Research

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Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections:

a systematic review and meta-analysis of primary care studies

Abstract

Background
Most patients with respiratory tract infections (RTIs) are prescribed antibiotics in general practice. However, there is little evidence that antibiotics bring any value to the treatment of most RTIs. Point-of-care C-reactive protein testing may reduce antibiotic prescribing.

Aim
To systematically review studies that have examined the association between point-of-care (POC) C-reactive protein testing and antibiotic prescribing for RTIs in general practice.

Design and setting
Systematic review and meta-analysis of randomised controlled trials and observational studies.

Method
MEDLINE® and Embase were systematically searched to identify relevant publications. All studies that examined the association between POC C-reactive protein testing and antibiotic prescribing for patients with RTIs were included. Two authors independently screened the search results and extracted data from eligible studies. Dichotomous measures of outcomes were combined using risk ratios (RRs) with 95% confidence intervals (CIs) either by fixed or random-effect models.

Results
Thirteen studies containing 10 005 patients met the inclusion criteria. POC C-reactive protein testing was associated with a significant reduction in antibiotic prescribing at the index consultation (RR 0.75, 95% CI = 0.67 to 0.83), but was not associated with antibiotic prescribing at any time during the 28-day follow-up period (RR 0.85, 95% CI = 0.70 to 1.01) or with patient satisfaction (RR 1.07, 95% CI = 0.98 to 1.17).

Conclusion
POC C-reactive protein testing significantly reduced antibiotic prescribing at the index consultation for patients with RTIs. Further studies are needed to analyse the confounders that lead to the heterogeneity.

Keywords
antibiotic prescribing; meta-analysis; point-of-care C-reactive protein testing; primary care; respiratory tract infections.

INTRODUCTION

Respiratory tract infections (RTIs) are among the most common acute conditions leading to patients seeking consultations in general practice.[1] About 80% of patients with RTIs are prescribed antibiotics.[2] However, RTIs are most often self-limiting and seldom require antibiotics for treatment.[3] The increased use of antibiotics is significantly associated with the development of drug-resistant bacteria. Clinical guidelines do not support routine antibiotic treatment for patients with RTIs.[4]

Diagnostic uncertainty often leads to increased inappropriate antibiotic prescribing.[5,6] C-reactive protein (CRP) is an acknowledged biomarker to diagnose bacterial infection. The level of CRP can be measured by point-of-care (POC) testing, which is easy to perform in general practice. The robustness and accuracy of POC CRP testing have been proved by many diagnostic studies.[7–9] POC CRP testing plays an important role in decreasing diagnostic uncertainty and guiding antibiotic treatment decisions.

To examine the impact of CRP measurement on antibiotic prescribing in patients with RTIs, many randomised controlled trials (RCTs) and observational studies have been conducted.[10–13] However, they did not reach consistent conclusions. For example, Bjerrum et al[10] and Cals et al[13] concluded that POC CRP testing significantly reduced antibiotic prescribing for patients with RTIs. However, Gonzales et al[11] found there was no difference in antibiotic prescribing between POC CRP tested and control patients. In addition, these studies had small sample sizes and thus lacked a more convincing statistical power to clarify whether the use of POC CRP testing in general practice can reduce antibiotic prescribing.

This article describes a systematic review and meta-analysis that were conducted to study the association between family physician use of POC CRP testing and antibiotic prescribing for RTIs in general practice.

METHOD

Eligibility
Studies were included that examined patients who had been diagnosed with RTIs; and compared the antibiotic prescribing rate of a POC CRP testing group with a no-POC CRP testing group. Studies were included if they were RCTs (including parallel-group RCTs, cluster RCTs, crossover RCTs, and factorial RCTs) or observational studies.

Literature search
Literature searches were conducted on 6 June 2013 using the electronic databases MEDLINE® (1946 to present) and Embase

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How this fits in

This study is the first to investigate the relationship between point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections. The results indicate that point-of-care C-reactive protein testing significantly reduces antibiotic prescribing for patients with respiratory tract infections.

(1980 to present). Appendix 1 shows the search terms used.

Selection of studies

Two authors independently evaluated the articles for inclusion. Any discrepancies were resolved by further discussion and consultation from a third author. The selection process by means of a flow chart is presented in Figure 1.

Data extraction

A standardised data extraction form was

used. The following information was extracted: first author name, publication year, setting, study design, age, sex, location of RTIs, sample size (POC CRP testing/no-POC CRP testing) (Table 1).

The primary outcome of interest was antibiotic prescribing at the index consultation, which was defined as those patients using antibiotics immediately and those filling a delayed prescription.[13] The secondary outcomes were antibiotic prescribing at any time during the 28-day follow-up period and patient satisfaction.

Assessment of risk of bias

The risk of bias for the included RCTs and observational studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias[14] and the Newcastle-Ottawa scale,[15] respectively. Two authors independently assessed the methodological quality of studies. Any discrepancies were resolved by a third author.

Statistical analysis

Heterogeneity was quantified by means of I^2, with a predefined significance threshold of 40%.[16] If a significant trend for heterogeneity was observed, a random effect model via generic inverse variance weighting was used to combine the effect. Otherwise, a fixed-effects model was used to calculate the pooled effects.[17] Results were expressed as relative risk (RR) with 95% confidence intervals (CIs) for dichotomous variables. Results were considered statistically significant when $P<0.05$. Revman software (version 5.2) was used. This software was available through the Cochrane Collaboration.

Subgroup analyses were carried out for the primary outcome with study design (parallel-group RCTs, cluster RCTs and observational studies) and location of RTIs (upper RTIs and lower RTIs). Sensitivity analyses were also performed for the primary outcome to restrict the analyses to European studies and to restrict the analyses to English language studies. No protocol of the present review has been published or registered.

RESULTS

Literature search

A total of 2529 citations were identified. After excluding 602 duplicate records, two authors screened 1927 titles and abstracts to identify the potentially relevant studies. In total 37 full-text articles were assessed for eligibility. Of these, 13 studies were included in qualitative synthesis,[10–13,18–26] and subsequently all

Figure 1. Flow chart of study selection.
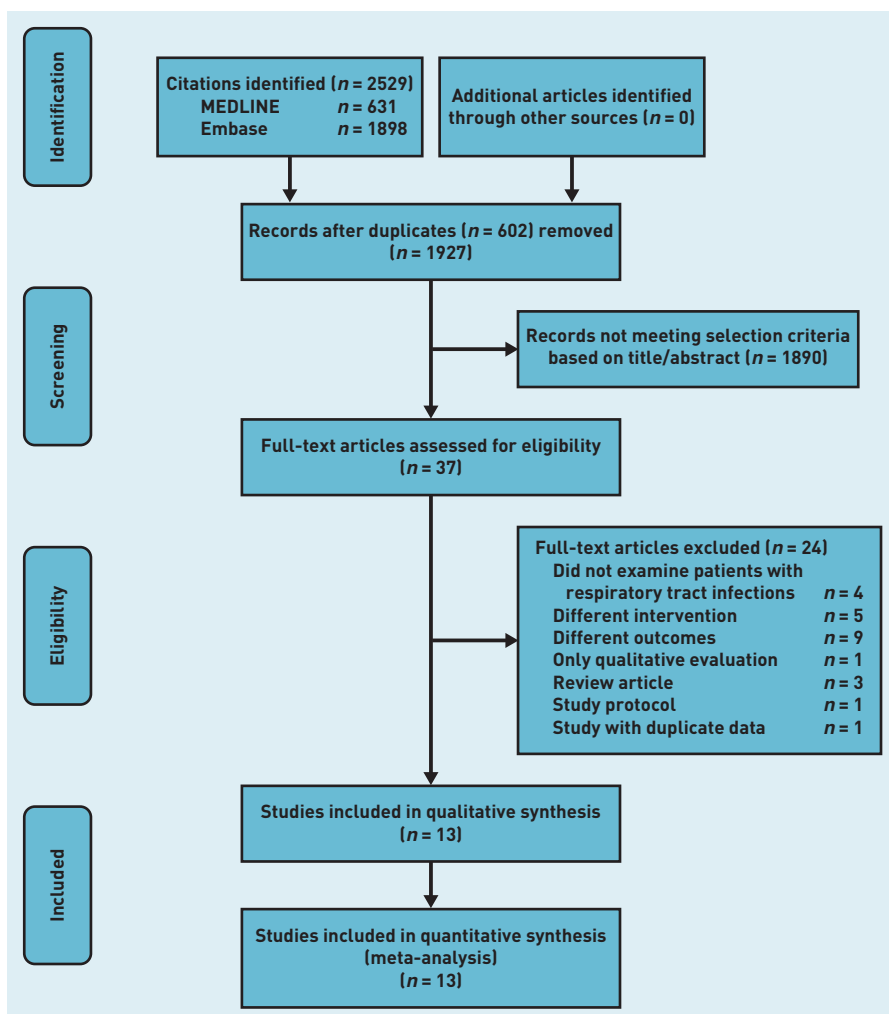
Table 1. Characteristics of the included studies

Author	Publication year	Setting	Study design	Mean age, years	Female sex, (%)	Location of RTI lower RTI (%)	Sample size (CRP testing/ no CRP testing)	NOS score for OS
Bjerrum et al[10]	2004	Denmark	OS	NA	NA	0 (0)[a]	281/86	7
Cals et al[20]	2009	Netherlands	Cluster RCT	49.8	265 (61.5)	431 (100)	227/204	NA
Cals et al[13]	2010	Netherlands	Parallel-group RCT	44.3	179 (69.4)	107 (41.5)	129/129	NA
Cals et al[19]	2011	Netherlands	Cluster RCT	48.5	135 (58.7)	230 (100)	110/120	NA
Cals et al[21]	2013	Netherlands	Cluster RCT	49.9	235 (62.0)	NA	203/176	NA
Diederichsen et al[25]	2000	Denmark	Parallel-group RCT	37.0	465 (57.3)	NA	414/398	NA
Fagan[18]	2001	Norway	OS	NA	NA	NA	122/202	6
Gonzales et al[11]	2011	US	Parallel-group RCT	NA	86 (65.6)	88 (67.2)	69/62	NA
Jakobsen et al[22]	2010	Norway	OS	NA	438 (87.1)	NA	372/131	7
Kavanagh et al[24]	2011	Ireland	OS	NA	NA	NA	60/60	6
Llor et al[23]	2012a	Spain	OS	NA	NA	5385 (100)	545/4840	6
Llor et al[12]	2012b	Spain	OS	39.8	543 (65.0)	0 (0)[a]	208/628	6
Melbye et al[26]	1995	Norway	Parallel-group RCT	NA	NA	229 (100)	108/121	NA

[a]All patients had upper respiratory tract infections. CRP = C-reactive protein. NA = not applicable. NOS = Newcastle-Ottawa Scale. OS = observational study. RCT = randomised controlled trial. RTI = respiratory tract infection.

13 studies met the final eligibility criteria for meta-analysis. The detailed selection process is outlined in Figure 1.

Description of studies
There were 13 studies with a total of 10 005 patients with RTIs,[10–13,18–26] which studied the association between POC CRP testing and antibiotic prescribing. Of the 13 included studies, four studies were conducted in the Netherlands,[13,19–21] three in Norway,[18,22,26] two in Denmark,[10,25] two in Spain,[12,23] one in Ireland,[24] and one in the US.[11] Four studies were parallel-group RCTs.[11,13,25,26] Three studies were cluster RCTs.[19–21] Six studies were observational studies.[10,12,18,22–24] Table 1 summarises the basic characteristics of the included studies.

Assessment of risk of bias
Complete risk of bias assessment was performed for all studies. The six observational studies were scored using the Newcastle-Ottawa scale:[10,12,18,22–24] four studies got six stars,[12,18,23,24] and two studies got seven stars[10, 22] (Table 1). Results of the assessment for the seven RCTs (four parallel-group RCTs and three cluster RCTs) are shown in Table 2.

Antibiotic prescribing at the index consultation
All the 13 studies provided information on antibiotic prescribing at the index consultation to calculate the overall effect size.[10–13,18–26] Twelve of these studies reported a decreased antibiotic prescribing

Table 2. The risk of bias of included RCTs and cluster RCTs

		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Studies	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally prespecified
Cals et al[20]	2009	H	H	H	U	L	L	U
Cals et al[13]	2010	U	U	H	U	L	L	U
Cals et al[19]	2011	H	H	H	U	L	L	U
Cals et al[21]	2013	H	H	H	U	L	L	U
Diederichsen et al[25]	2000	U	U	H	U	U	L	U
Gonzales et al[11]	2011	L	L	H	U	L	L	U
Melbye et al[26]	1995	U	U	H	U	U	L	U

H = high risk of bias. L = low risk of bias. U = unclear risk of bias.

Study or Subgroup	CRP testing Events	CRP testing Total	No CRP testing Events	No CRP testing Total	Weight	Risk ratio IV. Random (95% CI)
Bjerrum 2004	166	281	67	86	9.4%	0.76 (0.65 to 0.88)
Cals 2009	70	227	108	204	7.5%	0.58 (0.46 to 0.74)
Cals 2010	56	129	73	129	7.1%	0.77 (0.60 to 0.98)
Cals 2011	43	110	82	120	6.8%	0.57 (0.44 to 0.74)
Cals 2013	64	203	96	176	7.2%	0.58 (0.45 to 0.74)
Diederichsen 2000	179	414	184	398	9.3%	0.94 (0.80 to 1.09)
Fagan 2001	87	122	175	202	9.9%	0.82 (0.73 to 0.93)
Gonzales 2011	26	69	19	62	3.5%	1.23 (0.76 to 1.99)
Jakobsen 2010	129	372	46	131	6.7%	0.99 (0.75 to 1.30)
Kavanagh 2011	27	60	35	60	5.2%	0.77 (0.54 to 1.10)
Llor 2012[a]	239	545	2992	4840	10.4%	0.71 (0.64 to 0.78)
Llor 2012[b]	97	208	521	628	9.3%	0.56 (0.48 to 0.65)
Melbye 1995	60	108	73	121	7.7%	0.92 (0.74 to 1.15)
Total (95% CI)		2848		7157	100.0%	0.75 (0.67 to 0.83)
Total events	1243		4471			

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 49.70$, df = 12 ($P<0.001$); $I^2 = 76\%$
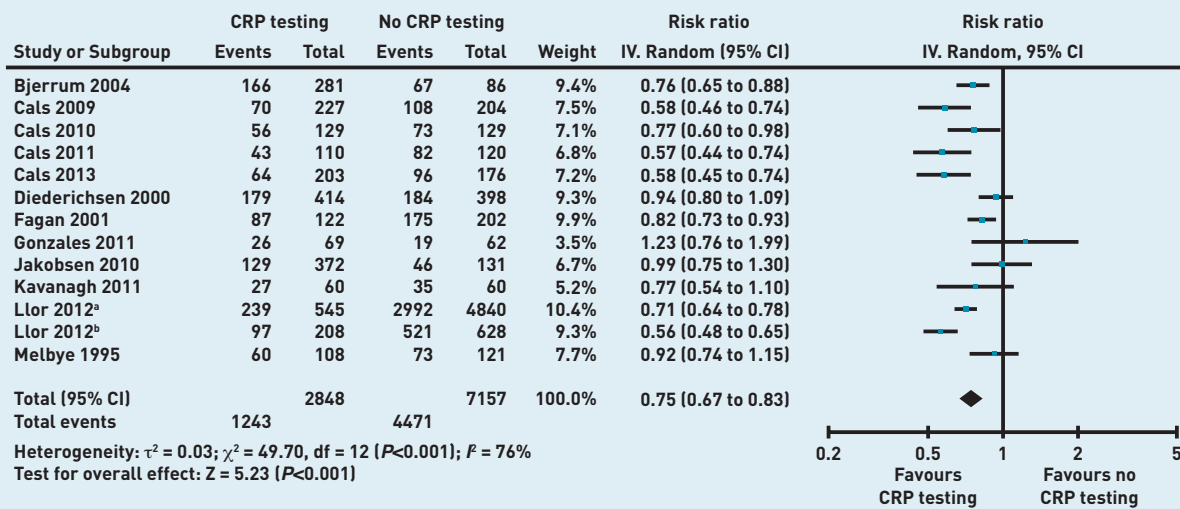Test for overall effect: Z = 5.23 ($P<0.001$)

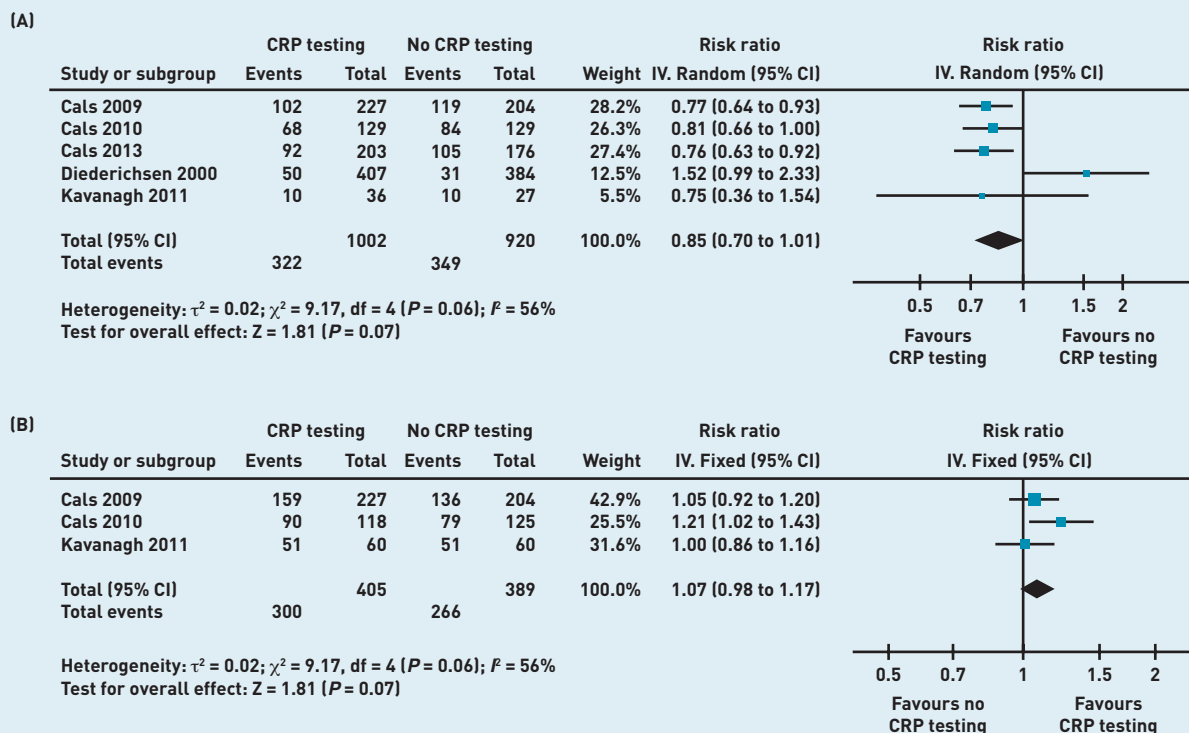**Figure 2. Antibiotic prescribing at the index consultation. IV = inverse variance.**

Figure 3. Antibiotic prescribing at any time during the 28-day follow-up period and patient satisfaction. IV = inverse variance.

rate in the POC CRP testing group.[10,12,13,18–26] Eight of them were significant.[10,12,13,18–21,23] Pooling of the mean proportion showed that 43.6% of patients with RTIs in the POC CRP testing group and 62.5% of patients with RTIs in the no-POC CRP testing group were prescribed antibiotics. The meta-analysis showed that POC CRP testing was associated with a significant reduction in antibiotic prescribing at the index consultation (RR 0.75, 95% CI = 0.67 to 0.83; $P<0.001$ for heterogeneity; $I^2 = 76\%$) (Figure 2).

Antibiotic prescribing at any time during the 28-day follow-up period

Five studies provided information on antibiotic prescribing at any time during the 28-day follow-up period, with a total of 1922 patients with RTIs to calculate the overall

(A)

Study or subgroup	CRP testing Events	CRP testing Total	No CRP testing Events	No CRP testing Total	Weight	Risk ratio IV. Random (95% CI)
Cals 2009	102	227	119	204	28.2%	0.77 (0.64 to 0.93)
Cals 2010	68	129	84	129	26.3%	0.81 (0.66 to 1.00)
Cals 2013	92	203	105	176	27.4%	0.76 (0.63 to 0.92)
Diederichsen 2000	50	407	31	384	12.5%	1.52 (0.99 to 2.33)
Kavanagh 2011	10	36	10	27	5.5%	0.75 (0.36 to 1.54)
Total (95% CI)		1002		920	100.0%	0.85 (0.70 to 1.01)
Total events	322		349			

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 9.17$, df = 4 ($P = 0.06$); $I^2 = 56\%$
Test for overall effect: Z = 1.81 ($P = 0.07$)

(B)

Study or subgroup	CRP testing Events	CRP testing Total	No CRP testing Events	No CRP testing Total	Weight	Risk ratio IV. Fixed (95% CI)
Cals 2009	159	227	136	204	42.9%	1.05 (0.92 to 1.20)
Cals 2010	90	118	79	125	25.5%	1.21 (1.02 to 1.43)
Kavanagh 2011	51	60	51	60	31.6%	1.00 (0.86 to 1.16)
Total (95% CI)		405		389	100.0%	1.07 (0.98 to 1.17)
Total events	300		266			

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 9.17$, df = 4 ($P = 0.06$); $I^2 = 56\%$
Test for overall effect: Z = 1.81 ($P = 0.07$)

Antibiotic prescribing and patient satisfaction estimated from meta-analysis of RTI patients with point-of-care CRP testing (intervention group) versus no point-of-care CRP testing (control group). (A) Antibiotic prescribing at any time during the 28-day follow-up period. (B) Patient satisfaction.

Table 3. Results of subgroup and sensitivity analyses for antibiotic prescribing at the index consultation

Subgroup and sensitivity analyses	Number of studies	Weighted estimates, % (95% CI)	Heterogeneity test
Subgroup analyses			
1. Study design			
Parallel-group RCTs	4	0.91 (0.82 to 1.01)	$I^2 = 13\%$, $P = 0.33$
Cluster RCTs	3	0.58 (0.50 to 0.67)	$I^2 = 0\%$, $P = 0.99$
OSs	6	0.74 (0.65 to 0.85)	$I^2 = 76\%$, $P<0.001$
2. Location of RTIs			
Upper RTIs	3	0.68 (0.54 to 0.84)	$I^2 = 76\%$, $P = 0.01$
Lower RTIs	5	0.70 (0.60 to 0.83)	$I^2 = 63\%$, $P = 0.03$
Sensitivity analyses			
European studies	12	0.73 (0.66 to 0.82)	$I^2 = 76\%$, $P<0.001$
English language studies	11	0.73 (0.64 to 0.82)	$I^2 = 76\%$, $P<0.001$

OS = observational study. RCT = randomised controlled trial. RTI = respiratory tract infection.

effect size.[13,20,21,24,25] Four of these studies showed a decreased antibiotic prescribing rate in the POC CRP testing group.[13,20,21,24] Two of them were significant.[20,21] Pooling of the mean proportion showed that 32.1% of patients in the POC CRP testing group and 37.9% of patients in the no-POC CRP testing group were prescribed antibiotics. The meta-analysis showed a non-significant effect on antibiotic prescribing at any time during the 28-day follow-up period (RR 0.85, 95% CI = 0.70 to 1.01; $P = 0.06$ for heterogeneity; $I^2 = 56\%$) (Figure 3A).

Patient satisfaction
Three studies reported patient satisfaction, with 794 patients.[13,20,24] Two of these studies reported increased patient satisfaction in the POC CRP testing group.[13,20] One of them was significant.[13] The combined results indicated a non-significant increase of patient satisfaction in the POC CRP testing group (RR 1.07, 95% CI = 0.98 to 1.17; $P = 0.24$ for heterogeneity; $I^2 = 30\%$) (Figure 3B).

Subgroup analyses
Subgroup analyses were performed for the primary outcome according to study design (parallel-group RCTs, cluster RCTs and observational studies) and location of RTIs (upper RTIs and lower RTIs). In the subgroup of cluster RCTs, observational studies, patients with upper RTIs and lower RTIs, the overall results all showed significant reductions of antibiotic prescribing in the POC CRP testing group. In the subgroup of parallel-group RCTs, the overall result demonstrated a non-significant reduction of antibiotic prescribing in the POC CRP testing group (Table 3).

Sensitivity analysis
To test the robustness of the results, the analyses were restricted to the 12 European studies[10,12,13,18–26] and to the English language studies.[10–13,19–25] Pooled data from the European studies and pooled data from the English language studies continued to demonstrate a significant reduction of antibiotic prescribing in the POC CRP testing group (Table 3).

DISCUSSION
Summary
This meta-analysis comprehensively summarised the current evidence from 13 studies on the association between POC CRP testing and antibiotic prescribing for RTIs in general practice. POC CRP testing was found to significantly decrease antibiotic prescribing at the index consultation. Although there was significant heterogeneity in the meta-analysis, results from the sensitivity analysis were consistent, which strengthened the robustness of the conclusion.

Strengths and limitations
Patients with upper RTIs and patients with lower RTIs were included in the analysis. The meta-analysis of primary outcome included 13 eligible studies. A previous systematic review that studied the association between POC CRP testing and antibiotic prescribing only included patients with lower RTIs and identified five studies.[27] Comprehensive search strategies were performed to identify relevant studies. The search was not restricted to English language articles. Two grey literature articles[18,26] were identified from non-English language journals and were included in the analyses.

Due to limitations of time, money and human resources, the meta-analysis was based on aggregated data extracted from the published full-text articles, rather than individual patient data requested from the researchers of the eligible studies. Meta-analysis that is merely based on aggregated level data has limitations in conducting subgroup analyses.[28] It is not always possible to explore the sources of heterogeneity.[29] In this study, significant heterogeneity was identified. Although subgroup analyses were conducted according to location of the RTIs and study design, the heterogeneity still existed within subgroups of upper RTIs, lower RTIs, and subgroups of observational studies. Future research needs to collect original data and conduct individual patient meta-analyses to find more potential reasons for the heterogeneity.

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Comparison with existing literature

To the authors knowledge, this is the first meta-analysis that aims to summarise all the research evidence that has studied the association between POC CRP testing and antibiotic prescribing in patients with RTIs. A systematic review conducted by Engel *et al*[27] concentrated on patients with lower RTIs only. They included both randomised and observational studies. Their results showed that POC CRP testing was associated with a significant reduction in antibiotic prescribing (RR 0.6, 95% CI = 0.5 to 0.7). It is consistent with the subgroup result of lower RTIs in the current study.

Implications for research and practice

For each patient with a RTI, family physicians have to decide whether to prescribe antibiotics for them. POC CRP testing can facilitate RTI consultation and decision making in general practice. If POC CRP is tested and the test result shows that the CRP level is low, it is most likely that the family physician will not prescribe antibiotics for this patient.

Family physicians should be aware of the problems that arise from over-prescription of antibiotics, which may drive antibiotic resistance. Reduced antibiotic prescribing in general practice is associated with reduced local antibiotic resistance.[30] The POC CRP test is an office-based and cost-effective test.[19,31] There are few limitations for its applicability in general practice. This study has indicated that POC CRP testing in general practice is associated with significant reductions in antibiotic prescribing at the index consultation for patients with RTIs. Further individual patient data meta-analyses and studies with large sample sizes are needed to investigate the potential confounders that lead to the heterogeneity.

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Appendix 1. Search terms

ID	Search
#1	((exp Respiratory Tract Diseases/) OR (exp Respiratory Tract Infections/) OR ((respiratory adj3 (infection* or disease* or symptom*)).tw.) OR (exp Sick Building Syndrome/) OR (exp Otitis Media/) OR (exp Common Cold/) OR (exp Influenza, Human/) OR (exp Asthma/) OR (exp Rhinitis/) OR (exp Sinusitis/) OR (exp Cough/) OR (exp pharyngitis/) OR (exp laryngitis/) OR ((laryngotracheobronchit*).ti,ab.) OR (exp tonsillitis/) OR (exp peritonsillar abscess/) OR (exp croup/) OR (exp epiglottitis/) OR ((supraglottit*).ti,ab.) OR ((rhinosinusit*).ti,ab.) OR (exp otitis media/))
#2	((C reactive protein).ti,ab.)
#3	((exp anti-infective agents/) OR (exp anti-bacterial agents/) OR ((anti-biotic* or antibiotic* or anti-infect* antiinfect* or antibacteria* or anti-bacteria*).ab,ti.) OR ((microbicide* or anti-microbi* or antimicrobi* or microbi*).ab,ti.) OR ((beta-lactam* or betalactam* or B-lactam* or aminoglycoside* or vancomycin).ab,ti.))
#4	(#1 AND #2 AND #3)

No restriction was placed on the publication language. References were also screened from retrieved articles and reviews to identify additional articles that met the eligibility criteria.