# Primary care

## Diagnostic value of C reactive protein in infections of the lower respiratory tract: systematic review

Victor van der Meer, Arie Knuistingh Neven, Peterhans J van den Broek, Willem J J Assendelft

Leiden University Medical Center, Albinusdreef 2, PO Box 9600, 2300 RC, Leiden, Netherlands
Victor van der Meer *junior researcher, Department of Medical Decision Making*
Peterhans J van den Broek *professor, Department of Infectious Diseases*
Arie Knuistingh Neven *senior researcher, Department of General practice and Nursing Home Medicine*
Willem J J Assendelft *professor, Department of General Practice and Nursing Home Medicine*

Correspondence to: V van der Meer V.van_der_Meer@lumc.nl

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### Abstract

**Objectives** To evaluate the diagnostic accuracy of C reactive protein in detecting radiologically proved pneumonia and to evaluate how well it can discriminate between bacterial and viral infections of the lower respiratory tract.
**Data sources** Medline and Embase (January 1966 to April 2004), with reference checking.
**Study selection** We included articles comparing C reactive protein with a chest radiograph or with microbiological work-up as a reference test. Two authors independently assessed methodological items.
**Results** None of the studies met all validity criteria. Six studies used an infiltrate on chest radiograph as reference test. Sensitivities ranged from 10% to 98%, specificities from 44% to 99%. For adults, the relation of C reactive protein with an infiltrate (in a subgroup analysis of five studies) showed an area under the curve of 0.80 (95% confidence interval 0.75 to 0.85). In 12 studies, the relation of C reactive protein with a bacterial aetiology of infection of the lower respiratory tract was studied. Sensitivities ranged from 8% to 99%, specificities from 27% to 95%. These data were epidemiologically and statistically heterogeneous, so overall outcomes could not be calculated.
**Conclusion** Testing for C reactive protein is neither sufficiently sensitive to rule out nor sufficiently specific to rule in an infiltrate on chest radiograph and bacterial aetiology of lower respiratory tract infection. The methodological quality of the diagnostic studies is generally poor. The evidence does not consistently and sufficiently support a wide introduction of C reactive protein as a rapid test to guide antibiotics prescription.

### Introduction

Although bacterial pneumonia occurs much less often than other infections of the lower respiratory tract, in studies more than 70% of acute infections of the lower respiratory tract are treated with antibiotics.[1 2] Additional information is needed in order to detect bacterial pneumonia and to differentiate between this diagnosis and other respiratory tract infections. C reactive protein is often proposed as the solution.[3] This is a protein of the acute phase, synthesised by hepatocytes. Its production is stimulated mainly by interleukin 6, interleukin 1 β, and tumour necrosis factor α in response to infection or tissue inflammation.[4] C reactive protein has been studied as a screening device for inflammation, a marker for disease activity, and as a diagnostic adjunct.[5] However, its role in differentiating bacterial from viral infections is not proved.[6 7] With the availability of rapid or bedside tests, particularly in general practice, determining its diagnostic value is of increasing importance. We assessed the value of C reactive protein in the detection of radiologically proved pneumonia. In addition, we evaluated whether C reactive protein can differentiate bacterial from viral infections of the lower respiratory tract.

### Methods

We searched the databases Medline (January 1966 to April 2004) and Embase (January 1980 to April 2004). This strategy included the medical subject headings and text words "C-reactive protein", "pneumonia", "acute bronchitis", and "lower respiratory tract infection", and the text words "C reactive protein" and "lower respiratory infection". We supplemented the search by reference checking. The complete search strategy is available from the first author (VvdM).

#### Selection of studies

On the basis of title and abstract, full text articles were selected. We aimed to include studies that compared C reactive protein with a chest radiograph (tackling our first research question), or microbiological work-up (discriminative value for bacterial and viral aetiology). We excluded articles concerning immunocompromised patients, patients treated in intensive care units, or patients with hospital acquired pneumonia.

#### Quality assessment

We used the guidelines of the Cochrane methods group on systematic reviews of screening and diagnostic tests to assess the quality of the studies[8] (table A on bmj.com). Lijmer et al defined four methodological

P+ *Additional tables showing validity criteria and the results of the test performance of C reactive protein are on bmj.com*

ELPS *This is the abridged version of an article that was posted on bmj.com on 24 June 2005: http://bmj.com/cgi/doi/10.1136/bmj.38483.478183.EB*

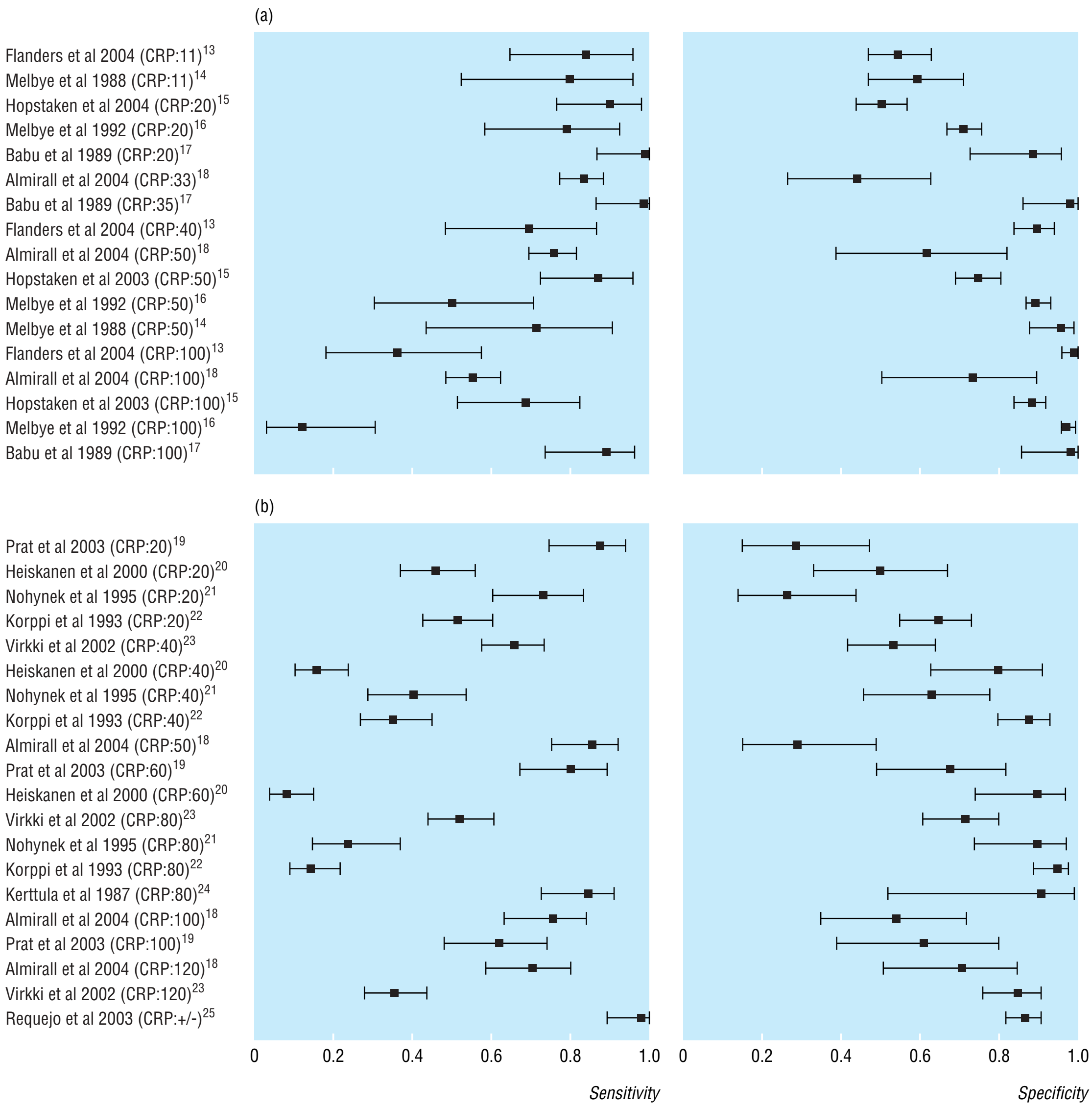


**Fig 1** Sensitivity-specificity plot (with 95% confidence intervals) of C reactive protein in relation to radiological detection of an infiltrate (top) or bacterial aetiology (bottom). Measurements of C reactive protein are presented in ascending order

criteria that overestimate the accuracy of a diagnostic test if these standards are not applied.[9] We used these Lijmer criteria to test robustness in the sensitivity analysis.[10]

Two authors (VvdM and AKN) independently assessed study quality. Disagreements were solved after discussion.

### Data extraction

We constructed cross tables for calculating sensitivity and specificity for different cut-off points and extracted cut-off points for C reactive protein values. We aimed to extract three cross tables for three different values per study. Where necessary we contacted authors for additional data. All studies with quantitative information were eligible for statistical analysis.

### Statistical analysis

For all studies, we extracted sensitivity, specificity, and positive and negative likelihood ratios for different cut-off points. We applied a statistical model for summarising performances of diagnostic tests based on that of Midgette et al.[11 12] We calculated Spearman's correlation of true positive rates and true negative rates. We calculated areas under the curve for each study to follow inverse correlation. We used a DerSimonian Laird $\gamma^2$ test to test for heterogeneity of these areas under the curve. We drew a summary receiver operating characteristic curve if data were homogeneous. We investigated the possibility of subgroup analysis and reported outcomes. We based a priori defined subgroups on age, setting, and sex.

We performed a sensitivity analysis by pooling separately the studies that met all four Lijmer criteria and those that did not.

## Results

Of the 165 citations in Medline and 340 citations in Embase, we retrieved 22 full text copies on the basis of title and abstract. After exclusions, 17 studies were included for quality assessment and 13 for quantitative analysis (see bmj.com).

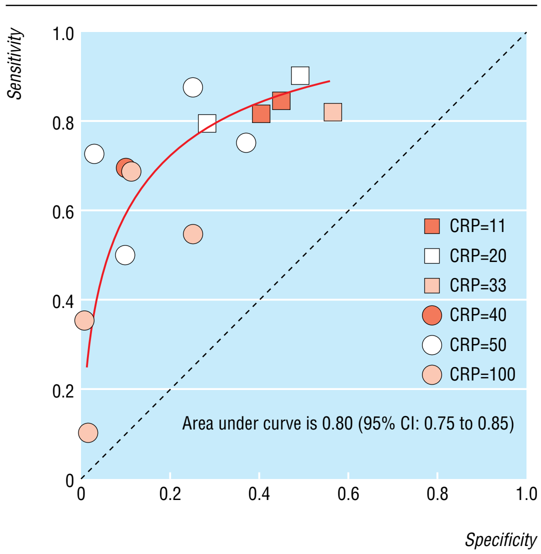


**Fig 2** Summary receiver operating characteristic curve of five studies dealing with the radiological detection of an infiltrate in adults

### Quality assessment

The results of the quality assessment according to validity criteria are on bmj.com. Initial agreement between the two quality assessors was 82.5% ($\kappa = 0.68$).

### Study characteristics

Regarding our first research question, all studies but one dealt with adults. Three studies were done in primary care, two in secondary care, and one in primary and secondary care.

Of the studies dealing with our second research question, most dealt with children, although five assessed adults. Two studies were conducted in a mixed primary and secondary care population; all others included secondary care populations.

### Test performance

The results of the test performance of C reactive protein with regard to the detection of an infiltrate on a chest radiograph or to the detection of a bacterial aetiology of lower respiratory tract infection are shown in table B on bmj.com and figure 1.

*Detection of an infiltrate*

With respect to our first research question, we derived 17 data points out of six studies (n = 1178; the number is determined by the number of patients contributing to a data point). Sensitivities ranged from 10% to 98%, specificities from 44% to 99%. Sensitivity and specificity were inversely related: Spearman's correlation coefficient was $-0.33$, $P < 0.01$ ($\chi^2$ test). Subgroup analysis in adults (five studies providing 14 data points) resulted in a Spearman's $\rho$ of $-0.82$, $P = 0.40$ ($\chi^2$ test). Figure 2 shows the summary receiver operating characteristic curve of this homogeneous subgroup. The area under the curve is 0.80 (95% confidence interval 0.75 to 0.85).

Sensitivity analysis of the areas under the curves of the studies that fulfilled all Lijmer criteria (area under the curve 0.84, 95% confidence interval 0.78 to 0.90) and those that did not (0.74, 0.65 to 0.83) showed robustness of the data.

*Bacterial aetiology*

Of the 12 studies dealing with our second research question, we obtained sufficient quantitative data to calculate sensitivity, specificity, and likelihood ratios for eight studies (n = 1096).

Sensitivities ranged from 8% to 99%, specificities from 27% to 95%. Spearman's $\rho$ for these eight studies was $-0.49$, $P < 0.01$ ($\chi^2$ test). Subgroup analysis in children resulted in a Spearman's $\rho$ of $-0.65$, $P < 0.01$ ($\chi^2$ test). A summary receiver operating characteristic curve for children could not be drawn because of statistical heterogeneity.

None of the studies fulfilled all four of the Lijmer criteria, so it was not possible to compare studies of different methodological quality.

## Discussion

C reactive protein testing is neither sufficiently sensitive to rule out nor sufficiently specific to rule in both an infiltrate on chest radiograph and bacterial aetiology of lower respiratory tract infection. The diagnostic value of C reactive protein has been studied to an insufficient degree. Few studies are available, and their methodological quality is generally poor.

### First research question: infiltrate on radiograph

We assessed the diagnostic accuracy of C reactive protein in detecting radiologically defined pneumonia. We found an area under the curve of 0.80 (95% confidence interval 0.75 to 0.85) in adults. The clinical applicability of these results depends largely on the epidemiological characteristics of a population. In general practice, where the prevalence of radiographically evident pneumonia is low,[26] the positive predictive value will be lower and the negative predictive value will be higher than in populations with a higher pretest probability of an infiltrate on chest radiograph.

The area under the curve of figure 2 is based on only five studies. None of these fulfilled all the validity criteria, and only three met the methodologically important criteria, as reported by Lijmer.[9] Moreover, the data refer to a subgroup of adults, so nothing can be concluded with regard to children.

### Second research question: bacterial aetiology

We investigated the diagnostic accuracy of C reactive protein in detecting bacterial aetiology of lower respiratory tract infection. Studies were highly heterogeneous, both statistically and epidemiologically. None of the studies met all of Lijmer's criteria and six of eight studies concerned children, mostly in a secondary care environment. Unfortunately, useful quantitative data were lacking in four studies of adults.

### Methodological considerations

We included all studies with usable quantitative data (sensitivity, specificity, and likelihood ratios) in the statistical analysis, irrespective of the quality assessment. In the sensitivity analysis we compared areas under the curve of the studies that met the Lijmer criteria with those that did not. Although the studies considered for our first research question were of variable methodological quality, the data for the subgroup of adults were robust. For our second research question we were not able to pool and compare the areas under the curve because of statistical heterogeneity.

## What is already known on this topic

Irrational prescription of antibiotics for respiratory tract infections is partly caused by diagnostic uncertainty about presence of an infiltrate and about bacterial aetiology

Tests for C reactive protein are increasingly used to guide antibiotic prescribing for infections of the lower respiratory tract

Some recently published studies report useful diagnostic accuracy of C reactive protein in infections of the lower respiratory tract

## What this study adds

C reactive protein testing is neither sufficiently sensitive to rule out nor specific enough to rule in an infiltrate on chest radiograph and bacterial aetiology of infections of the lower respiratory tract

The use of tests for C reactive protein to guide antibiotic prescription in lower respiratory tract infection is not consistently supported by the present evidence

**Quality of included studies**

We used the guidelines of the Cochrane methods group on systematic reviews of screening and diagnostic tests to assess the quality of the included studies, but we did not assess the quality of the reference standard for each study. The results of a chest radiograph and of microbiological work-up depend on the methods used. New microbiological techniques have been developed in recent decades, the presence of an infiltrate depends on the duration of illness and the relation between bacterial colonisation and pathogenesis of lower respiratory tract infection cannot always be established.

**Limitations of the model**

We applied a statistical model for diagnostic reviews, based on that of Midgette et al.[11 12] The methods using a summary receiver operating characteristic curve deals with the problem of different cut-off points in studies and is useful in providing an overall diagnostic accuracy by means of the area under the curve. However, it does not directly provide an exclusive estimate of optimal sensitivity and specificity. The question of which C reactive protein value can be used to obtain optimal sensitivity and specificity can unfortunately not be answered.

## Conclusion

The current evidence does not consistently and sufficiently support a wide introduction of C reactive protein as a rapid test to guide antibiotic prescription.

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