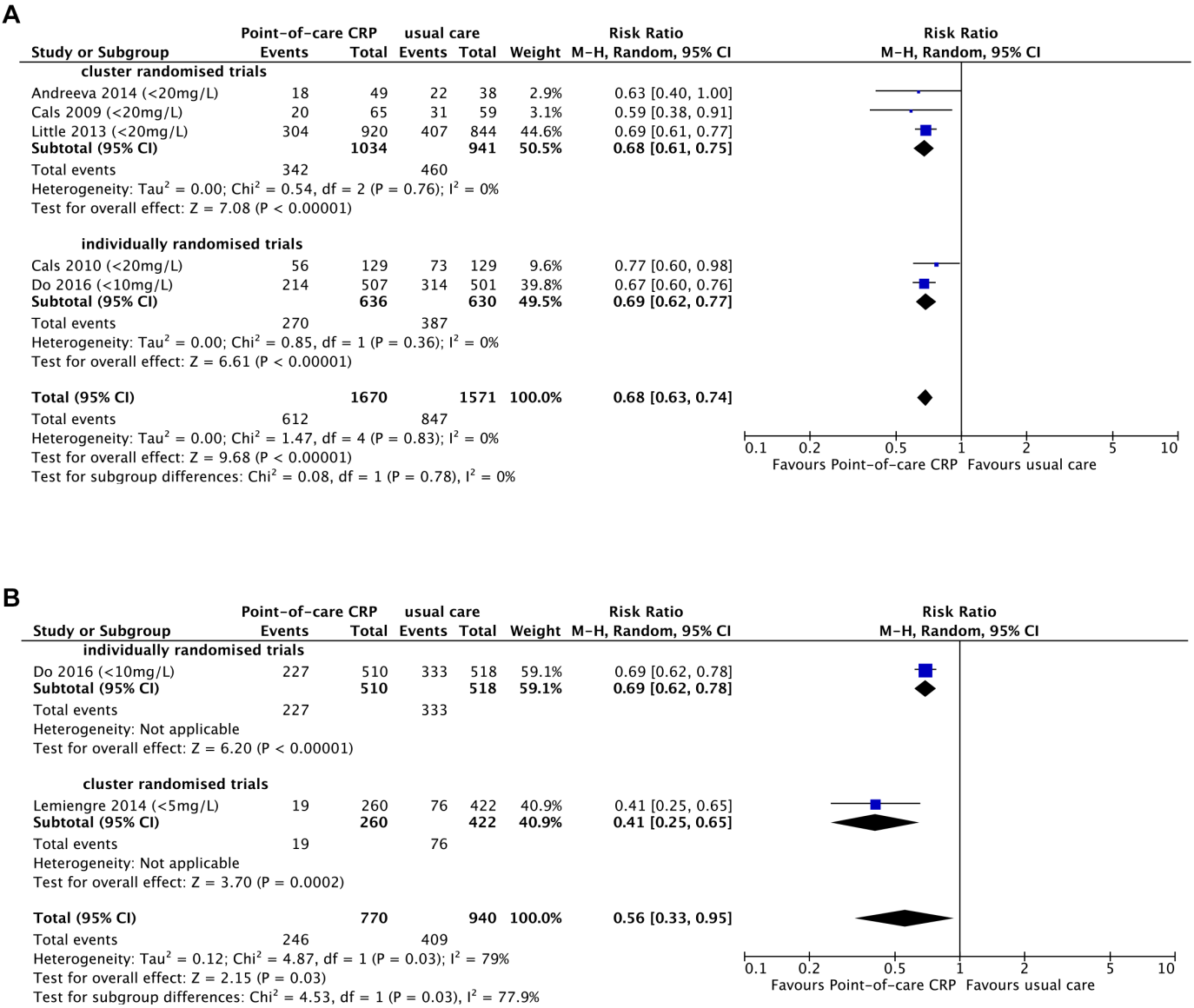

Figure 2 Forest plot of comparison: point-of-care CRP versus usual care, outcome: antibiotic prescribing at index consultation: (A) RCTs, adults only, if cut-off guidance applied; (B) RCTs, children only, if cut-off guidance applied. CRP cut-off used to withhold antibiotic treatment between brackets. CRP, C reactive protein; M-H, Mantel-Haenszel; RCTs, randomised controlled trials.

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 to 0.99) at moderate heterogeneity (I^2=46%) for the five available RCTs.[19 20 42 44 54] 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] (online supplementary file 7).

The single case–control study found a larger effect with an RR 0.46 (95% CI 0.37 to 0.57).[56]

Referral and admission to hospital

We found no difference in the number of patients referred to a hospital (overall RR 0.84 (95% CI 0.44 to 1.61) with low heterogeneity (I^2=18%)[9 51 52] (online supplementary file 8). Three RCTs reporting the number of patients admitted to hospital showed a non-significant increase when POC CRP was used with an RR 1.24 (95% CI 0.64 to 2.43, I^2=18%).[9 21 54]

Reconsultation

Reconsultations were not different for patients receiving POC CRP compared with usual care, in the five RCTs (RR 1.09 (95% CI 0.93 to 1.27, I^2=0% in each subgroup, I^2 for subgroup differences (individually randomised RCTs vs cluster RCTs was 45%))[19–21 42 54] and the before–after study (RR 1.56 (95% CI 0.73 to 3.32))[47] (online 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

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 53	1.03	0.93 to 1.14	0
Clinical recovery within 28 days	19 42 44	0.94	0.69 to 1.28	0
Patient satisfaction	19 20 54	0.82	0.55 to 1.21	48
	47	1.00	0.43 to 2.34	NA
RTIs during follow-up (registered by the GP)	43	−16%	−30% to −2%	NA
No of additional tests	9 52	1.17	0.79 to 1.72	0
No of chest X-rays	42	0.72	0.53 to 0.98	NA
Time to symptom resolution	54	+0 days	−19 to +19 days	NA
Adherence to antibiotic treatment	48	+8.9%	+3.4% to +14.4%	NA

CRP, C reactive protein; GP, general practitioners; NA, not applicable; POC, point-of-care, RTI, respiratory tract infections.

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[48] (online supplementary file 10).

Publication bias

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

DISCUSSION

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

This review focused on the clinical impact of POC CRP on patient-relevant outcomes in ambulatory care, emphasising the importance of moving above and beyond the diagnostic accuracy of POC tests and examining their effect on clinical decision-making.[58] 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-regressions have shown that 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 CIs around our effect estimates, emphasising 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.[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 POC CRP in ambulatory care,[9 60] including a recent individual patient data meta-analysis that concluded that adding CRP measurements to the diagnostic workup in ambulatory care improved risk classification of patients suspected of pneumonia.[60] Systematic reviews have mainly prioritised antibiotic prescribing rate in RTIs and found a significant reduction when POC CRP was used, similar to our findings.[15 61] The current National Institute for Health and Care Excellence 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 an 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, POC 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 POC 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-centred 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 (eg, 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 under-reported and the impact on hospital admission rates has yet to be confirmed. Future studies should focus on the potential harms and assess the 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 the 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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Contributors JYV and JJL did data extraction. JYV performed the analyses, which were discussed with JJL, CG, PST, TA, PJT, GH, AvdB. JYV drafted this report and JJL, CG, PST, TA, PJT, GH and AvdB codrafted 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. JYV 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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Provenance and peer review Not commissioned; externally peer reviewed.

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

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