Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care (Review)

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[Intervention Review]

Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New, published in Issue 11, 2014.
Review content assessed as up-to-date: 16 January 2014.

Citation: Aabenhus R, Jensen JUS, Jørgensen KJ, Hróbjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. *Cochrane Database of Systematic Reviews* 2014, Issue 11. Art. No.: CD010130. DOI: 10.1002/14651858.CD010130.pub2.

ABSTRACT

Background

Acute respiratory infections (ARIs) are by far the most common reason for prescribing an antibiotic in primary care, even though the majority of ARIs are of viral or non-severe bacterial aetiology. Unnecessary antibiotic use will, in many cases, not be beneficial to the patients' recovery and expose them to potential side effects. Furthermore, as a causal link exists between antibiotic use and antibiotic resistance, reducing unnecessary antibiotic use is a key factor in controlling this important problem. Antibiotic resistance puts increasing burdens on healthcare services and renders patients at risk of future ineffective treatments, in turn increasing morbidity and mortality from infectious diseases. One strategy aiming to reduce antibiotic use in primary care is the guidance of antibiotic treatment by use of a point-of-care biomarker. A point-of-care biomarker of infection forms part of the acute phase response to acute tissue injury regardless of the aetiology (infection, trauma and inflammation) and may in the correct clinical context be used as a surrogate marker of infection, possibly assisting the doctor in the clinical management of ARIs.

Objectives

To assess the benefits and harms of point-of-care biomarker tests of infection to guide antibiotic treatment in patients presenting with symptoms of acute respiratory infections in primary care settings regardless of age.

Search methods

We searched CENTRAL (2013, Issue 12), MEDLINE (1946 to January 2014), EMBASE (2010 to January 2014), CINAHL (1981 to January 2014), Web of Science (1955 to January 2014) and LILACS (1982 to January 2014).

Selection criteria

We included randomised controlled trials (RCTs) in primary care patients with ARIs that compared use of point-of-care biomarkers with standard of care. We included trials that randomised individual patients as well as trials that randomised clusters of patients (cluster-RCTs).

Data collection and analysis

Two review authors independently extracted data on the following outcomes: i) impact on antibiotic use; ii) duration of and recovery from infection; iii) complications including the number of re-consultations, hospitalisations and mortality; iv) patient satisfaction. We assessed the risk of bias of all included trials and applied GRADE. We used random-effects meta-analyses when feasible. We further analysed results with a high level of heterogeneity in pre-specified subgroups of individually and cluster-RCTs.

Main results

The only point-of-care biomarker of infection currently available to primary care identified in this review was C-reactive protein. We included six trials (3284 participants; 139 children) that evaluated a C-reactive protein point-of-care test. The available information was from trials with a low to moderate risk of bias that address the main objectives of this review.

Overall a reduction in the use of antibiotic treatments was found in the C-reactive protein group (631/1685) versus standard of care (785/1599). However, the high level of heterogeneity and the statistically significant test for subgroup differences between the three RCTs and three cluster-RCTs suggest that the results of the meta-analysis on antibiotic use should be interpreted with caution and the pooled effect estimate (risk ratio (RR) 0.78, 95% confidence interval (CI) 0.66 to 0.92; I^2 statistic = 68%) may not be meaningful. The observed heterogeneity disappeared in our preplanned subgroup analysis based on study design: RR 0.90, 95% CI 0.80 to 1.02; I^2 statistic = 5% for RCTs and RR 0.68, 95% CI 0.61 to 0.75; I^2 statistic = 0% for cluster-RCTs, suggesting that this was the cause of the observed heterogeneity.

There was no difference between using a C-reactive protein point-of-care test and standard care in clinical recovery (defined as at least substantial improvement at day 7 and 28 or need for re-consultations day 28). However, we noted an increase in hospitalisations in the C-reactive protein group in one study, but this was based on few events and may be a chance finding. No deaths were reported in any of the included studies.

We classified the quality of the evidence as moderate according to GRADE due to imprecision of the main effect estimate.

Authors' conclusions

A point-of-care biomarker (e.g. C-reactive protein) to guide antibiotic treatment of ARIs in primary care can reduce antibiotic use, although the degree of reduction remains uncertain. Used as an adjunct to a doctor's clinical examination this reduction in antibiotic use did not affect patient-reported outcomes, including recovery from and duration of illness. However, a possible increase in hospitalisations is of concern. A more precise effect estimate is needed to assess the costs of the intervention and compare the use of a point-of-care biomarker to other antibiotic-saving strategies.

PLAIN LANGUAGE SUMMARY

Use of rapid point-of-care testing for infection to guide doctors prescribing antibiotics for acute respiratory infections in primary care settings

Review question

We reviewed the evidence of the effect and safety of a rapid test of infection at point-of-care for using antibiotics in people with acute respiratory infections (ARIs) (e.g. common colds) in primary care.

Background

Antibiotic treatment is common in ARIs despite the fact that the vast majority are caused by viruses, against which antibiotics are ineffective and unnecessary. The concern is that antibiotics may cause side effects and are directly associated with antibiotic resistance in common bacteria, causing treatment failure and complications, including death. Antibiotics have a modest, if any, effect against the majority of ARIs. Their use must be balanced against risking higher levels of antibiotic resistance, side effects and costs. Biomarkers of infection are proteins or components of the immune system that participate in the body's acute response to infection. No tests are currently able to provide perfect diagnostic accuracy for infections. This could lead to over- as well as under-diagnosis. Some tests have been developed that assess the presence of infections by looking for certain of these biomarkers. These are rapid tests that may be used during the consultation by primary care doctors when people go to see them with symptoms of an ARI. In the correct clinical context these point-of-care tests could assist primary care doctors by identifying people with infections that are most likely to respond

to antibiotics. We looked at the evidence for these tests to assess the possible harms and benefits of implementing such a strategy in primary health care.

Study characteristics

We included six studies with a total of 3284 participants with ARIs from primary care settings (point-of care test: C-reactive protein). Two of the included studies received direct financial support from manufacturers. The evidence is current to January 2014.

Key results

The only point-of-care biomarker of infection currently available to primary care identified in the review was C-reactive protein. A reduction in antibiotic use is likely to be achieved by a C-reactive protein point-of-care test but due to differences in the designs of the included studies, it was not possible to obtain a precise effect estimate of the reduction. There were no deaths in the studies and we did not find evidence suggesting that time to recovery from ARIs and their duration were longer, nor that levels of patient satisfaction or number of re-consultations were affected in the C-reactive protein group. However, a possible increase in the risk of hospital admission cannot be ruled out.

Quality of the evidence

We ranked the evidence as of moderate quality according to the GRADE levels due to an imprecise effect estimation.

Conclusion

Used as an adjunct to a doctor's clinical examination point-of-care tests (e.g. C-reactive protein) can reduce antibiotic use in ARIs in general practice. The possibility of an increased risk of hospital admission suggests that care must be taken in how these tests are used. A more precise effect estimate is needed to assess the costs of the intervention and compare the use of a point-of-care biomarker to other antibiotic-saving strategies.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Point-of-care biomarker for infection compared with standard of care for guiding antibiotic therapy in acute respiratory infections

Patient or population: patients with acute respiratory infections
Settings: primary care
Intervention: point-of-care biomarker (C-reactive protein) test
Comparison: standard care

Outcomes	Illustrative comparative risks* (95% CI)		Effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Standard care	C-reactive protein				
Mortality (C-reactive protein) Follow-up: 28 days	-	-	-	3284 (6)	⊕⊕⊕⊕ **high**	No participants died in these studies
No. of antibiotic prescriptions (C-reactive protein) *Index* consultation	**Individual RCTs: study population**		**RR 0.90** (0.80 to 1.02)	1309 (3)	⊕⊕⊕◯ **moderate**	I^2 statistic = 5%
	519 per 1000	**467 per 1000** (415 to 529)				
	Cluster-RCTs: study population		**RR 0.68** (0.61 to 0.75)	1975 (3)		I^2 statistic = 0%
	525 per 1000	**357 per 1000** (320 to 394)				
No. of antibiotic prescriptions (C-reactive protein) Follow-up: **28** days	**Individual RCTs: study population**		**RR 0.87** (0.75 to 1.02)	497 (2)	⊕⊕⊕◯ **moderate**[1]	I^2 statistic = 7%

	623 per 1000	**542 per 1000** (467 to 635)				
	Cluster-RCTs: study population		**RR 0.68** (0.51 to 0.91)	211 (2)		I^2 statistic = 19%
	629 per 1000	**428 per 1000** (321 to 572)				
Clinical recovery. No. of participants with at least 'substantial improvement' Follow-up: **7** days	**Individual RCTs: study population**		**RR 1.03** (0.93 to 1.14)	1264 (3)	⊕⊕⊕○ **moderate**[1]	I^2 statistic = 0%
	414 per 1000	**426 per 1000** (385 to 472)				
Clinical recovery Follow-up: **28** days	**Individual and cluster-RCTs: study population**		**RR 0.94** (0.69 to 1.28)	527 (3)	⊕⊕⊕○ **moderate**[1]	I^2 statistic = 0%
	758 per 1000	**713 per 1000** (523 to 970)				

*The **assumed risk** was calculated as the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]We downgraded the GRADE judgement to moderate as the heterogeneity, albeit well explained, generates imprecision in the main effect estimate.

BACKGROUND

Description of the condition

Treating acute respiratory infections (ARIs) with antibiotics is common in primary care settings, despite their predominant (> 70%) viral aetiology (Gonzales 2001; Goossens 2005; Harnden 2007; Pavia 2011), and the fact that antibiotic treatment is of marginal benefit in uncomplicated cases (Arroll 2005; Butler 2009; Butler 2011; Little 2013b; Meropol 2013). Antibiotic use is associated with antibiotic resistance, which in turn leads to ineffective treatments and increased healthcare costs (Carlet 2011; Smith 2013). Limiting unnecessary antibiotic prescriptions in primary care settings is pivotal in reducing bacterial resistance to antibiotics at both societal (Gonzales 2001; Bronzwaer 2002; Sande-Bruinsma 2008) and individual levels (Costelloe 2010), as well as reducing the risk of side effects. A reduction in antibiotic prescriptions in primary care settings will have a large impact on the total use of antibiotics, as the majority of antibiotic prescriptions are issued in primary care settings (Danmap 2010; Goossens 2005). Nevertheless, patient safety must be carefully assessed to minimise the risk of under-treatment of serious bacterial infections.

Other types of interventions to reduce antibiotic use have been studied, for example, educational interventions (Arnold 2009), where use of multifaceted approaches and communication skills training have been effective (Butler 2012; Gjelstad 2013). A policy of delayed antibiotic prescription can also reduce antibiotic use (Spurling 2011).

The decision to prescribe antibiotics for an ARI in primary care settings is challenging and often based solely on clinical symptoms (Hopstaken 2005a), an approach known to have both low sensitivity and specificity (Hoare 2006; Metlay 1997) and high inter-observer variability (Wipf 1999). In accordance with this, there is evidence of substantial between-practitioner differences (Stocks 2002), and geographical variation in antibiotic prescribing patterns (Matthys 2007).

Description of the intervention

Biomarkers of infection, such as white blood cell levels, procalcitonin and C-reactive protein, form part of the acute immune response and are activated by endogenous and exogenous stimuli following tissue injury due to infectious and non-infectious conditions such as inflammation and trauma. Circulating levels are low in healthy people, but when stimulated synthesis and recruitment is rapid (less than 20 hours) levels remain high as long as the inflammation and tissue damage persists and then decline rapidly (Becker 2004; Volanakis 2001). Biomarkers of infection act as surrogate measures of the immune response to infection and may reflect the severity of the condition (i.e. degree of tissue damage and immune activation) (Aabenhus 2011; Kruger 2009; Schuetz 2012), but cannot determine aetiology or predict an infiltrate on chest X-rays (Holm 2007; van der Meer 2005). No currently available test is able to provide perfect diagnostic accuracy, and false negative as well as false positive results may occur, leading to possible over- as well as under-treatment of ARIs. However, in the correct clinical context biomarkers may guide appropriate antibiotic prescriptions in selected cases by ruling out a serious bacterial infection and identify patients in whom no benefit from antibiotic treatment can be anticipated (Melbye 2011; Schuetz 2012). A point-of-care test exists for some of these biomarkers to be performed at, or near, the site of patient care, delivering quick test results that can influence clinical decisions (Table 1).

The decision to prescribe antibiotics for an ARI is guided by prespecified cut-off values specific to the individual point-of-care test but the test cannot replace clinical skills and expertise, and test results may be overruled on clinical grounds.

How the intervention might work

Following a regular clinical examination that suggests presenting symptoms are indeed compatible with an ARI, a point-of-care biomarker may assist the clinician to assess the likelihood of a serious bacterial infection versus a less severe bacterial or viral infection, thus identifying those patients most likely to benefit from antibiotics (Aabenhus 2011; Hopstaken 2003; Melbye 2011; Schuetz 2012). If after the clinical examination the clinician is confident in the decision to initiate or withhold antibiotic treatment, there is no need for a point-of-care test. Possible detrimental effects of point-of-care biomarkers include suboptimal use of time, costs, handling errors, patient dissatisfaction and false negative values that can lead to lack of necessary antibiotic treatments or false positive values that may increase inappropriate antibiotic use. Studies indicate that the use of point-of-care tests during consultations is acceptable to both doctors and patients (Butler 2008; Wood 2011).

Why it is important to do this review

Avoiding both over- and under-treatment with antibiotics in primary care settings is important to limit antibiotic resistance and exposure of patients to unnecessary risks. Debate concerning the effect of using point-of-care biomarkers is ongoing as published reviews have shown conflicting results (Engel 2011; Huang 2013; Schuetz 2012). However, additional potential relevant studies have been published since then and only the review of procalcitonin assessed patient safety outcomes in a systematic way (Schuetz 2012). We included studies of all available point-of-care biomarkers of infection used for ARIs in our review. Updates of this review will include studies of additional point-of-care tests as they become available.

OBJECTIVES

To assess the benefits and harms of point-of-care biomarker tests of infection to guide antibiotic treatment in patients presenting with symptoms of acute respiratory infections in primary care settings regardless of age.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials (RCTs) and cluster-RCTs.

Types of participants

Primary care patients of all ages with symptoms from, or a diagnosis of, an ARI at study entry. Symptoms of ARI were defined as cough, discoloured/increased sputum, fever, runny nose, respiratory distress, feeling unwell, or combinations of focal and systemic symptoms having a duration of less than four weeks. Diagnoses included lower or upper respiratory tract infection, pneumonia, bronchitis, acute exacerbations of chronic obstructive pulmonary disease or asthma, pharyngitis, tonsillitis, laryngitis, rhinosinusitis, common cold, acute otitis media or influenza.

Types of interventions

Point-of-care biomarkers of infection to guide antibiotic treatment for ARI in primary care settings. We only included studies of biomarker point-of-care tests for infections available for general use. Specific diagnostic tests like the Strep A test or Monospot were not included in this review. The biomarkers we considered were C-reactive protein, procalcitonin and white blood cell count. The comparator was standard care.

Types of outcome measures

Primary outcomes

1. Number of patients given an antibiotic prescription at the index consultation and at 28 days follow-up.
2. Number of patients with substantial improvement (including full recovery) at day seven.
3. Total mortality at 28 days follow-up.

Secondary outcomes

1. Number of patients in need of a re-consultation at 28 days follow-up.
2. Number of patients in need of a hospital admission at 28 days follow-up.
3. Duration of the ARI (e.g. mean or median days with restrictions in daily activities due to the infection).
4. Number of satisfied patients.
5. Number of patients with substantial improvement (including full recovery) at 28 days follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 12) (accessed 16 January 2014), MEDLINE (1946 to January week 2, 2014), EMBASE (2010 to January 2014), CINAHL (1981 to January 2014), Web of Science (1955 to January 2014) and LILACS (1982 to January 2014). The search strategy used for CENTRAL and MEDLINE is described in Appendix 1. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search EMBASE (Appendix 2), CINAHL (Appendix 3), Web of Science (Appendix 4) and LILACS (Appendix 5). We applied no language or publication restrictions.

Searching other resources

Trials

We searched the trials registries of the US National Institutes of Health (www.clinicaltrials.gov) and the World Health Organization (www.who.int/ictrp) in March 2013 for completed and ongoing trials. We repeated the search in WHO ICTRP in January 2014.

Abstracts

We checked abstracts presented at the following conferences from 2000 onwards.

1. British Thoracic Society (BTS) - winter and summer meetings.
2. Primary Care Respiratory Society (PCRS) - UK National Primary Care Conference.
3. Infectious Diseases Society of America (IDSA).

Correspondence

We contacted experts in the field to identify published, non-published or ongoing studies eligible for inclusion. We also contacted companies that manufacture point-of-care biomarkers (Thermo-Fisher, Hoffmann-LaRoche, Orion Diagnostica, Axis-Shield, Hemocue and Siemens Diagnostica).

Reference lists

We checked reference lists of included articles.

Data collection and analysis

Selection of studies

Two authors (RA and J-U SJ) independently assessed titles and abstracts identified through the searches. We collected and assessed full-text copies of potentially eligible articles. We resolved disagreements through discussion involving the remaining authors, when necessary.

Data extraction and management

Two authors (RA, J-U SJ) independently extracted data and information on study design from the included trials and entered the information into a data extraction form. We contacted the authors if outcome data or trial characteristics were not complete. We extracted the following data.

1. Trial characteristics: unit of randomisation; allocation sequence generation; concealment of allocation; blinding; number of participants; number of intervention arms; length of follow-up.
2. Patient characteristics: baseline characteristics (mean (or median) age; gender; co morbidities); number of patients randomised to each intervention arm; number of patients completing the trial; basis for inclusion in study; types of ARIs and duration; exclusion criteria.
3. Intervention characteristics: type of point-of-care biomarker and corresponding specified cut-off values for guidance of antibiotic prescribing if any.
4. Outcome measures: all available primary and secondary outcome measures specified for this review.

We converted ranking scales on recovery and patient satisfaction to dichotomised outcomes by collapsing response categories when needed. For cluster-RCTs we extracted intra-cluster correlation coefficients.

Assessment of risk of bias in included studies

Two authors (RA, J-U SJ) independently assessed the risk of bias of included studies using the 'Risk of bias' tool in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included assessment of sequence generation, allocation concealment, blinding (participants, personnel and outcome assessors), incomplete outcome data and selective outcome reporting bias, as well as other sources of bias. We searched for incomplete outcome data and selective outcome reporting by comparing the methods and results section with the trial protocols when available.

For cluster-RCTs, we specifically checked for other sources of bias including selection bias, baseline imbalance between clusters, loss of clusters and incorrect analysis (Higgins 2011). We ranked the quality of evidence according to the four-level Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Higgins 2011).

Measures of treatment effect

We reported the treatment effect as a risk ratio (RR) with 95% confidence intervals for each dichotomised outcome. We calculated the risk difference (RD) to estimate the number needed to test (NNT), indicating the NNT with a point-of-care test to save one antibiotic prescription. When we could not pool the results we presented them qualitatively.

Unit of analysis issues

The unit of analysis was the individual patient. For cluster-RCTs we adjusted the unit of analysis by calculating the design effect to modify sample sizes and inflate confidence intervals (CIs) accordingly (Higgins 2011).

Dealing with missing data

We did a worst-case scenario analysis where we considered missing outcome data as treatment failures in the intervention group and treatment successes in the control group.

Assessment of heterogeneity

We investigated heterogeneity using the I^2 statistic with a cut-off value of 40% to indicate important inconsistencies (Higgins 2011).

Data synthesis

We calculated a weighted estimate for the selected outcomes by means of a random-effects meta-analysis, using the Review Manager software (RevMan 2014), when possible.

Subgroup analysis and investigation of heterogeneity

We preplanned the following subgroup analyses.

1. Cluster-RCTs versus individual RCTs.
2. Type of point-of-care test.
3. Trials with low risk of bias versus high risk of bias.

Sensitivity analysis

We planned a sensitivity analysis for our primary outcomes using a fixed-effect model. However, this was not performed due to the substantial heterogeneity of data.

RESULTS

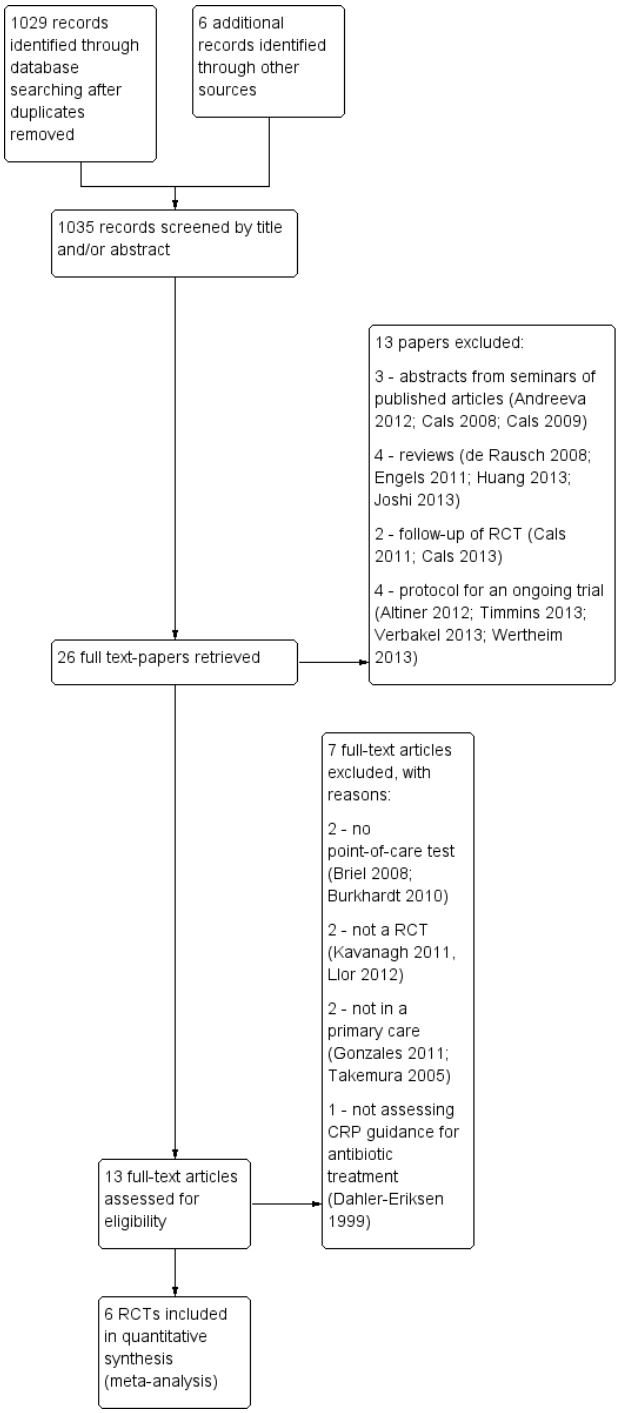
Description of studies

See: Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies.

Results of the search

The search flowchart is presented as Figure 1. We found six eligible studies, with a total of 3284 patients recruited from primary care settings. Diagnoses were predominately lower acute respiratory infections (75%) (Table 2). The only point-of-care biomarker included in the review was C-reactive protein. We found no studies that compared different kinds of biomarkers.

Figure 1. Study flow diagram.



Included studies

The included studies were conducted between 1995 and 2013 in Europe and Russia. Three trials were cluster-RCTs (Andreeva 2013; Cals 2009; Little 2013a) and three were individually RCTs (Cals 2010; Diederichsen 2000; Melbye 1995). Inclusion criteria differed among studies. Diederichsen 2000 and to a lesser extent Melbye 1995 used broad inclusion criteria, while the four newest studies used specific diagnostic criteria for lower and/or upper ARIs. We noted appreciable differences between the C-reactive protein cut-off values applied to guide antibiotic treatment, ranging from vague indications to specific recommendations for initiating and/or withholding antibiotic treatment (Table 3). Test results were made available to the doctors as part of the initial clinical assessment in the newest four studies, while Melbye 1995 only made results available to doctors after the initial clinical decision. The exact set-up was left to the participating doctors to accommodate in the Diederichsen 2000 study. The doctor could overrule C-reactive protein guidance in all trials. Outcome assessment was based on medical records regarding the number of antibiotic prescriptions, while secondary outcomes such as clinical recovery were patient-reported, using diaries and questionnaires, or follow-up visits at the clinics (Andreeva 2013; Melbye 1995).

Melbye 1995 was terminated by the principal investigator after one year without reaching the target inclusion rate due to an interim analysis that showed no difference between groups and also due to lack of interest from the participating general practitioners.

Diederichsen 2000 was the only study to include all age groups, including 139 children. The remaining studies only included participants older than 18 years.

Two studies received economic funding from manufacturers of C-reactive protein point-of-care tests (Cals 2010; Melbye 1995). Andreeva 2013 received test kits and/or reagents for the study. On-site training in C-reactive protein devices was performed by manufacturers in two studies (Diederichsen 2000; Little 2013a).

We successfully contacted a total of four study authors for additional details and in the case of Diederichsen 2000, we obtained raw data to calculate the number of patients with substantial improvement and to differentiate between children and adults.

Excluded studies

We excluded two RCTs using procalcitonin to guide antibiotic use in primary care because the analysis was not performed at the point-of-care (Briel 2008; Burkhardt 2010). Two RCTs were not conducted in a primary care setting (Gonzales 2011; Takemura 2005), and two studies used a before-and-after design (Kavanagh 2011; Llor 2012). We also excluded Dahler-Eriksen 1999, as this study did not assess C-reactive protein to guide antibiotic treatment decisions.

Risk of bias in included studies

We assessed the risk of bias for each study and this is presented graphically in Figure 2 and summarised in Figure 3. For further information on included studies see Characteristics of included studies.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

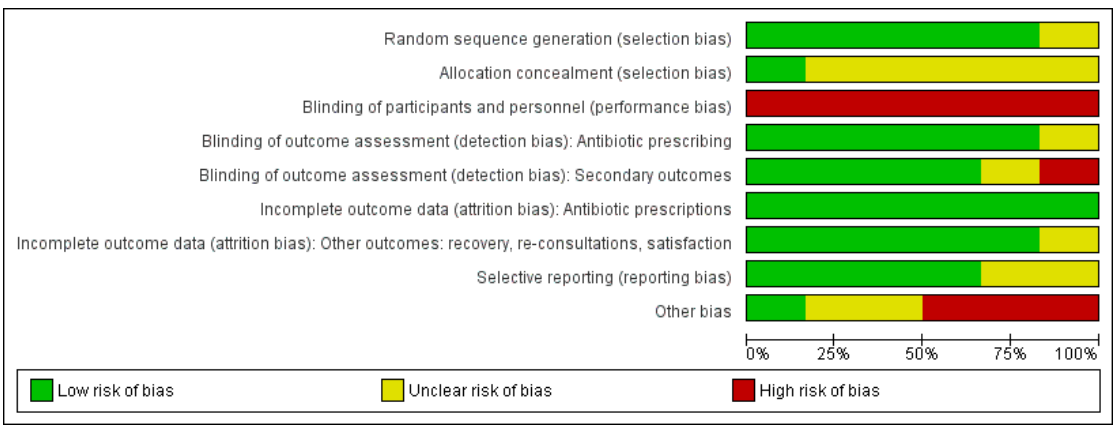
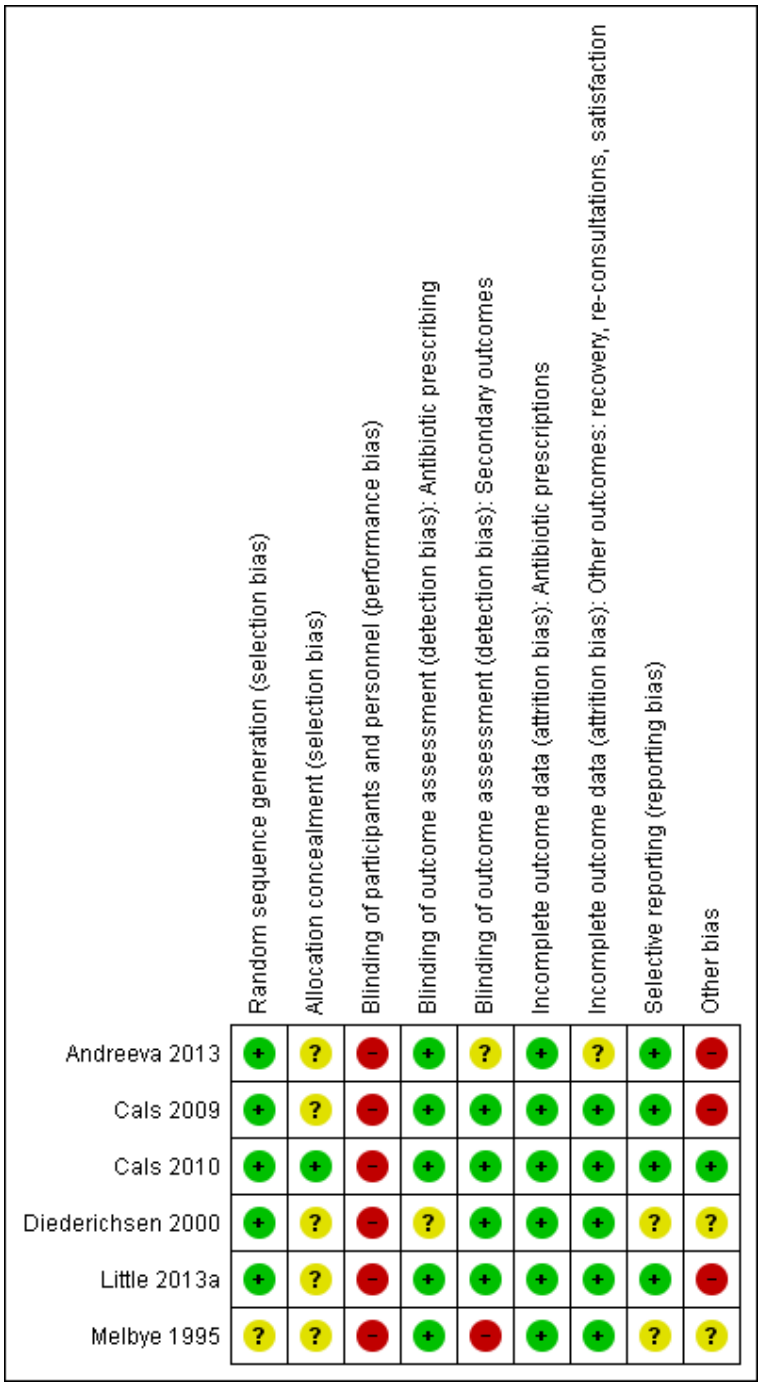


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The cluster-RCTs used computer randomisation programs to allocate practices to the intervention or control arms (Andreeva 2013; Cals 2009; Little 2013a). Cals 2010 used sequentially numbered, opaque, sealed envelopes prepared in different block sizes by an independent research team. Diederichsen 2000 provided no information on the sequence generation but state they used "pre-randomised sealed envelopes in blocks of 34". Melbye 1995 did not specify the randomisation procedure but according to the principal investigator this was adequately done at study sponsor level. Allocation concealment of individual patients does not apply to cluster-RCTs at practice level, so we graded this as 'unclear' risk of bias.

Blinding

This intervention did not lend itself to blinding at clinician level as the intervention was used in management decisions and all clinicians are considered non-blinded. Assessment of antibiotic use was based on electronic or paper records. Clinical recovery was based on diaries and questionnaires completed by the patient and did not involve study personnel in the majority of studies. However, Melbye 1995 and Andreeva 2013 assessed clinical recovery non-blinded at a follow-up visit.

Incomplete outcome data

We successfully retrieved incomplete reported outcome data on the use of antibiotic prescriptions by contacting the individual study authors when needed. Data on clinical recovery rates ranged from 90% to 98% in completeness between studies. Information necessary for subgroup analyses of serious versus non-serious infections could not be obtained as this was not reported and exact diagnoses not recorded. However, we were able to obtain data on the effect of C-reactive protein on antibiotic use for lower versus upper ARIs.

Selective reporting

We did not suspect selective reporting but only newer studies had a published protocol. All outcomes were reported as intention-to-treat.

Other potential sources of bias

Selection (recruitment) bias is a risk in cluster-RCTs as care providers assigned to the intervention group can select which patients to test (inclusion was at the discretion of the care provider). This means that patients with a higher than average likelihood that the test might change the clinical decision could preferentially be enrolled, e.g. those patients that the care provider perceived could be convinced that an intervention was not needed if a test was performed. This may exaggerate the estimated effect relative to more widespread use in clinical practice. However, measures to limit this 'active' recruitment by participating doctors were in place, e.g. by requirements for consecutive enrolment of the first eligible patients that presented in each practice. In the study by Cals 2009, significantly more patients in the control group had abnormalities on auscultation (60.3% versus 46.7%, P value = 0.005), a parameter closely linked to antibiotic prescription (Jakobsen 2010). However, in the larger study by Little 2013a symptom severity scores were balanced between groups.

Contamination bias is possible in individual RCTs as the general practitioner may gradually learn to foresee which patients have low C-reactive protein levels and apply this acquired skill in the control group. As most patients will have low values of C-reactive protein this would lead to decreased antibiotic prescription in the control group and underestimate the effect of the test.

Inclusion bias may occur in both trial designs as general practitioners may be reluctant to include patients with severe disease given the risk that antibiotic treatment is not recommended according to the test result. In individual RCTs, this potential bias would be non-discriminative as opposed to the cluster-RCTs, where this could be a discriminative bias. This may lead to a lower estimate of the effect of biomarkers in individual RCTs (a priori risk of antibiotic treatment is low in both groups) but may overestimate the effect in cluster-RCTs (a priori risk of antibiotic treatment is different between intervention (low) and control groups (normal)).

Effects of interventions

See: **Summary of findings for the main comparison**

Primary outcomes

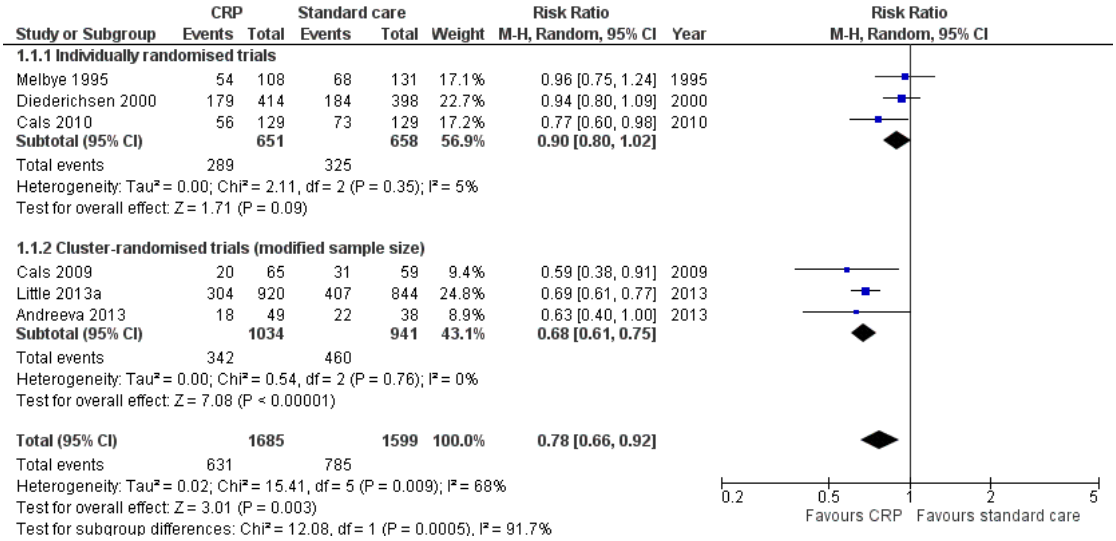
1. Number of patients given an antibiotic prescription at the index consultation and at 28 days follow-up

See Summary of findings for the main comparison.

All six studies, including 3284 patients (mean age 46, standard deviation (SD) 17), reported point estimates in favour of the C-reactive protein test to reduce the number of antibiotic prescriptions in acute respiratory infections. The pooled result for all included trials showed a statistically significant effect of C-reactive protein testing on the number of antibiotic prescriptions issued in primary care settings for acute respiratory infections (ARIs) (risk ratio (RR) 0.78, 95% confidence interval (CI) 0.66 to 0.92; I^2 statistic = 68%) (Analysis 1.1; Figure 4), but with considerable heterogeneity. The heterogeneity disappeared in our pre-planned

subgroup analysis of cluster-randomised controlled trials (RCTs) versus individual RCTs, suggesting that it may not be meaningful to pool all trials.

Figure 4. Forest plot of comparison: 1 C-reactive protein - antibiotic prescribing: all trials, outcome: 1.1 C-reactive protein - antibiotics prescribed at index consultation. All trials (cluster-RCTs modified sample size):.

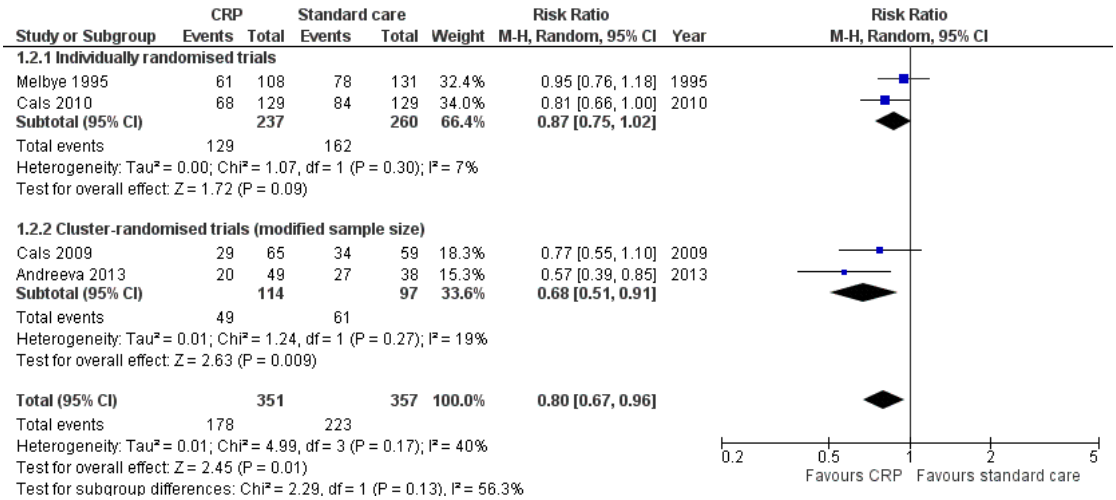


The individual RCTs (N = 1309) indicated a reduction in antibiotic use (RR 0.90, 95% CI 0.80 to 1.02; I^2 statistic = 5%) (Analysis 1.1.1; Figure 4), although the result was not statistically significant, while the cluster-RCTs (N = 1975) showed a more pronounced effect (RR 0.68, 95% CI 0.61 to 0.75) (Analysis 1.1.2; Figure 4).

We calculated the number needed to test (NNT) to save one antibiotic prescription at the index consultation as 20 for individual RCTs and six for cluster-RCTs (Table 4).

The effect found at index consultation on the reduction in antibiotic use was maintained at day 28 and no evidence was found that patients in the C-reactive protein group needed additional antibiotic treatment between the index consultation and 28 days of follow-up compared to standard of care (Analysis 1.2; Figure 5).

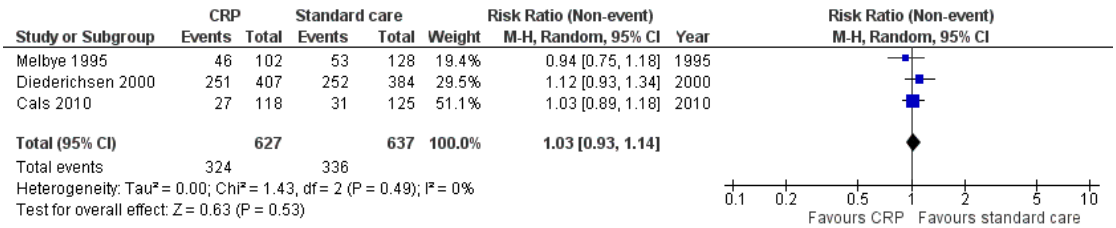
Figure 5. Forest plot of comparison: 1 C-reactive protein - antibiotic prescribing: all trials, outcome: 1.2 C-reactive protein - antibiotics prescribed within 28 days (cluster-RCT with modified sample size).



2. Number of patients with substantial improvement (including full recovery) at day seven

We found no differences in clinical recovery (defined as at least substantial improvement) at day seven between groups (Analysis 2.1; Figure 6).

Figure 6. Forest plot of comparison: 4 C-reactive protein - Patient recovery day 7: Individually randomised trials, outcome: 2.1 Substantial improvement day 7.



3. Total mortality at 28 days follow-up

No deaths or serious complications were reported in any of the studies.

Secondary outcomes

1. Number of patients in need of a re-consultation at 28 days follow-up

There were no significant differences in re-consultation rates (Analysis 3.1).

2. Number of patients in need of a hospital admission at 28 days follow-up

Five of the six studies reported that there had been no hospitalisations in the follow-up period. Little 2013a reported a total of 30 hospitalisations in 4264 patients, 22 in the C-reactive protein group versus eight in the control group (crude RR 2.53, 95% CI 1.13 to 5.66). However, when adjusting for the design effect of cluster-RCTs by modifying sample sizes, this difference ceased to be statistically significant (RR 2.45, 95% CI 0.65 to 9.19). Information on hospital admissions was obtained through a medical history review in 15 cases. The reasons were cardiac (two); respiratory (eight), generally unwell/fever (two); gastrointestinal symptoms (two); sinusitis (one). All hospitalisations may not have been directly related to the intervention. However, an increase in the risk of hospitalisation in the C-reactive protein group cannot be ruled out, although the absolute event rate is low. Data were not available to determine the number of hospitalised patients who were initially withheld from receiving antibiotic treatment, nor the C-reactive protein level at index consultation.

3. Duration of the acute respiratory infection (e.g. mean or median days with restrictions in daily activities due to the infection)

Three studies reported on this outcome but a pooled analysis could not be performed due to differences in assessing duration of symptoms (Table 5). Cals 2009 reported no differences in the median symptom duration to full recovery, while Cals 2010 also provided this measure as a mean number of days. Little 2013a reported the time to resolution of symptoms rated moderately bad or worse. No differences were observed in any of these patient-reported measures.

4. Number of satisfied patients

We detected no differences. However, the substantial heterogeneity (I^2 statistic = 45%) detected and the fact that only two studies reported on this outcome does not allow us to draw clear conclusions (Analysis 4.1).

5. Number of patients with substantial improvement (including full recovery) at 28 days of follow-up

We found no differences in clinical recovery (defined as at least substantial improvement) at day 28 between groups (Analysis 5.1).

Sensitivity and subgroup analyses

As substantial heterogeneity related to trial designs was present, we omitted the pre-planned sensitivity analysis using a fixed-effect meta-analysis.

Trials with low versus high risk of bias: as the intervention did not lend itself to blinding, we chose to omit this component when selecting studies with a low risk of bias. Accordingly, Cals 2010 was the only trial with a low risk of bias (Figure 3). The result of this trial was RR 0.77, 95% CI 0.60 to 0.98.

Only one study, Diederichsen 2000, reported specifically on the effect in children (N = 139) and found no significant effect (RR 1.09, 95% CI 0.70 to 1.71) (Analysis 6.1). Individual disease labelling in severe versus less severe diseases as planned in the protocol was not possible due to lack of data. However, the effect of the C-reactive protein test on antibiotic prescriptions was similar in upper and lower ARIs (Analysis 7.1).

To assess the substantial heterogeneity and the subgroup differences detected, we performed a post hoc analysis of the newer studies (Andreeva 2013; Cals 2009; Cals 2010; Little 2013a), with specific guidance on antibiotic prescription if C-reactive protein levels were < 20 mg/L. This analysis showed a significant reduction in antibiotic use (RR 0.69, 95% CI 0.62 to 0.76; I^2 statistic = 0%) (Analysis 8.1).

Sensitivity analyses assuming a worst-case scenario, where all patients in the C-reactive protein group lost to follow-up did not improve and all patients in the control group lost to follow-up did substantially improve, also showed no significant differences (day seven; RR 1.10, 95% CI 0.99 to 1.21; I^2 statistic = 0% and day 28; RR 1.11, 95% CI 0.84 to 1.48; I^2 statistic = 0%) (Analysis 9.1; Analysis 9.2).

A summary of the secondary outcomes is presented in Table 6.

DISCUSSION

Summary of main results

We identified and analysed six randomised trials with 3284 participants. Our results indicate that C-reactive protein point-of-care tests to guide antibiotic prescription in lower as well as upper acute respiratory infections (ARIs) in general practice can reduce antibiotic use and it is unlikely that the intervention increases morbidity. No studies reported that deaths had occurred in either the intervention or control groups.

A precise estimate of the reduction in antibiotic use was not obtained due to substantial heterogeneity between trials that were likely related to differences in design. Individual RCTs showed a statistically non-significant relative reduction of antibiotic prescriptions (risk ratio (RR) 0.90, 95% confidence interval (CI) 0.80 to 1.02; I^2 statistic = 5%), while cluster-RCTs at the general practice level reported a statistically significant reduction (RR 0.68, 95% CI 0.61 to 0.75; I^2 statistic = 0%). We note that individual point estimates from all trials indicated a reduction in antibiotic use.

In this context and despite being prone to bias, the cluster-RCT method may be considered a more pragmatic design that more closely reflects everyday practice, where C-reactive protein testing is either available or not in a given general practice.

The observed heterogeneity may also in part be explained by the different inclusion criteria and C-reactive protein algorithms applied, where restrictive recommendations on antibiotic use generally showed a more pronounced effect (Table 3). Newer studies (published in the last five years) provide guidance on when to withhold or initiate antibiotic treatment using specific cut-off values.

No differences were found regarding patient-reported outcomes. No deaths or serious adverse events were reported, but one trial reported an increase in hospitalisations in the C-reactive protein group (Little 2013a). However, the absolute numbers of events were low (22 versus 8 events in 4264 patients) and the finding was non-significant when adjusting for the design effect. Nevertheless, this suggests that the suspected benefits of reducing antibiotic use in ARIs (de-medicalisation, containing development of antibiotic resistance, costs and fewer side effects) must be balanced against the potential safety concerns of a small increased risk of hospitalisation. C-reactive protein may be an adjunct to the physical examination but cannot replace clinical skills and appropriate safety-netting must be applied.

Overall completeness and applicability of evidence

The included trials were mainly from European countries with considerable differences in antibiotic use and organisation of primary care. The studies had high levels of completeness for both primary (100%) and secondary outcomes (90% to 98%) and all results were reported as intention-to-treat. All studies provided a measure of clinical recovery and four studies used very similar case report forms and C-reactive protein algorithms (Andreeva 2013; Cals 2009; Cals 2010; Little 2013a). The algorithms obviously affect both patient safety and the potential reduction in antibiotic use, as does the a priori likelihood of antibiotic use in any given patient population. By including different algorithms in this review, we regard the findings as a 'proof of concept', but identification of an optimal algorithm was not possible.

This review encompassed different respiratory infections with varying anatomical localisation, but C-reactive point-of-care testing was associated with a similar reduction in antibiotic use for both upper and lower ARIs.

Intra-cluster coefficients to inflate the confidence intervals of cluster-RCTs were provided (Cals 2009; Little 2013a), to allow inclusion in our meta-analysis. We had pre-specified a random-effects model to account for an expected moderate heterogeneity among included trials regarding study design (cluster-RCTs versus individual RCTs), and differences in the C-reactive protein algorithms and inclusion criteria (Table 3).

Only the two oldest trials did not show a significant effect on antibiotic prescriptions (Diederichsen 2000; Melbye 1995), which could partly be because the use of antibiotics in primary care in Europe has increased overall during the last decade (Adriaenssens 2011). If this increase in antibiotic use mainly reflects excessive prescriptions, the net effect of C-reactive protein guidance may have increased.

Many patients express worries about their symptoms and seek medical re-assurance of the benign course of their illness. However, general practitioners are often faced with varying degrees of uncertainty in their management decision and a point-of-care test to rule out serious infection may increase confidence and acceptance of the decision not to use antibiotic treatment (Stanton 2010). E-learning or short seminars can be used to achieve the necessary skills for interpretation of the test results in clinical practice (Cals 2009; Yardley 2013).

The results of this review should not be generalised to include children or patients with severe co-morbidities and/or immunocompromised patients.

Quality of the evidence

The available information was from trials with a low to moderate risk of bias that address the main objectives of this review. Included studies provided data on antibiotic use at index consultation and reported at least one measure of patient safety or recovery. One of the primary outcomes (antibiotic use) was directly observed and not assessor-dependent. This intervention did not lend itself to blinding of the provider as its purpose was to influence clinical decisions, but studies were otherwise well reported and appeared to be of moderate to good quality. The studies included patients relevant to a European primary care context.

The relatively small number of individual RCTs, adding a total of 40% of the cases, is of some concern. However, we accounted for the included cluster-RCTs by inflating confidence intervals accordingly and assessing the increased risk of bias from selection and allocation concealment. We preplanned subgroups of analysis based on study design.

However, due to the considerable heterogeneity in the pooled analysis of all trials we have presented subgroup results. The observed heterogeneity may well be explained by differences in study design (individual RCTs versus cluster-RCTs) and the different C-reactive protein algorithms applied (Table 3). Our decision to downgrade the quality of the evidence was primarily driven by imprecision of the estimated effect of the pooled analysis on antibiotic prescribing (Summary of findings for the main comparison).

Potential biases in the review process

To the best of our knowledge, no bias was introduced in the review process.

Agreements and disagreements with other studies or reviews

To our knowledge only two other studies have systematically reviewed the evidence for C-reactive protein point-of-care tests to guide antibiotic prescription in primary care. Engel 2011 concluded that current evidence did not support the use of C-reactive protein in primary care for this purpose. However, no meta-analyses were performed without a stated reason. Huang 2013, on the other hand, reported a reduction in antibiotic use for ARIs (RR 0.75, 95% CI 0.67 to 0.83) but with considerable heterogeneity (I^2 statistic = 76%). However, the main meta-analysis included both RCTs as well as observational studies. Also, both reviews did not include the two latest trials (Andreeva 2013; Little 2013a), adding a total of 1851 patients to the analysis with a weight of 9.2% and 24.6%, respectively.

Studies have reported that the C-reactive protein test may not be sufficiently sensitive and specific to be of diagnostic value in primary care where the incidence of serious bacterial infection is low (Falk 2009; van der Meer 2005), but it forms part of a number of prediction rules for pneumonia (Steurer 2011; van Vugt 2011), and its use is advocated in the most recent European guidelines on the management of lower ARIs (Woodhead 2011). Of note, C-reactive protein is no perfect test and a risk exists for over- as well as under-treatment with antibiotics. This highlights the importance of limiting the use of this tool to a correct clinical context: a doctor stating that the symptoms presented are caused by an acute respiratory tract infection and uncertainty exists regarding the potential benefit of antibiotic therapy.

A Cochrane review suggests that the biomarker procalcitonin (currently unavailable as point-of-care test for primary care) could be a safe and effective tool to guide decisions about antibiotic treatment of ARIs (Schuetz 2012). The results of this review are in line with these recommendations.

Of note, studies comparing communication training to C-reactive protein point-of-care testing showed similar potential to reduce antibiotic use, while an additive effect was observed when both C-reactive protein tests and training sessions in communication skills were combined (Cals 2009; Little 2013a).

AUTHORS' CONCLUSIONS

Implications for practice

Use of C-reactive protein point-of-care tests as an adjunct to clinical examination likely reduces antibiotic use in primary care patients with acute (lower as well as upper) respiratory infections without affecting patient recovery rates or the duration of illness. However, a possible small increased risk of hospitalisation cannot be ruled out and safety-netting should accompany use of a point-of-care C-reactive protein test. The attending physician must balance this risk against the benefit of reduced antibiotic use including costs, fewer side effects and drug interactions, de-medicalisation of self limiting illness and less risk of antibiotic resistance.

At present C-reactive protein is the only point-of-care biomarker available in primary care settings that may assist in guiding antibiotic prescribing for ARIs.

Implications for research

A more precise effect estimate regarding antibiotic use is needed to assess the cost-effectiveness of this intervention. Despite the pragmatic design of cluster-RCTs, a risk of overestimating the true effect remains.

Furthermore, as clinical and geographic variation between the included trials was limited, validation of C-reactive protein guidance in ARIs globally is needed. As expected, the most pronounced effect of the intervention occurred in studies with a restrictive C-reactive protein strategy. As no fatalities occurred and the absolute risk of hospital admission was below 1%, a C-reactive protein level < 20 mg/L to rule out serious respiratory infection seems fairly safe and we recommend its use also in future trials.

The vast majority of participants in the trials were middle aged adults (mean age 46, standard deviation (SD) 17), highlighting the need for additional studies on children and people aged over 70 years.

The cost-effectiveness of C-reactive protein tests should be assessed prior to a widespread implementation of C-reactive protein guidance as standard practice.

ACKNOWLEDGEMENTS

We wish to thank Sarah Thorning from the Cochrane ARI Group for assistance with the electronic search. We also wish to thank the following people for commenting on the draft protocol and review: Amanda Roberts, Janet Wale, Anette Holm, Renato Seligman, Robert Ware, Mark Jones and Inge Axelsson.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Andreeva 2013

Methods	Non-blinded cluster-randomised clinical trial, multicentre in 8 General Practice offices with a total of 18 doctors in Arkhangelsk and Murmansk regions, Russia
Participants	Inclusion criteria: adult patients (> 18 years) with index case of lower respiratory tract infection/acute cough for less than 28 days Exclusion criteria: previously seen by GP for infection in question, immunocompromised status, ongoing treatment with oral corticosteroids Included in this analysis: 179 (48% and 39% were upper respiratory tract infections in intervention and control arm) (number tested for eligibility not stated)
Interventions	Guiding antibiotic decisions in primary care with a single point-of-care measurement of C-reactive protein Algorithm used in this study: C-reactive protein level < 20 mg/L, antibiotics usually not needed. C-reactive protein levels > 50 mg/L, antibiotic prescribing could be indicated taking into account the duration of illness Doctors were given training sessions in lower respiratory tract infection/acute cough and C-reactive protein testing
Outcomes	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)
Notes	Clinical trials reg. NCT01794819 Clinical recovery was assessed with a 5-point scale at a follow-up visit after 14 days Adherence to C-reactive protein suggested cut-offs (28% of patients with C-reactive protein < 20 mg/L were prescribed antibiotics) Before and after study was simultaneously performed and used as a sensitivity analysis Funding: none stated. Kits were provided by manufacturer and C-reactive protein readers were acquired at a reduced price Kit used: the Afinion test system (Axis-Shield, Norway) Training sessions on the use of C-reactive protein was given over 2 sessions including practical and theoretical information A sample size calculation was performed quote: "The sample sizes were based on a hypothesis of 20% reduction in antibiotic prescribing in the intervention group compared to the control group." Power 90% and false positive difference < 5%. The sample size 72 in each group was reached. 20 control patients from 2 GPs were excluded due to incomplete registrations. Intracluster coefficients were not provided

	Symptom severity was similar between groups but feeling unwell and experiencing interference with daily activities was more common in the intervention group. Wheeze and perceived patient preference for antibiotics occurred more often in the control group The primary outcome was number of antibiotic prescriptions and the study reported a significant reduction in the number of antibiotic prescriptions in the intervention arm of the study at index consultation (37.6% versus 58.9%; P value = 0.006) and after 14 days (40.6% versus 71.8%; P value = 0.0001). Also the number of referrals for chest radiography was significantly lower in the C-reactive protein group (P value = 0.004). No difference was seen in re-consultation rates nor the recovery rate between groups as determined on follow-up at day 14 on a 5-point scale (fully recovered; almost recovered; slightly improved; unchanged or worse). Sensitivity analysis performed as a before and after study with 11 of the 18 participating GPs found significant reductions due to introduction of C-reactive protein testing

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Cluster-randomisation into 2 groups was performed with GPs as units. Allocation sequence was performed by computer-generated numbers by second author
Allocation concealment (selection bias)	Unclear risk	Individual patient allocation concealment was not performed as the unit of randomisation was doctors and/or practices. Quote "based on this list [of clusters] and using the allocations sequence, the first author assigned clusters to interventions."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Interventions are targeted at the level of the GP. Cluster-randomisation was performed at the GP office level. Non-blinded trial where physicians and patients knew which treatment modality was used
Blinding of outcome assessment (detection bias) Antibiotic prescribing	Low risk	Data on antibiotic prescribing were obtained from medical records at end of study
Blinding of outcome assessment (detection bias) Secondary outcomes	Unclear risk	Unclear who (GPs, clinic personal or study group) performed this assessment, but patient recovery was determined at a follow-up consultation on day 14 using a 5-item recovery scale
Incomplete outcome data (attrition bias) Antibiotic prescriptions	Low risk	Follow-up for antibiotic prescribing and use 179/179 (100%)

Andreeva 2013 (*Continued*)

Incomplete outcome data (attrition bias) Other outcomes: recovery, re-consultations, satisfaction	Unclear risk	Recovery data were available in 176/179 (98%) on day 14. However, there are inconsistencies in table 2 as % are calculated on enrolled patients and not on patients providing data. Data not reported for re-consultations in final publication but provided in draft version of published paper. No data on patient satisfaction were collected
Selective reporting (reporting bias)	Low risk	Primary outcomes and all secondary outcomes reported are in accordance with study protocol, but primary outcome not precisely defined (within 14 days). However, data from index consultation and after 14 days provided after correspondence with investigators
Other bias	High risk	Risk of selection bias due to cluster-randomised design. Baseline characteristics identified differences between groups. 20 patients (20%) were omitted post-randomisation from 2 GPs in the control arm due to incomplete case report forms

Cals 2009

Methods	Non-blinded, cluster-randomised (practice level) clinical trial, multicentre in 20 primary care practices in the Netherlands
Participants	Inclusion criteria: adults (> 18 years) with suspected lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign) Exclusion criteria: aged 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 Included in this analysis: 431 patients with lower respiratory tract infection, 110 C-reactive protein; 84 communication skills training; 117 C-reactive protein + communication skills training; 120 control. Total of 227 C-reactive protein group versus 204 no test group
Interventions	Guiding antibiotic decisions in primary care with a single point-of-care measurement of C-reactive protein, communication skills training or a combination thereof Algorithm used in this study: recommended cut-off values: Patients with C-reactive protein levels lower than 20 mg/L: bacterial infection was considered highly unlikely and antibiotic prescribing was discouraged. Patients with C-reactive protein levels higher than 100 mg/L: bacterial infection was considered likely and immediate antibiotic prescribing was recommended. Patients with C-reactive protein levels between 20 and 99 mg/L: delayed prescribing was recommended

Cals 2009 (*Continued*)

	Physician could deviate from algorithm at any time
Outcomes	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
Notes	Trial registration ISRCTN85154857 Cluster-randomised at practice level as general practitioners trained in communication skills were unable to shift at random between using new skills and usual care 8-week run-in to enable familiarisation Patient diary to assess clinical recovery Funding: public Kit used: Nycocard II Reader (Axis-Shield, Norway) 4 groups were compared: C-reactive protein testing (1), communication training (2), communication training and C-reactive protein testing (3) and usual care (4). A factorial analysis plan was prespecified: C-reactive test (cells 1 + 3) compared with no test (cells 2 + 4) while controlling for the effect of communication training. No statistical significant interaction (P value = 0.78) was found between the interventions. Half an hour of guidance and training on the use of C-reactive protein testing in the consultation was given by the study team, including C-reactive protein cut-off values for recommending or withholding antibiotic treatment. An 8-week run-in period to ensure familiarisation with the C-reactive protein test was done prior to recruitment. Sample size calculations allowed for detection of a reduction in antibiotic use from 80% to 60% (power 80%, follow-up 90%) and target inclusion (400) was reached. Clinical recovery was assessed by a 28-day diary (on day 4, 14 and 28 a postcard or telephone reminder was sent to ensure completion of diaries). Primary analysis was intention-to-treat A significantly reduced use of antibiotics was found in the C-reactive protein group at index consultation (RR 0.58, CI 46 to 0.74) and day 28 (RR 0.77, CI 0.64 to 0.93) . No difference in the patient recovery rate was observed at day 7 or day 28. Patient satisfaction and number of re-consultations was comparable between groups Intracluster coefficients provided. Significant differences between auscultation abnormalities in the 2 groups. Sensitivity analysis showed no differences in previous antibiotic treatment of subsample (14 general practitioners) but patients enrolled in study were younger than registered patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Practices were randomised by a computer program balancing for recruitment potential. Random permuted blocks of 4 were

Cals 2009 (*Continued*)

		generated
Allocation concealment (selection bias)	Unclear risk	Individual patient allocation concealment was not performed as the unit of randomisation was doctors and/or practices. No information on how doctors were allocated into the generated groups was provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Interventions are targeted at the level of the general practitioner. Cluster-randomised at practice level as general practitioners trained in communication skills were unable to shift at random between using new skills and usual care Non-blinded trial where physicians and patients knew which treatment modality was used
Blinding of outcome assessment (detection bias) Antibiotic prescribing	Low risk	Data on antibiotic prescribing and re-consultations were obtained from medical records after 28 days
Blinding of outcome assessment (detection bias) Secondary outcomes	Low risk	Data on antibiotic prescribing were obtained from medical records at day 28. Patient reminders (phone or mail) to complete the diary were sent on day 4, 14, 28
Incomplete outcome data (attrition bias) Antibiotic prescriptions	Low risk	Follow-up for antibiotic prescribing: C-reactive protein versus control 431/431 (100%)
Incomplete outcome data (attrition bias) Other outcomes: recovery, re-consultations, satisfaction	Low risk	Patient recovery assessed as median scores of illness duration and median daily symptom scores provided, but not possible to calculate substantial improvement at specific time points. Follow-up for re-consultations and patient satisfaction ranged from 88% to 93%
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol
Other bias	High risk	Risk of selection bias due to lack of individual randomisation

Cals 2010

Methods	Open randomised clinical trial, multicentre in 11 primary care practices in the Netherlands
Participants	Inclusion criteria: adult (> 18 years) with index case of: i) lower respiratory tract infection (cough < 4 weeks, + 1 focal and + 1 systemic symptom or sign) ii) Rhinosinusitis < 4 weeks, + 2 symptoms or signs Exclusion criteria: aged under 18 years, antibiotic use or hospitalisation within the previous 14 days, non-fluent in Dutch, immunocompromised status or need for immediate hospitalisation Included in this analysis: 258 (107 lower respiratory tract infection, 151 rhinosinusitis) out of 258 randomised patients (tested for eligibility 270). Follow-up 100% on primary outcome
Interventions	Guiding antibiotic decisions in primary care with a single point-of-care measurement of C-reactive protein Algorithm used in this study: recommended cut-off values: Patients with C-reactive protein levels lower than 20 mg/L: bacterial infection was considered highly unlikely and antibiotic prescribing was discouraged. Patients with C-reactive protein levels higher than 100 mg/L: bacterial infection was considered likely and immediate antibiotic prescribing was recommended. Patients with C-reactive protein levels between 20 and 99 mg/L: delayed prescribing was recommended Physician could deviate from algorithm at any time
Outcomes	Primary outcome • Antibiotic use (delayed + 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
Notes	Netherlands national trials register (NTR 1112) Intention-to-treat analysis Funding: Orion Diagnostica Espoo, Finland The C-reactive protein test was performed by nurses and made available to the general practitioner to be used in addition to clinical assessment. Practice nurses were instructed in the use of C-reactive protein testing and a 30-minute practice based seminar on the use of C-reactive protein and C-reactive protein cut-off values for immediate antibiotics, delayed antibiotics or withhold antibiotic treatment was given by the study team. A 4-week run-in period was done prior to start of inclusion to allow for familiarisation with the C-reactive protein test A sample size calculation was performed to allow detection of a 20% reduction with a power of 80%, allowing for a 5% loss to follow-up, resulting in a total of 200 patients to be recruited Clinical recovery was measured by a patient diary to be completed for the first 7 days. Patients not recovered by day 7, were followed-up by phone interview on day 14 or 28

	Study results indicated a significant reduction in the number of antibiotic prescriptions in the C-reactive protein group at index consultation (RR 0.77, CI 0.56 to 0.98) and at 28 days (RR 0.81, CI 0.62 to 0.99). This effect was primarily due to fewer fillings of delayed prescriptions. Clinical recovery rates were similar across groups. Patient satisfaction was more pronounced in the C-reactive protein group (P value = 0.03) Sensitivity analysis was performed to evaluate clustering by way of a multilevel analysis. The effect size remained significant. Baseline characteristics were balanced

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by: Quote: "remote independent research team, using permuted block randomisation to ensure similar enrolment in both groups."
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes (SNOSE). Different block sizes were chosen to prevent the allocation sequence from being anticipated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded trial where physicians and patients knew if C-reactive protein levels were used for guidance of antibiotic treatment. C-reactive protein levels were only communicated in the intervention arm. In 13 patients allocated to the control arm the C-reactive protein level was revealed after the consultation. In 1 case the C-reactive protein level of a patient in the control arm was revealed to the physician with no implications for the management. The impact of using C-reactive protein levels to guide antibiotic prescribing was the intervention being tested and as such could not be blinded
Blinding of outcome assessment (detection bias) Antibiotic prescribing	Low risk	Data on antibiotic prescribing and re-consultations was obtained from electronic medical records accessed on day 28. Patient-reported outcomes were assessed by clinical diaries and (Quote) "Patients who indicated they had not recovered from their illness on day 7 were contacted by the research team by telephone to follow up and record whether they had recovered on day 14 or day 28."

Cals 2010 (*Continued*)

Blinding of outcome assessment (detection bias) Secondary outcomes	Low risk	Re-consultations documented from electronic medical records on day 28. Patients not recovered at day 7 (when diary was handed in) were contacted by the research team by telephone on day 14 and day 28
Incomplete outcome data (attrition bias) Antibiotic prescriptions	Low risk	Follow-up for antibiotic prescribing and use 258/258 (100%)
Incomplete outcome data (attrition bias) Other outcomes: recovery, re-consultations, satisfaction	Low risk	Recovery was assessed at day 7 (243/258; 94%), also assessed as median scores of illness duration and median daily symptom scores provided. Re-consultation data were complete. Patient-reported outcomes were available on recovery and satisfaction in the range between 91% to 97%
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol
Other bias	Low risk	-

Diederichsen 2000

Methods	Open randomised clinical trial, multicentre in 35 single-handed primary care practices in Denmark
Participants	Inclusion criteria: all patients with index case of respiratory infection Exclusion criteria: previously seen by general practitioner for infection in question, patients who had streptococcal rapid testing performed, patients with chronic inflammatory diseases Included in this analysis: 812 (30 acute otitis media, 129 rhinosinusitis, 507 chest, 102 other) out of 812 randomised patients (no. of patients tested for eligibility not stated)
Interventions	Guiding antibiotic decisions in primary care with a single point-of-care measurement of C-reactive protein Algorithm used in this study: strict cut-off values were not given, but information was provided that a normal C-reactive protein level was below 10 mg/L and that C-reactive protein levels below 50 mg/L were seldom the result of bacterial infection
Outcomes	Primary outcome • Antibiotic use at index consultation Secondary outcome • Patient-reported morbidity after 1 week
Notes	No strict inclusion and exclusion criteria but dependent on physicians opinion, may lack generalisability Kit used: Nycocard II Reader (Axis-Shield, Norway). On-site training in the use of CRP device provided by manufacturer

Diederichsen 2000 (*Continued*)

	Funding: none stated It is unclear when and how the C-reactive protein values were made available to the doctors. No direct recommendations of antibiotic treatment according to a C-reactive protein cut-off value was given, but normal values were communicated to GPs (< 11 mg/L) and that results < 50 mg/L seldom were the result of bacterial infection A sample size calculation was not described Clinical recovery was assessed by a self reported questionnaire chart that was returned to the project leader after 7 days No significant difference in the use of antibiotic prescriptions was found; children and adults combined (RR 0.94, CI 0.80 to 1.09). Clinical improvement on day 7 in the C-reactive protein group stated "unchanged or increased morbidity" more frequently than controls (OR 1.6, CI 1.0 to 2.6). This was especially the case for participants not prescribed antibiotics and with normal C-reactive protein values (OR 2.2, CI 1.1 to 4.4). 25% (57/233) of patients with C-reactive protein < 11 mg/L received antibiotic treatment as did 51% (50/98) of patients with values between 11 mg/L and 25 mg/L We obtained raw data to calculate patients substantially improved on day 7. We also tried to include data from 7-day antibiotic description (authors state that no added antibiotic consumption was noted), however even with raw data it was not possible to be entirely sure which data to include: we have done an analysis including the presumed antibiotic use at 7 days (CRP 190/407 versus 186/384): an extra 13 scripts in the 7 days which did not change the interpretation of the meta-analysis on antibiotic use at day 28 (0.85, 95% CI 0.73 to 0.98), I^2 statistic = 47%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	No information given on the randomisation process in publication. Authors state randomisation was adequately done using a computer program
Allocation concealment (selection bias)	Unclear risk	Quote: "each patient drew one of 34 pre-randomised sealed envelopes..."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded trial where physicians and patients knew if C-reactive protein levels were used for guidance of antibiotic treatment. The impact of using C-reactive protein levels to guide antibiotic prescribing was the intervention being tested and as such could not be blinded
Blinding of outcome assessment (detection bias) Antibiotic prescribing	Unclear risk	Registration and consent chart sent to project leader with details on treatment from index consultation

Diederichsen 2000 (*Continued*)

Blinding of outcome assessment (detection bias) Secondary outcomes	Low risk	Patients handed in diary on day 7. Patients with missing or incomplete diaries were contacted by research team by telephone or letter on day 14
Incomplete outcome data (attrition bias) Antibiotic prescriptions	Low risk	Follow-up for antibiotic prescribing at index consultation 812/812 patients (100%). Antibiotic use at day 7 was assessed but not provided in publication. Quote "No statistically significant differences were found."
Incomplete outcome data (attrition bias) Other outcomes: recovery, re-consultations, satisfaction	Low risk	Patient-reported outcomes of recovery day 7 were available in 792/812 patients (98%) . Re-consultation data not provided in publication, but (Quote) "No statistically significant differences were found". Satisfaction was not assessed
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Unclear risk	Recruitment was not strictly regulated but baseline characteristics of patients were balanced. Quote "Each day during the study period the first or the first 2 patients, whichever was more practical, who consulted the general practitioner because of respiratory infection were asked to participate in the study." This limits externalisation of results

Little 2013a

Methods	Non-blinded cluster-randomised (practice level) clinical trial, multinational with 246 primary care practices in Spain, England, Wales, Poland, Belgium, the Netherlands
Participants	Inclusion criteria for**practices:** no prior participation in interventions to reduce antibiotic use; recruited more than 10 patients in the baseline audit Inclusion criteria for **patients**:**lower respiratory tract infection:** aged 18 years and over; consulting for the first time with acute cough (up to 28 days duration) as the main symptom, or alternatively where cough was not the most prominent symptom (e.g. fever, malaise) but where the clinician considered acute LRTI was the main diagnosis. Pneumonia was not an exclusion criterion.**Upper respiratory tract infection:** aged 18 years and over; consulting for the first time and judged by the physician to be another acute respiratory infection (sore throat, otitis media, sinusitis, influenza and/or coryzal illness) Exclusion criteria: a non-infective working diagnosis (e.g. pulmonary embolus; heart failure; oesophageal reflux; allergy); antibiotic use in the previous month; unable to provide informed consent (dementia; psychosis; severe depression); pregnant; immunolog-

	ical 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 Included in this analysis: 4264 patients at follow-up; 2224 to the C-reactive protein group versus 2040 to the no test group 80% of patients had lower respiratory tract infections and the remainder upper respiratory tract infections
Interventions	Guiding antibiotic decisions in primary care with a single point-of-care measurement of C-reactive protein, communication skills training or a combination thereof Algorithm used in this study: recommended cut-off values: C-reactive protein $\leq$ 20 mg/L: self limiting ARI, withhold antibiotics; C-reactive protein 21 to 50 mg/L: Majority of patients have self limiting ARI, withhold antibiotics, in most cases; C-reactive protein 51 to 99 mg/L. Withhold antibiotics in the majority of cases and consider delayed antibiotics in the minority of cases; C-reactive protein $\geq$ 100 mg/L: Severe infection, prescribe antibiotics Physicians could deviate from algorithm at any time
Outcomes	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
Notes	Trial registration ISRCTN99871214 Cluster-randomised at practice level as general practitioners trained in communication skills were unable to shift at random between using new skills and usual care Funding: public Kit used: Quickread C-reactive protein, Orion Diagnostica (Espoo, Finland). On-site training to practices in their use provided by manufacturer Following training, prior to data collection, there was a run-in period for physicians to practice using the device A baseline audit (October 2010 to December 2010) functioned to characterise patients and the 'everyday' prescribing behaviour of clinicians A cluster-randomised design was chosen to minimise contamination within practices (since more than 1 physician per practice could participate) and because a practice-based meeting was part of the intervention. Following a baseline audit to determine the antibiotic prescription rate 4 groups were compared: C-reactive protein testing (1) , communication training (2), communication training and C-reactive protein testing (3) and usual care (4). A factorial analysis plan was prespecified where groups were combined: C-reactive test (cells 1 + 3) compared with no test (cells 2 + 4) while controlling for the effect of communication training. No statistical significant interaction was found between the interventions, although a synergistic effect was noted. 446 practices approached, 259 agreed to participate, 228 practices contributed with data. Compliance with the intervention (training) was good, with completion of all the training modules

	in 99/113 (88%) of the C-reactive protein group, 94/108 (87%) of the communication group and 116/127 (91%) of the combined group The intervention consisted of an estimated 30-minute Internet training module on the use of C-reactive protein to target antibiotics for serious infections and providing C-reactive protein cut-off values for recommending or withholding antibiotic treatment Compliance with the intervention was good with 90% (215/240) of participating doctors having completed the Internet training module. The interaction term between C-reactive protein and communication training on the primary outcome (number of antibiotic prescriptions) was not significant (P value = 0.41) Sample size calculations were done to allow detection of a reduction in antibiotic use of 10% (50% to 40%) (power 80%) and adjusting for clustering with intracluster coefficients (ICC) of 0.16 and 0.06 determined a sample size of minimum 2600 patients and maximum 5400 The primary outcome of antibiotic prescribing was assessed at index consultation. Secondary outcomes were re-consultations (including hospitalisations) with new and worsening symptoms documented by medical notes review. Symptom severity and duration: a) severity 2 to 4 days after index consultation and b) duration of symptoms rated moderately bad or worse. These outcomes were assessed by patient diary and mailed to study team upon completion. A telephone reminder was given to postal non-responders The study reported a significantly reduced use of antibiotics in the C-reactive protein group at index consultation (33% versus 58%) (RR 0.54, CI 0.42 to 0.69) (adjustment for baseline antibiotic prescribing, GP and practice). No significant difference in the patient number of re-consultations were recorded (RR 1.06, CI 0.80 to 1.40), however an increase in hospital admissions was present in the C-reactive protein group that disappeared with adjustment for various potential confounders including clinical presentation weakened the association to be of borderline significance (P value = 0.06). Information on the hospital admissions was available in 15 cases; the reasons stated being cardiac (2) ; respiratory (8), generally unwell/pyrexia (2); gastrointestinal symptoms (2); sinusitis (1). We were unable to obtain the percentages of hospital admissions in the C-reactive protein not initially prescribed an antibiotic. No study-related deaths were reported. A similar resolution of symptoms rated moderately bad or worse was observed (median 5 days, IQR 3 to 9 days), as was symptom severity 2 to 4 days after index consultation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation of practices was performed by study team, stratified by network (country) by computer-generated random numbers, balanced for recruitment potential
Allocation concealment (selection bias)	Unclear risk	Centralised randomisation. Quote ".. physicians and patients were blind to initial group allocation"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Interventions are targeted at the level of the general practitioners. Cluster-randomised at practice level as GP trained in communi-

Little 2013a (*Continued*)

		cation skills were unable to shift at random between using new skills and usual care Non-blinded trial where physicians and patients knew which treatment modality was used
Blinding of outcome assessment (detection bias) Antibiotic prescribing	Low risk	Data on antibiotic prescribing was obtained from case report forms after index consultation
Blinding of outcome assessment (detection bias) Secondary outcomes	Low risk	Re-consultations documented by medical notes review. Symptom severity and duration by patient diaries with reminders (phone and/or mail)
Incomplete outcome data (attrition bias) Antibiotic prescriptions	Low risk	Follow-up for antibiotic prescribing and use was complete: 4264/4264 (100%)
Incomplete outcome data (attrition bias) Other outcomes: recovery, re-consultations, satisfaction	Low risk	The study reports on the time to resolution of symptoms rated moderately bad or worse and recovery was not possible to assess at specific time points. Patient satisfaction was not reported. Data on re-consultations were available in 4121/4264 (97%)
Selective reporting (reporting bias)	Low risk	Outcomes correspond to study protocol
Other bias	High risk	Risk of selection bias present due to lack of individual randomisation

Melbye 1995

Methods	Open randomised clinical trial, multicentre in 10 primary care practices in Norway
Participants	Inclusion criteria: adult (> 18 years) with subjective complaint of i) pneumonia, bronchitis or asthma or ii) 1 of the following symptoms: cough, shortness of breath, chest pain on deep inspiration or cough Exclusion criteria: aged under 18 years, patients with sore throat, blocked nose, pain in ears or sinuses. Patients with angina-like chest pain were also excluded Included in this analysis: 239 (108 C-reactive protein group, 131 controls) out of 239 randomised patients (245 eligible patients)
Interventions	Guiding antibiotic decisions in primary care with a single point-of-care measurement at the end of consultation Algorithm used in this study: recommended cut-off values: Duration of illness < 24 hours and C-reactive protein levels lower than 50 mg/L; no change in clinical decision. C-reactive protein levels > 50 mg/L; immediate antibiotic prescribing was recommended

	Duration of illness 1 to 6 days and C-reactive protein levels < 11 mg/L; no antibiotics recommended. Patients with C-reactive protein levels between 11 and 49 mg/L; no change in clinical decision. C-reactive protein levels > 50 mg/L; immediate antibiotic prescribing was recommended Duration of illness > 7 days and C-reactive protein levels < 11 mg/L; no antibiotics recommended. Patients with C-reactive protein levels between 11 and 24 mg/L; no change in clinical decision. C-reactive protein levels > 25 mg/L; immediate antibiotic prescribing was recommended Physicians could deviate from algorithm at any time, but reasons to do so should be stated
Outcomes	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
Notes	Study was stopped after 1 year and prior to estimated power calculation of 260 patients had been included due to lack of interest from participating doctors and interim analysis showed that the null hypothesis was not subject to change regardless Kit used: Nycocard II Reader (Axis-Shield, Norway) Funding: Nycomed Pharma A sample size calculation was performed to allow detection of 20% difference in the number of antibiotic prescriptions with 90% power (target inclusion of 260 patients). The study was terminated after 1 year by the principal investigator without reaching the target inclusion due to an interim analysis that found no difference between groups, and also due to the lack of interest from participating GPs. Low adherence to protocol and C-reactive protein values only available after initial decision on clinical management. Baseline characteristics of patients were balanced Clinical recovery was assessed at a follow-up visit health personal preferably at the practice, alternatively on phone 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%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated. Correspondence with principal investigators stating that randomisation was adequate and performed by sponsor at sponsor level. No additional details provided
Allocation concealment (selection bias)	Unclear risk	Not explicitly stated, but participants were unaware of group allocation until after con-

Melbye 1995 (*Continued*)

		sent to participate in study was obtained, however study personnel are not accounted for
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non-blinded trial where physicians were only communicated the C-reactive protein results in the intervention arm. The impact of using C-reactive protein levels to guide antibiotic prescribing was the intervention being tested and as such could not be blinded. Participants were not informed of the C-reactive protein results
Blinding of outcome assessment (detection bias) Antibiotic prescribing	Low risk	Data on antibiotic use were obtained from medical records
Blinding of outcome assessment (detection bias) Secondary outcomes	High risk	Health personal responsible for C-reactive protein testing and randomisation performed follow-up interviews with patients at 7 and 21 days in health clinic or on phone
Incomplete outcome data (attrition bias) Antibiotic prescriptions	Low risk	Follow-up for antibiotic prescribing and use 239/239 (100%)
Incomplete outcome data (attrition bias) Other outcomes: recovery, re-consultations, satisfaction	Low risk	Recovery data were available in 230/239 (96%) at day 7 and in 219/239 (92) at day 21. Re-consultations and patient satisfaction were not assessed
Selective reporting (reporting bias)	Unclear risk	All outcomes are reported, but no study protocol available
Other bias	Unclear risk	Premature study stop guided by preliminary study results before target inclusion was met, indicating that principal investigator had access to data

ARI: acute respiratory infection
CI: confidence interval
CRP: C-reactive protein
GP: General Practitioner
IQR: interquartile range
LRTI: lower respiratory tract infection
OR: odds ratio
RR: risk ratio

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Briel 2008	Not a point-of-care biomarker (procalcitonin) used in study
Burkhardt 2010	Not a point-of-care biomarker (procalcitonin) used in study
Dahler-Eriksen 1999	Not assessing C-reactive protein to guide antibiotic prescriptions
Gonzales 2011	Not in a primary care setting
Kavanagh 2011	Not a randomised controlled trial
Llor 2012	Not a randomised controlled trial
Takemura 2005	Not in a primary care setting

Characteristics of ongoing studies *[ordered by study ID]*

Altiner 2012

Trial name or title	Converting habits of antibiotic prescribing for respiratory tract infections in German primary care (CHANGE-2)
Methods	3-arm cluster-randomised trial with units being general practitioners and practice-based paediatricians. Sample size was calculated to detect a relative reduction of 30% between groups: target inclusion 480 participants but inflating for clustering yields a sample size of 13,160 in 188 practices
Participants	Eligible participants are health-insured in the same company (AOK), a minimum age of 3 months, first visit due to an acute respiratory infection (both upper and lower) and otherwise healthy
Interventions	The interventions are A) communication training; B) communication training and point-of-care test (C-reactive protein test and/or rapid antigen detection testing); C) usual care. Communication training will be given at to small groups in 1 seminar based session. All tests are provided free of charge and staff and physicians will receive training on performing the test and when to use point-of-care tests
Outcomes	Physicians antibiotic prescriptions rates over 3 winters. Secondary outcomes include re-consultation rates, complications (including hospital admissions)
Starting date	10 September 2012
Contact information	Annette Diener, Institute of General Practice, Rostock University Medical Centre, 18055 Rostock, Germany. Email anette.diener@med.uni.rostock.de
Notes	Recruiting

Timmins 2013

Trial name or title	A pilot study on the effects of adding C-reactive protein point-of-care testing in the management of acutely ill children in primary care
Methods	Cohort study with nested randomised controlled trial
Participants	Children aged 1 month to 16 years presenting to out-of-hours with an acute illness of a maximum of 5 days with a temperature of >= 38 °C. Planned sample size 700
Interventions	The intervention arm consists of a finger prick test to measure C-reactive protein. Comparator is standard of care
Outcomes	1) Difference in antibiotic prescription rates; 2) Difference in referrals; 3) Difference in additional testing rates; 4) Difference in hospital admission; 5) Acceptability of the blood test by children and their parents/caregivers; 6) Impact of the blood test on the GP's diagnostic certainty; 8) Impact of the vital signs measurements applied on percentiles and prediction score on GP's diagnostic certainty
Starting date	8 July 2013
Contact information	David Timmins, Department of Primary Health Care 23-28 Hythe Bridge Street OX1 2ET Oxford, United Kingdom. Email david.timmins@phc.ox.ac.uk
Notes	Recruiting. Public funding

Verbakel 2013

Trial name or title	Validation of a vital signs and symptoms decision tree and the effect of a point-of-care C-reactive protein test, oxygen saturation, a brief intervention and a parent leaflet on diagnosing, antibiotic prescribing rate and parental satisfaction in acutely ill children in primary care
Methods	4-arm, randomised, single-blind (subject) study with factorial assignment
Participants	Patients aged 1 month to 16 years with an acute illness for a maximum of 5 days are included consecutively. Target inclusion 6000
Interventions	The 4 arms of the study include 1) usual care; 2) use of C-reactive protein point-of-care test; 3) brief intervention and parent leaflet; 4) C-reactive protein point-of-care test and brief intervention and parent leaflet
Outcomes	Primary outcome measures: serious infection (time frame: 1 year); immediate antibiotic prescribing rates Secondary outcome measures: parental satisfaction; parental concern; use of other diagnostic tests and medical services (including re-consultation); cost-effectiveness; impact of the communicator style on the effect of the intervention (interaction)
Starting date	January 2013
Contact information	Jan Y Verbakel. Katholieke Universiteit Leuven, Belgium. Email: jan.verbakel@med.kuleuven.be

Verbakel 2013 (*Continued*)

Notes	Recruiting

Wertheim 2013

Trial name or title	Efficacy of point-of-care (POC) C-reactive protein testing to reduce inappropriate use of antibiotics for acute respiratory infections (ARIs) in the primary health care setting of Hanoi - a randomised controlled trial
Methods	Open-label, randomised, parallel-group study
Participants	Patients aged 6 to 65 years visiting 1 of 10 district health centres in Hanoi with a suspected acute respiratory tract infection
Interventions	Participants in the control group will be treated according to routine care. Participants in the intervention arm will have a C-reactive protein rapid point-of-care test, the results of which will be available to the healthcare practitioner to contribute to their diagnosis and treatment decisions
Outcomes	Primary outcome: proportion of patients receiving any antibiotic (time frame 2 weeks) Secondary outcomes: durations of symptoms; frequency of re-consultations; frequency of serious adverse events
Starting date	Not yet recruiting
Contact information	Nga Thuy Do and Heiman FL Wertheim. National Hospital for Tropical Diseases, Hanoi, Vietnam and Oxford University Clinical Research Unit. Email:heiman.weitheim@gmail.com, ngadtt@oucru.org
Notes	Not yet recruiting

DATA AND ANALYSES

Comparison 1. CRP - Antibiotic prescribing: all trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CRP - Antibiotics prescribed at index consultation. All trials (cluster-randomised with modified sample size)	6	3284	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.66, 0.92]
1.1 Individually randomised trials	3	1309	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.02]
1.2 Cluster-randomised trials (modified sample size)	3	1975	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.61, 0.75]
2 CRP - Antibiotics prescribed within 28 days (cluster-randomised trials with modified sample size)	4	708	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.67, 0.96]
2.1 Individually randomised trials	2	497	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.75, 1.02]
2.2 Cluster-randomised trials (modified sample size)	2	211	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.51, 0.91]

Comparison 2. CRP - No. of patients substantially improved day 7: individually randomised trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical recovery day 7	3	1264	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.93, 1.14]

Comparison 3. CRP - Number of re-consultations within 28 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CRP - Number of re-consultations at follow-up within 28 days	4	2486	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.93, 1.27]
1.1 Individually randomised trials	1	258	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.89, 2.30]
1.2 Cluster-randomised trials (modified sample size)	3	2228	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.24]

Comparison 4. CRP - Patient satisfaction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CRP - Patient satisfaction	2	674	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.57, 1.08]

Comparison 5. CRP - No. of patients substantially improved at follow-up within 28 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical recovery day 28 (cluster-randomised trials with modified sample size; ICC0. 06)	3	527	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.69, 1.28]
2 Clinical recovery day 28: sensitivity analysis (ICC 0.01)	3	739	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.73, 1.25]
3 Clinical recovery day 28: sensitivity analysis (ICC 0.12)	3	429	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.65, 1.27]

Comparison 6. CRP - Subgroup analysis: Children versus adults. Antibiotic prescribing at index consultation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Children	1	139	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.70, 1.71]
2 Adults (cluster-randomised trials with modified sample size)	6	3145	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.66, 0.90]
2.1 Individually randomised trials	3	1170	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.79, 1.00]
2.2 Cluster-randomised trials (modified sample size)	3	1975	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.60, 0.75]

Comparison 7. CRP - Subgroup analysis: upper respiratory tract infections versus lower respiratory tract infections

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antibiotics prescribed at index consultation: Cluster-randomised with modified sample size	2	2024	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.63, 0.78]
1.1 Upper respiratory tract infections	2	510	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.58, 0.90]
1.2 Lower respiratory tract infections	2	1514	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.62, 0.78]

Comparison 8. CRP - Algorithms with specific cut-offs to rule out serious disease (< 20 mg/L) (sensitivity analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CRP - Antibiotic prescribing when algorithms provide clear cut-offs to rule out (< 20 mg/L)	4	2233	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.62, 0.76]
1.1 Individual trials	1	258	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.60, 0.98]
1.2 Cluster-randomised trials. Modified sample size	3	1975	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.60, 0.75]
2 CRP - Recovery at day 7	1	243	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.89, 1.18]
3 CRP - Recovery at follow-up (max 28 days)	2	608	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.75, 1.41]

Comparison 9. CRP - Sensitivity analysis: missing data. Patient recovery (worst case)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CRP - Patient recovery day 7: missing data in CRP = not recovered	3	1309	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.99, 1.21]
2 Patient recovery day 28: missing data in CRP = not recovered. Cluster-randomised trials with modified sample size	3	549	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.84, 1.48]

ADDITIONAL TABLES

Table 1. Overview of biomarkers of infection used in acute respiratory infection trials in primary care settings

Biomarker	Status	Handling	Biochemistry
C-reactive protein (CRP)	POC* test available	Droplet blood from finger prick. Results in approximately 3 minutes. Uninfected adult controls have levels < 10 mg/L	Inflammatory cytokines trigger C-reactive protein release by the liver. Levels of C-reactive protein increase within 6 to 18 hours, peaking at 48 to 72 hours
Leukocyte count	POC test available	Droplet blood from finger prick. Results in approximately 3 minutes. Uninfected adult controls have leukocyte levels < 9 x 10^9/L and neutrocyte levels < 7 x 10^9/L	Cells of the immune system activated by inflammatory cytokines and foreign antigens
Procalcitonin (PCT)	POC test not available**	Uninfected adult controls have levels < 0.05 nanogram/mL	Inflammatory cytokines and bacterial endotoxins trigger release of PCT from parenchymal tissues. Levels of PCT increase within 2 to 6 hours, peaking at 24 to 48 hours

*POC: point-of-care

**No POC test in desired target range (0.05 to 0.50 nanogram/mL)

Table 2. CRP - Baseline characteristics of included patients*

Parameter	Studies	C-reactive protein group	Control group
Age, mean (SD)[a]	Cals 2009; Cals 2010; Diederichsen 2000; Little 2013a	45.3 (16.8)	46.0 (17.2)
Gender (female) % (n/N)	All studies	62.8 (2012/3203)	64.3 (1916/2980)
Current smokers	Andreeva 2013; Cals 2009; Cals 2010; Little 2013a	44.9 (1187/2639)	45.0 (1079/2396)
Co-morbidity[b]	Andreeva 2013; Cals 2009; Cals 2010; Little 2013a	21.2 (563/2652)	19.6 (472/2403)
Primary diagnosis			
Unclassified upper ARI[c]	Andreeva 2013; Little 2013a	21.5 (499/2325)	21.1 (446/2118)
Otitis media	Diederichsen 2000	3.3 (13/394)	4.5 (17/374)
Common cold	Melbye 1995	13.9 (15/108)	16.8 (22/131)

Table 2. CRP - Baseline characteristics of included patients* (*Continued*)

Rhinosinusitis	Cals 2010; Diederichsen 2000	27.3 (143/523)	27.2 (137/502)
Total upper ARI[d]	Andreeva 2013; Cals 2010; Diederichsen 2000; Little 2013a; Melbye 1995	22.7 (670/2956)	22.6 (622/2752)
Pneumonia	Andreeva 2013; Melbye 1995	7.7 (16/209)	14.4 (30/209)
LRTI/acute cough	All studies	74.3 (2364/3183)	73.5 (2173/2956)
Bronchitis	Melbye 1995	37.9 (41/108)	32.1 (42/131)
Exacerbations of COPD or asthma	Melbye 1995	14.8 (16/108)	8.4 (11/131)
Total lower ARI[e]	All studies	76.8 (2446/3183)	70.5 (2271/2956)
Influenza	Melbye 1995	8.3 (9/108)	9.2 (12/131)
Other respiratory diseases	Diederichsen 2000; Melbye 1995	13.3 (67/502)	13.1 (66/505)

*Crude numbers provided from all studies regardless of design.
[a] Melbye 1995 reported the median age: 50 (range 18 to 83) in the C-reactive protein arm versus 44 (18 to 82) in the control arm.
[b] Chronic obstructive pulmonary disease (COPD); asthma; heart disease; diabetes mellitus.
[c] Acute respiratory infection.
[d] Any upper acute respiratory infections.
[e] Any lower acute respiratory infections.

Table 3. Characteristics of inclusion and CRP algorithms of included studies

Study	Randomisation	Inclusion criteria	Algorithm used
Melbye 1995	Individual	Adults (> 18 years) with subjective complaint of i) pneumonia, bronchitis or asthma (no further description) or ii) 1 of the following symptoms: cough, shortness of breath, chest pain on deep inspiration or when coughing	Duration of illness **< 24 hours** and C-reactive protein levels lower than 50 mg/L; no change in clinical decision. C-reactive protein levels > 50 mg/L; immediate antibiotic prescribing was recommended Duration of illness **1 to 6 days** and C-reactive protein levels < 11 mg/L; no antibiotics recommended. Patients with C-reactive protein levels between 11 and 49 mg/L; no change in clinical decision. C-reactive protein levels > 50 mg/L; immediate antibiotic prescribing was recommended Duration of illness **> 7 days** and C-reactive

Table 3. Characteristics of inclusion and CRP algorithms of included studies (*Continued*)

			protein levels < 11 mg/L; no antibiotics recommended. Patients with C-reactive protein levels between 11 and 24 mg/L; no change in clinical decision. C-reactive protein levels > 25 mg/L; immediate antibiotic prescribing was recommended
Diederichsen 2000	Individual	All patients with a respiratory infection (no further description)	Strict cut-off values were not given, but information was provided that a normal C-reactive protein level was **< 10 mg/L** and that C-reactive protein levels **< 50 mg/L** were seldom the result of bacterial infection
Cals 2009	Cluster	Adults (> 18 years) with suspected LRTI (cough < 4 weeks AND 1 focal sign/symptom (shortness of breath, wheezing, chest pain, auscultation abnormalities) AND 1 systemic sign/symptom (fever > 38 °C, perspiring, headache, myalgia, feeling generally unwell)	C-reactive protein levels **< 20 mg/L**: pneumonia extremely unlikely and antibiotic prescribing discouraged C-reactive protein levels between **20 to 50 mg/L**: pneumonia very unlikely C-reactive protein levels between **50 to 100 mg/L**: clear infection. Acute bronchitis most likely, possible pneumonia C-reactive protein **> 100 mg/L**: severe infection. Pneumonia more likely. Immediate antibiotic prescribing was recommended C-reactive protein levels between 20 and 99 mg/L: consider delayed prescribing
Cals 2010	Individual	Adults (> 18 years) with: i) LRTI (cough < 4 weeks) AND 1 focal sign/symptom (shortness of breath, wheezing, chest pain, auscultation abnormalities) AND 1 systemic sign/symptom (fever > 38 °C, perspiring, headache, myalgia, feeling generally unwell) ii) Rhinosinusitis < 4 weeks AND 1 symptom (history of rhinorrhoea, blocked nose) 1 symptom or sign (purulent rhinorrhoea, unilateral facial pain, headache, teeth pain, pain when chewing, maxillary/frontal pain when bending over, worsening of symptoms after initial improvement)	C-reactive protein levels lower **< 20 mg/L**: bacterial infection was considered highly unlikely and antibiotic prescribing was discouraged C-reactive protein levels **> 100 mg/L**: bacterial infection was considered likely and immediate antibiotic prescribing was recommended C-reactive protein levels between **20 to 99 mg/L**: consider delayed prescribing
Little 2013a	Cluster	Adults (> 18 years) with: i) LRTI/acute cough (up to 28 days duration) as the main symptom, or alternatively where cough was not the most prominent symptom (e.g. fever, malaise), but where the clinician	C-reactive protein $\leq$ **20 mg/L**: self limiting ARI, withhold antibiotics C-reactive protein **21 to 50 mg/L**: majority of patients have self limiting ARI, withhold antibiotics, in most cases

Table 3. Characteristics of inclusion and CRP algorithms of included studies (*Continued*)

		considered acute LRTI was the main diagnosis. Pneumonia was not an exclusion criterion ii) URTI: as with LRTI, but judged by the physician to be another acute respiratory infection (sore throat, otitis media, sinusitis, influenza and/or coryzal illness)	C-reactive protein **51 to 99 mg/L**: withhold antibiotics in the majority of cases and consider delayed antibiotics in the minority of cases C-reactive protein ≥**100 mg/L**: severe infection, prescribe antibiotics
Andreeva 2013	Cluster	Adults (> 18 years) with LRTI/acute cough (including acute bronchitis, pneumonia and infectious exacerbations of COPD or asthma) for less than 28 days	C-reactive protein **< 20 mg/L** antibiotics usually not needed C-reactive protein **> 50 mg/L** antibiotic prescribing could be indicated taking into account the duration of illness

All studies stated that physicians could deviate from the algorithm at any time.
ARI: acute respiratory infection
COPD: chronic obstructive pulmonary disease
LRTI: lower respiratory tract infection
URTI: upper respiratory tract infection

Table 4. Number needed to test to save one antibiotic prescribing

	NNT	95% CI
All trials	9	6 to 20
Individually RCT	20	-100 to 9
Cluster-RCT	6	5 to 8

Cluster-randomised trials with modified sample size
CI: confidence interval
NNT: number needed to test
RCT: randomised controlled trial

Table 5. Duration of symptoms

Study		Mean (SD)		Median (IQR)	
		C-reactive protein	Control	C-reactive protein	Control
Cals 2009[a]		-	-	22 (14 to 28)	22 (14 to 28)
Cals 2010[a]	LRTI	17.5 (9.2)	19.8 (9.5)	15.5 (9.5 to 28)	20 (13.5 to > 28)
	Rhinosinusitis	17.3 (9.3)	16.6 (9.9)	14 (10 to 28)	14 (7 to > 28)

Table 5. Duration of symptoms (*Continued*)

Little 2013[b]	LRTI	-	-	6 (3 to 9)	5 (3 to 9)
	URTI	-	-	5 (3 to 7)	4 (3 to 8)
	ARI	-	-	5 (3 to 9)	5 (3 to 9)

[a] Reported as time to full recovery.
[b] Reported as resolution of moderately bad or worse symptoms.
ARI: acute respiratory tract infection (LRTI + URTI)
IQR: interquartile range
LRTI: lower respiratory tract infection
SD: standard deviation
URTI: upper respiratory tract infection

Table 6. Summary of secondary outcomes

Outcome	Studies	Patients	Pooled results* RR (95% CI); I^2	Individually randomised RR (95% CI); I^2	Cluster-randomised RR (95% CI); I^2	Analysis
Antibiotic use day 28	4	715	0.80 (0.67 to 0.96); 40%	0.87 (0.75 to 1.02); 7%	0.68 (0.51 to 0.91); 19%	1.2
Recovery day 28 [a]	3	527	0.94 (0.69 to 1.28); 0%	-	-	5.1 to 5.3
Hospital admissions	6[b]	1764	-	-	2.45 (0.65 to 9.19)	-
Re-consultations	4	2228	1.08 (0.93 to 1.27); 0%	-	-	3.1
Patient satisfaction	2	674	0.79 (0.57 to 1.08); 45%	-	-	4.1

*When I^2 > 40%, separate analyses of individually and cluster-randomised trials are presented.
[a] Defined as at least substantial improvement.
[b] Little 2013a was the only trial with any cases of hospital admission. The calculation is done for this trial alone.

CONTRIBUTIONS OF AUTHORS

Protocol stage

Rune Aabenhus (RA) was responsible for drafting the protocol.

Review stage

RA and Jens-Ulrik S Jensen (J-U SJ) were responsible for selecting trials for inclusion and data extraction.
RA was responsible for entering data into Review Manager and analysing data.
RA was responsible for drafting the final review.
All authors were responsible for interpreting the analyses.

Update stage

RA and J-U SJ will be responsible for updating this review.

DECLARATIONS OF INTEREST

Rune Aabenhus: none stated.

Asbjørn Hróbjartsson: none stated.

Karsten Juhl Jørgensen: none stated.

Lars Bjerrum: none stated.

Jens-Ulrik S Jensen (J-U SJ): the organisation, of which J-U SJ is the leader (the PASS-study group), has received EUR 200,000 for sample transport and analysis from Brahms Diagnostica a.g. Hennigsdorf, Germany (now Thermo-Fischer), one among four producers of kits for procalcitonin analysis for the Procalcitonin and Survival Study (investigator-initiated and driven). This study was mainly sponsored by the Danish State. The last donation was made in 2008. J-U SJ received less than EUR 2000 during the last three years for travel expenses/speakers fee from Brahms Diagnostica a.g. J-U SJ does not have any other relationship to the former Brahms Diagnostic a.g. and has no ongoing relationship with Thermo-Fischer or other diagnostic companies.

SOURCES OF SUPPORT

Internal sources

- University of Copenhagen, Denmark.

Administrative support

- Nordic Cochrane Centre, Denmark.

Methodological support

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have changed the wording in types of interventions to clarify the eligible interventions in the review. These changes did not impact on the decision to include or exclude any specific studies.

We did not carry out the planned fixed-effect meta-analysis as a sensitivity measure due to the substantial heterogeneity of data.

We were unable to compare studies with serious infections (e.g. pneumonia) versus less serious infections (e.g. common cold and bronchitis) due to lack of data. However, we report reductions in antibiotic use by C-reactive protein guidance in upper ARI and lower ARI.

We have included a post hoc analysis of CRP algorithms of newer studies with a clear cut-off of 20 mg/L to withhold antibiotic treatment versus older studies without a clear cut-off to withhold antibiotic treatment.

NOTES

This review applies broad inclusion criteria, namely all patients with suspected acute respiratory infections (ARIs) in primary care and any point-of-care biomarker of infection available on the market today. As access to secondary diagnostic tests (chest X-ray, blood and sputum culture etc.) in primary care settings is often limited and results from such tests are not immediately available, the application of stringent diagnostic criteria is hampered, when treating an acute condition such as an ARI. For diseases that a priori do not need antibiotic treatment, such as acute bronchitis and the common cold, by performing a point-of-care test, a general practitioner (GP) (who may be in doubt as to whether antibiotics are needed) can use the results to guide appropriate antibiotic prescription, or to convince a patient that antibiotics are not necessary. Also, the broad inclusion criteria may enable generalisation of the study results to a range of ARI diagnoses in primary care settings of different geographical regions. This prognostic approach seeks to determine whether the patient is likely to benefit from an antibacterial drug and not on the specific diagnosis (Dinant 2007). Randomised controlled trials (RCTs) that measure the outcome of standard versus point-of-care tests to guide antibiotic prescribing may better estimate the utility of biomarkers to reduce antibiotic prescribing in patients with ARIs (Schuetz 2010). If the patient recovers without antibiotics at the same time and with comparable rates of complications (hospitalisation, mortality and number of re-infections), it may be decided that the infection was of non-bacterial origin or so mild that the immune defence system cleared the infection unassisted. Clinical skills and understanding of the diagnostic performances of the different point-of-care biomarkers are needed to manage the delicate balance of appropriate antibiotic treatment of an ARI to ensure the best outcome for the patient.

INDEX TERMS

Medical Subject Headings (MeSH)

*Point-of-Care Systems; Acute Disease; Anti-Bacterial Agents [*therapeutic use]; Biological Markers [blood]; C-Reactive Protein [*analysis]; Drug Resistance, Bacterial; Hospitalization [statistics & numerical data]; Primary Health Care; Randomized Controlled Trials as Topic; Respiratory Tract Infections [*diagnosis; *drug therapy]

MeSH check words

Humans