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Primary care

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

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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 not consistently and sufficiently supports a wide introduction of C reactive protein as a rapid test to guide antibiotics prescription.

Introduction

Infections of the lower respiratory tract are common in the community and comprise both acute bronchitis and pneumonia.[1 2] Differentiating between these two diagnoses by history and physical examination is challenging. However, several studies show that making a diagnosis of pneumonia, defined as a new infiltrate on a chest radiograph, on the basis of clinical findings is difficult.[3 4]

Differentiation between pneumonia and acute bronchitis is important because of the therapeutic consequences. Bacterial pneumonia should be treated with antibiotics, whereas acute bronchitis is usually self limiting.[5] Microbiological aetiology varies from 15-25% viral infection in radiologically proved pneumonia, to 15-40% viral infection in infection of the lower respiratory tract.[1 6–8]

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.[9 10] These data call for additional information, 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 of this clinical dilemma.[11] 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.[12] Since its identification in 1930, C reactive protein has been studied as a screening device for inflammation, a marker for disease activity, and as a diagnostic adjunct.[13] However, even though values of C reactive protein may reflect the severity of inflammation or tissue injury, its role in differentiating bacterial from viral infections is not proved.[14 15] With the availability of rapid or bedside tests, particularly in general practice, determining its diagnostic value is of increasing importance.[16 17] 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 performed an electronic search according to the most recent recommendations.[18 19 20] 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 included only articles in English.[21] We applied methodological filters for Medline and Embase.[20 22] 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, the first author (VvdM) selected full text articles. 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. Data that were published twice or more often were selected only once.

Additional tables and the results of the test performance of C reactive protein are on bmj.com

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.[19] Table A on bmj.com shows how we used these guidelines. Lijmer et al defined four methodological criteria that overestimate the accuracy of a diagnostic test if these standards are not applied.[23] We used these Lijmer criteria to test robustness in the sensitivity analysis.[24]

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

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. If this was not possible on the basis of the reported data, we contacted the authors and asked them to provide the required additional data. All studies with quantitative information were eligible for statistical analysis.

Statistical analysis

We used the κ statistic as a measure of agreement on quality assessment.[25] 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 that was based on that of Midgette et al.[18 26] 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 χ^2 test to test heterogeneity of these areas under the curve.[27 28] 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

Figure 1 summarises the search strategy and selection of the identified studies. Of the 165 citations in Medline and 340 citations in Embase, we retrieved 22 full text copies on the basis of title and abstract. Reference checking retrieved one additional study. We excluded five studies as they did not meet the inclusion criteria.[29 30 31 32 33] One study was conducted using both reference standards—radiology and microbiological aetiology.[34] One study was published in two different articles,[35 36] which meant that 17 studies were published in 18 articles.

Quality assessment

Table 1 shows the results of the quality assessment according to the validity criteria in table A (see bmj.com). Initial agreement between the two quality assessors was 82.5% (κ = 0.68).

Study characteristics

Table 2 lists the characteristics of the 17 studies included in the quality assessment. Regarding our first research question, all studies but one[38] dealt with adults. Three studies were done in primary care,[37 39 40] two in secondary care,[17 38] and one in a mixed population in primary and secondary care.[34]

Of the studies dealing with our second research question, most deal with children, although five of them assessed adults.[34 43 44 47 49] Two studies were conducted in a mixed primary and secondary care population[34 45]; all others included secondary care populations.

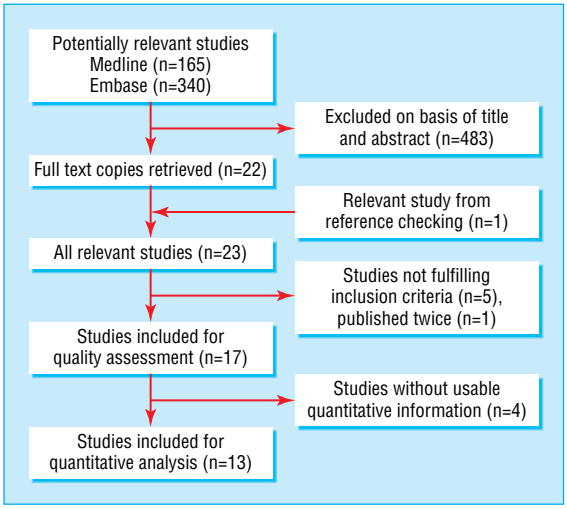

Fig 1 Flow of studies through the stages of the review

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 2.

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 (χ^2 test). Subgroup analysis in adults (five studies providing 14 data points) resulted in a Spearman's ρ of −0.82, P = 0.40 (χ^2 test).[17 34 37 39 40] Figure 3 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). Subgroups based on setting or sex could not be analysed, since they were too small (setting) or not available (lack of information on sex).

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)[17 37 40] and those that did not[34 39] (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). Four authors were not able to provide additional data, because these data were not available any more.[43 44 47 49] One did not respond.[50]

Sensitivities ranged from 8% to 99%, specificities from 27% to 95%. Spearman's ρ for these eight studies was −0.49, P < 0.01 (χ^2 test). Subgroup analysis in children (six studies providing 16 data points) resulted in a Spearman's ρ of −0.65, P < 0.01 (χ^2 test).[36 41 42 45 46 48] A summary receiver operating characteristic curve for children could not be drawn because of statistical heterogeneity. We could not perform subgroup analysis based on setting or sex because none of the studies was conducted in primary care and data on sex were not available.

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

Table 1 Quality assessment of the 17 studies

	Criteria for study validity						Criteria relevant to applicability of test results		
	Blind measurement*	Avoidance of verification bias*	Spectrum of the disease*	Avoidance of selection bias	Independent interpretation	Avoidance of treatment paradox	Setting*	Duration of illness	Demographic information (age)
Detection of infiltrate									
Flanders et al 2004[17]†	+	+	+	+	+	?	+	+	+
Almirall et al 2004[34]	?	+	–	+	?	?	+	–	+
Hopstaken et al 2003[37]†	+	+	+	+	?	?	+	+	+
Melbye et al 1992[39]	–	–	+	?	?	?	+	+	+
Babu et al 1989[38]	?	?	–	–	?	+	+	+	+
Melbye et al 1988[40]†	+	+	+	?	?	+	+	–	+
Discrimination between viral and bacterial aetiology									
Almirall et al 2004[34]	?	+	+	+	?	?	+	–	+
Prat et al 2003[41]	?	+	+	?	?	+	+	–	+
Requejo et al 2003[42]	?	+	+	?	?	?	–	–	–
Garcia Vazquez et al 2003[43]	?	+	+	+	?	+	+	–	+
Virkki et al 2002[36]	?	+	+	+	?	+	+	–	+
Hedlund et al 2000[44]	?	+	+	+	?	+	+	–	+
Heiskanen et al 2000[45]	?	+	+	+	?	+	+	–	+
Nohynek et al 1995[46]	?	+	+	?	?	+	+	+	+
Ortqvist et al 1995[47]	?	+	+	+	?	+	+	+	+
Korppi et al 1993[48]	?	+	+	?	?	+	+	–	+
Kerttula et al 1987[49]	?	+	+	+	?	+	+	+	+
McCarthy et al 1978[50]	?	+	+	+	?	+	+	–	+

Plus, minus or question mark were adjudged if criteria were present, absent, or not mentioned.
*Essential criteria defined by Lijmer et al.[23]
†Fulfilling all Lijmer criteria.

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

In the first part of the study, where 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,[51] 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 practical use of the sensitivities and specificities as presented in table B (see bmj.com) can be illustrated by using the data of one of the studies. If we consider, for example, the data of Melbye et al for a C reactive protein cut-off point of 20, sensitivity is 0.80, specificity is 0.72 with a prevalence of radiographically evident pneumonia of 5%. These data result in a positive predictive value of 12.7% and a negative predictive value of 98.6%.

However, the area under the curve of figure 3 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.[23] 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, making it impossible to provide an overall diagnostic accuracy. 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.[43 44 47 50]

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. In the future, more methodologically sound diagnostic studies need to be reported to be able to draw conclusions regarding the diagnostic accuracy of C reactive protein in infection of the lower respiratory tract. The recently formulated guidelines for diagnostic studies (STARD, www.consort-statement.org/stardstatement.htm) will probably have an important role in this process.

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 (infiltrate or no infiltrate) and of microbiological work-up (bacterial or viral aetiology) depend on the methods used. For example, the interpretation of chest radiographs is variable between radiologists, the presence of an infiltrate depends on the duration of illness, new microbiological techniques have been developed in recent decades, and the relation between bacterial colonisation and pathogenesis of lower respiratory tract infection cannot always be established.[52–56]

Table 2 Characteristics of 17 retrieved studies testing for C reactive protein in infections of the lower respiratory tract, with reference test infiltrate on chest radiograph (first research question) or aetiological microbiological diagnosis (second research question)

Author	Sample size	Age in years	Participants and setting
Detection of infiltrate			
Flanders et al 2004[17]	168	>18	Adults with acute cough at emergency department or acute care ambulatory clinic of the University of California, San Francisco, USA
Almirall et al 2004[34]	226	>14	Adults with symptoms of infection of the lower respiratory tract and focal signs presenting at primary or secondary care in the Maresme region, Spain
Hopstaken et al 2003[37]	246	18–89	Adults in the southern part of the Netherlands, who presented to their general practitioner with symptoms and signs of infection of the lower respiratory tract
Melbye et al 1992[39]	402	>18	Adults with symptoms suggestive of respiratory or throat infection in general practice, Norway
Babu et al 1989[38]	65	2 months-12	Children with a diagnosis of infection of the lower respiratory tract at Nehru Hospital, India
Melbye et al 1988[40]	71	>15	Adults who were treated with antibiotics by a general practitioner for a suspected pneumonia, Norway
Distinction between viral and bacterial aetiology			
Almirall et al 2004[34]	83	>14	Adults with symptoms of infection of the lower respiratory tract and focal signs presenting at primary or secondary care in the Maresme region, Spain
Prat et al 2003[41]	85	6 months-10	Children in the paediatric emergency department with clinical signs of infection of the lower respiratory tract or pneumonic infiltrate on a chest radiograph at University Hospital, Badalona, Spain
Requejo et al 2003[42]	111	Unclear	Children with suspected community acquired pneumonia at University Hospital, Sao Paulo, Brazil
Garcia Vazquez et al 2003[43]	258	>14	Adults with acute symptoms consistent of community acquired pneumonia at Hospital Clinic, Barcelona, Spain
Virkki et al 2002[36]	215	Unclear	Children with community acquired pneumonia admitted to Turku University Hospital, Finland
Hedlund et al 2000[44]	96	50–85	Adults with community acquired pneumonia admitted to the Department of Infectious Diseases at Danderyd Hospital, Sweden
Heiskanen et al 2000[45]	193	3 months-15	All cases of pneumonia (children) in the area of one town and three rural municipalities in eastern Finland
Nohynek et al 1995[46]	121	4 months-15	Children admitted to hospital for infection of the lower respiratory tract at Aurora Hospital, Helsinki, Finland
Ortqvist et al 1995[47]	196	>18	Adults with community acquired pneumonia admitted to Danderyd Hospital, Sweden
Korppi et al 1993[48]	209	<15	Children treated for infection of the middle respiratory tract* or the lower respiratory tract at Kuopio University Hospital, Finland
Kerttula et al 1987[49]	79	>15	Adults admitted for suspected community acquired pneumonia to Aurora Hospital, Helsinki, Finland
McCarthy et al 1978[50]	156	1 month-16	Children with radiologic pulmonary infiltrate at paediatric emergency room, Yale-New Haven Hospital, USA

*Term not specified by the authors of the original study.[48]

Limitations of the model

We applied a statistical model for diagnostic reviews, based on that of Midgette et al.[18 26] 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 methodological quality of the diagnostic studies is generally poor. The current evidence does not consistently and sufficiently support a wide introduction of C reactive protein as a rapid test to guide antibiotics prescription.

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Contributors: VvdM collected data, performed the analysis and wrote the manuscript. AKN performed the analysis and revised the paper. PJvdB extensively revised the paper. WJJA conceived the study and extensively revised the paper. VvdM and WJJA are guarantors.

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Ethical approval: Not required.

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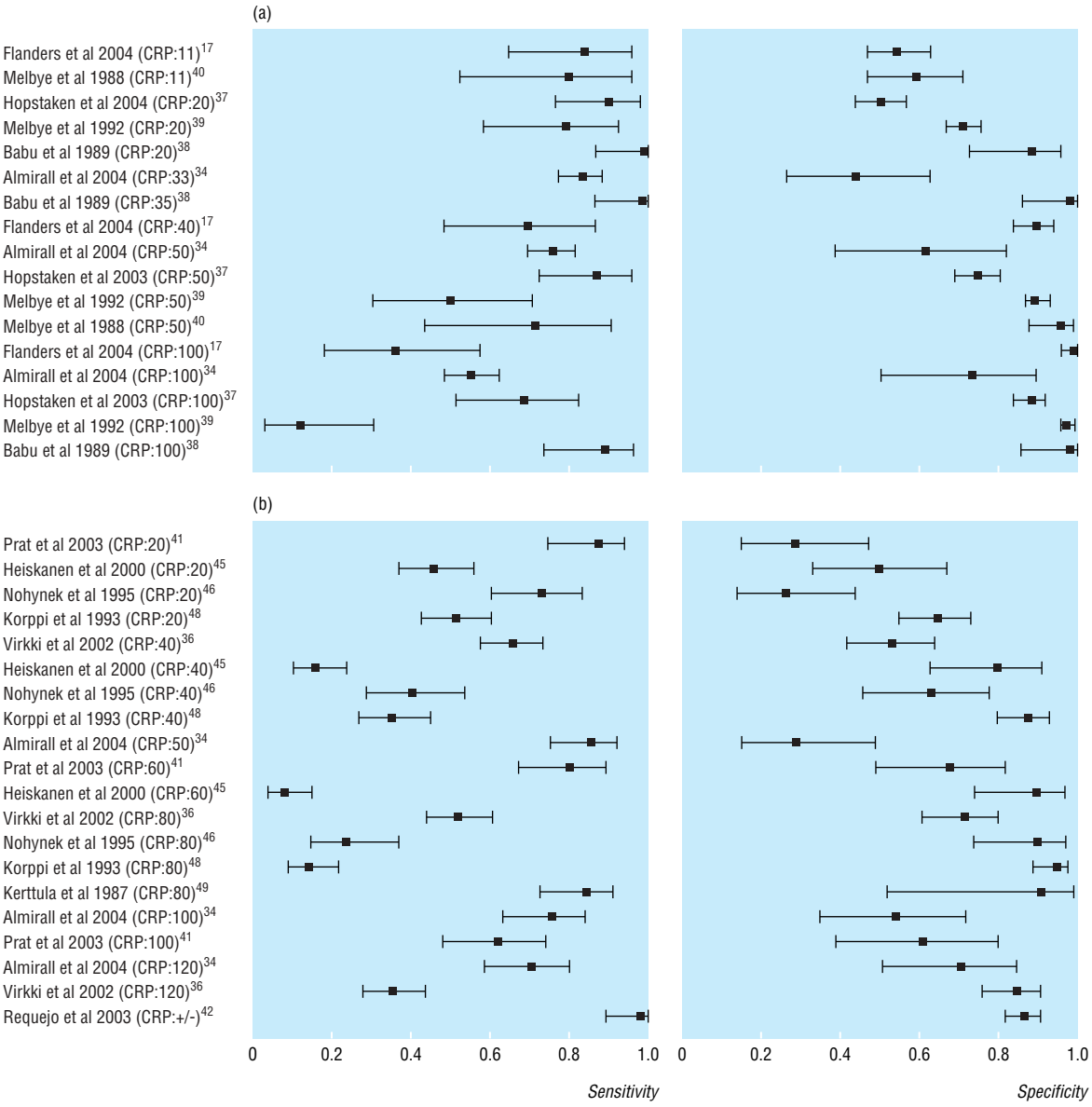

Fig 2 Sensitivity-specificity plot (with 95% confidence intervals) of C reactive protein in relation to detection of an infiltrate (top) or bacterial aetiology (bottom). Measurements of C reactive protein are presented in ascending order

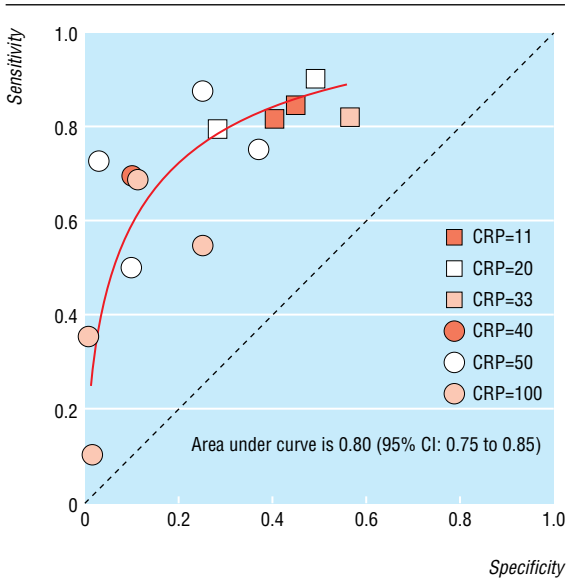

Fig 3 Summary receiver operating characteristic curve of five studies dealing with the radiological detection of an infiltrate in adults

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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

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