Cochrane Library

Cochrane Database of Systematic Reviews

Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia (Review)

Wang K, Gill P, Perera R, Thomson A, Mant D, Harnden A

Wang K, Gill P, Perera R, Thomson A, Mant D, Harnden A.
Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia.
Cochrane Database of Systematic Reviews 2012, Issue 10. Art. No.: CD009175.
DOI: 10.1002/14651858.CD009175.pub2.

www.cochranelibrary.com

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
WILEY

TABLE OF CONTENTS

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Diagnostic Test Accuracy Review]

Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia

Kay Wang[1], Peter Gill[1], Rafael Perera[1], Anne Thomson[2], David Mant[1], Anthony Harnden[1]

[1]Department of Primary Care Health Sciences, University of Oxford, Oxford, UK. [2]Department of Paediatrics, John Radcliffe Hospital, Oxford, UK

Contact: Kay Wang, Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, Oxon, OX2 6GG, UK. kay.wang@phc.ox.ac.uk.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New, published in Issue 10, 2012.

Citation: Wang K, Gill P, Perera R, Thomson A, Mant D, Harnden A. Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia. *Cochrane Database of Systematic Reviews* 2012, Issue 10. Art. No.: CD009175. DOI: 10.1002/14651858.CD009175.pub2.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Mycoplasma pneumoniae (*M. pneumoniae*) is a significant cause of community-acquired pneumonia in children and adolescents. Treatment with macrolide antibiotics is recommended. However, *M. pneumoniae* is difficult to diagnose based on clinical symptoms and signs. Diagnostic uncertainty can lead to inappropriate antibiotic prescribing, which may worsen clinical prognosis and increase antibiotic resistance.

Objectives

The objectives of this review are (i) to assess the diagnostic accuracy of symptoms and signs in the clinical recognition of *M. pneumoniae* in children and adolescents with community-acquired pneumonia; and (ii) to assess the influence of potential sources of heterogeneity on the diagnostic accuracy of symptoms and signs in the clinical recognition of *M. pneumoniae*.

Search methods

We searched MEDLINE (January 1950 to 26 June 2012) and EMBASE (January 1980 to 26 June 2012). We identified additional references by handsearching the reference lists of included articles and snowballing. We searched the reference lists of relevant systematic reviews identified by searching the Medion database, Database of Reviews of Effects 2012, Issue 6 (25 June 2012) and the Cochrane Register of Diagnostic Test Accuracy studies (2 July 2012). Experts in the field reviewed our list of included studies for any obvious omissions.

Selection criteria

We included peer-reviewed published studies which prospectively and consecutively recruited children with community-acquired pneumonia from any healthcare setting, confirmed the presence of *M. pneumoniae* using serology with or without other laboratory methods and reported data on clinical symptoms and signs in sufficient detail to construct 2 x 2 tables.

Data collection and analysis

One review author scanned titles to exclude obviously irrelevant articles. Two review authors independently scanned the remaining titles and abstracts, reviewed full-text versions of potentially relevant articles, assessed the quality of included articles and extracted data on study characteristics and the following clinical features: cough, wheeze, coryza, crepitations, fever, rhonchi, shortness of breath, chest pain, diarrhea, myalgia and headache.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

We calculated study-specific values for sensitivity, specificity and positive and negative likelihood ratios with 95% confidence intervals (CIs). We estimated the post-test probability of *M. pneumoniae* based on the absence or presence of symptoms and signs.

We calculated pooled sensitivities, specificities, positive and negative likelihood ratios with 95% CIs for symptoms and signs where data were reported by at least four included studies by fitting a bivariate normal model for the logit transforms of sensitivity and specificity. We explored potential sources of heterogeneity by fitting bivariate models with covariates using multi-level mixed-effects logistic regression. We performed sensitivity analyses excluding data from studies for which we were concerned about the representativeness of the study population and/or the acceptability of the reference standard.

Main results

Our search identified 8299 articles (excluding duplicates). We examined the titles and abstracts of 1125 articles and the full-text versions of 97 articles. We included seven studies in our review, which reported data from 1491 children; all were conducted in hospital settings. Overall, study quality was moderate. In two studies the presence of chest pain more than doubled the probability of *M. pneumoniae*. Wheeze was 12% more likely to be absent in children with *M. pneumoniae* (pooled positive likelihood ratio (LR+) 0.76, 95% CI 0.60 to 0.97; pooled negative likelihood ratio (LR-) 1.12, 95% CI 1.02 to 1.23). Our sensitivity analysis showed that the presence of crepitations was associated with *M. pneumoniae*, but this finding was of borderline statistical significance (pooled LR+ 1.10, 95% CI 0.99 to 1.23; pooled LR- 0.66, 95% CI 0.46 to 0.96).

Authors' conclusions

M. pneumoniae cannot be reliably diagnosed in children and adolescents with community-acquired pneumonia based on clinical symptoms and signs. Although the absence of wheeze is a statistically significant diagnostic indicator, it does not have sufficient diagnostic value to guide empirical macrolide treatment. Data from two studies suggest that the presence of chest pain more than doubles the probability of *M. pneumoniae*. However, further research is needed to substantiate this finding. More high quality large-scale studies in primary care settings are needed to help develop prediction rules based on epidemiological data as well as clinical and baseline patient characteristics.

PLAIN LANGUAGE SUMMARY

Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia

Chest infections are among the commonest reasons why children and young people go to see their doctor or nurse. At the moment, it is difficult for doctors and nurses to tell patients what type of infection they have based on their symptoms and signs. This can result in antibiotics being prescribed or withheld inappropriately. *Mycoplasma pneumoniae* (*M. pneumoniae*) is an important bacterial cause of chest infections in children and adolescents. This review assesses the value of clinical symptoms and signs in helping doctors and nurses decide whether a child or young person might have a chest infection caused by *M. pneumoniae*. We analysed data from seven studies including a total of 1491 children, all of which were conducted in hospital settings. We found that the presence of wheeze makes *M. pneumoniae* slightly less likely and the presence of crepitations (*i.e.* crackles heard on listening to the chest) makes *M. pneumoniae* slightly more likely. However, these clinical features are not sufficiently helpful to guide decisions about prescribing antibiotics for possible *M. pneumoniae* infections. Based on the results of two studies, the presence of chest pain doubles the likelihood of *M. pneumoniae*. However, further research in this area is needed, particularly in general practice and outpatient populations.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

SUMMARY OF FINDINGS

Summary of findings 1. Overview of studies and population characteristics

Patients/populations	Children and adolescents aged 18 years or younger diagnosed with community-acquired pneumonia based on clinical +/- radiological criteria. No evidence of serious underlying co-morbidity or immunocompromise
Settings	All included studies were conducted in hospital settings
Index tests	Clinical symptoms and signs: cough, wheeze, coryza, crepitations, fever, rhonchi, shortness of breath, headache, chest pain, diarrhea and myalgia
Reference standard	*M. pneumoniae* serology (i.e. high antibody titre on a single serum sample or a significant rise in antibody titre between paired acute and convalescent sera) with or without the use of additional laboratory tests such as culture or polymerase chain reaction (PCR) analysis
Importance	*M. pneumoniae* cannot be reliably diagnosed in children and adolescents with community-acquired pneumonia based on the absence or presence of individual clinical symptoms and signs. Absence of wheeze is a statistically significant diagnostic indicator, but does not have sufficient diagnostic value to guide empirical macrolide antibiotic treatment. Absence of wheeze is only 12% more likely in *M. pneumoniae*-positive versus *M. pneumoniae*-negative children. If empirical antibiotic treatment was given to children with community-acquired pneumonia in whom wheeze was not reported, 61% to 89% of children receiving antibiotics would be *M. pneumoniae*-negative (based on *M. pneumoniae* prevalence of 10% to 36%) and antibiotics would be withheld from 25% of *M. pneumoniae*-positive children
Studies	Published peer-reviewed studies (any design) including prospectively and consecutively recruited cohorts of children with community-acquired pneumonia from any healthcare setting. This review included 7 studies which reported data on 1491 children
Quality concerns	The most common concern was unclear reporting of baseline study population characteristics. We had concerns about the spectrum of patients recruited and the validity of the reference standard in one study (Agarwal 2009)

Summary of findings 2. Diagnostic value of clinical symptoms and signs - pooled results with 95% confidence intervals

Clinical feature (n = number of studies)	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Cough (n = 5)	0.89 (0.67 to 0.97)	0.15 (0.05 to 0.37)	1.04 (0.95 to 1.13)	0.78 (0.44 to 1.39)
Wheeze (n = 6)*	0.25 (0.17 to 0.36)	0.67 (0.56 to 0.76)	0.76 (0.60 to 0.97)	1.12 (1.02 to 1.23)
Coryza (n = 4)	0.32 (0.08 to 0.72)	0.66 (0.28 to 0.91)	0.95 (0.71 to 1.26)	1.03 (0.90 to 1.17)
Crepitations (n = 5)**	0.84 (0.78 to 0.88)	0.22 (0.14 to 0.32)	1.06 (0.96 to 1.18)	0.77 (0.52 to 1.12)

*The absence of wheeze remained a statistically significant diagnostic indicator when *M. pneumoniae* was diagnosed based on serology only (pooled LR+ 0.68, 95% CI 0.50 to 0.92; pooled LR- 1.24, 95% 1.03 to 1.51) (Chan 2001; Somer 2006). However, the absence of wheeze was no longer a statistically significant diagnostic indicator based on data from studies which used other laboratory tests alongside serology to diagnose *M. pneumoniae* (pooled LR+ 0.84, 95% CI 0.63 to 1.12; pooled LR- 1.06, 95% CI 0.96 to 1.18).

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

**Our sensitivity analysis excluding data from Agarwal 2009 found that the presence of crepitations was a weak diagnostic indicator of borderline statistical significance (pooled LR+ 1.10, 95% CI 0.99 to 1.23; pooled LR- 0.66, 95% CI 0.46 to 0.96).

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Target condition being diagnosed

Mycoplasma pneumoniae (*M. pneumoniae*) is a significant and treatable cause of respiratory tract infections in children and adolescents. Data from previous studies suggest that *M. pneumoniae* is responsible for up to 40% of community-acquired pneumonia in children over five years of age (Don 2005; Heiskanen-Kosma 1998; Korppi 2004) and its highest incidence is found in the five to nine-year age group (4 per 1000 children per year) (Hammerschlag 2001). *M. pneumoniae* tends to occur in epidemics lasting 12 to 15 months, which happen at approximately four-yearly intervals (Chalker 2011; Hammerschlag 2001). Estimates of the prevalence of *M. pneumoniae* are therefore extremely variable, ranging from 1% during endemic periods (Sopena 1999) to 50% during outbreaks within closed institutional settings (Broome 1980).

At the moment, *M. pneumoniae* is diagnosed retrospectively using laboratory methods. However, there is no single 'gold standard' for laboratory diagnosis of *M. pneumoniae*. Serology is currently the most widely available method. Serological assays may be based on a single high antibody titre or on paired acute and convalescent serum samples taken two to four weeks apart (Loens 2010). Other laboratory methods include culture and polymerase chain reaction (PCR). Culture can take several weeks and has poor sensitivity (Loens 2010). PCR techniques are more rapid and more sensitive than serology at detecting acute *M. pneumoniae* infections but are less widely available (Nilsson 2008).

Index test(s)

In this review, our index tests were clinical symptoms and signs: cough, wheeze, coryza (nasal symptoms, including runny nose, nasal congestion and sneezing), crepitations (crackles audible on chest examination), fever (reported as a symptom or according to temperature threshold defined in study), rhonchi (wheeze audible on chest examination), shortness of breath, chest pain, diarrhea, myalgia (muscle aches) and headache. These clinical features have been reported in several case series of children with laboratory-confirmed *M. pneumoniae* (Hsieh 2007; Othman 2005; Stevens 1978). This review formally assesses the diagnostic value of these symptoms and signs individually in the clinical recognition of *M. pneumoniae* in children and adolescents with community-acquired pneumonia.

Alternative test(s)

There are no alternative tests applicable to this review, since a range of clinical symptoms and signs are being studied.

Rationale

Acute respiratory tract infections represent one of the commonest reasons for medical consultations and prescription of antibiotics. Despite the recommendations of recent guidelines (NICE 2008), almost two-thirds of consultations for respiratory tract infections still result in antibiotic prescribing (Gulliford 2009). *M. pneumoniae* is an important cause of respiratory tract infections in children and adolescents. Macrolide antibiotics are recommended for the treatment of suspected *M. pneumoniae* infections (BTS 2011). However, it is difficult for clinicians to give patients accurate prognostic information or decide on appropriate antibiotic treatment in the absence of a microbiological diagnosis (Butler 2004). Diagnostic uncertainty can lead to inappropriate antibiotic prescribing, which may worsen clinical prognosis and increase antibiotic resistance within both communities (Goossens 2005) and individuals (Chung 2007). Macrolide-resistant strains of *M. pneumoniae* have recently been reported in France (Pereyre 2007), Japan (Morozumi 2008), Germany (Dumke 2010), Israel (Averbuch 2011) and China (Zhao 2012).

This review will help us assess whether the absence or presence of symptoms and signs might help clinicians decide which children with clinically suspected community-acquired pneumonia are most (and least) likely to benefit from empirical macrolide treatment at the time of initial presentation, when the results of laboratory tests for *M. pneumoniae* are not available.

OBJECTIVES

To assess the diagnostic accuracy of symptoms and signs in the clinical recognition of *M. pneumoniae* in children and adolescents with community-acquired pneumonia.

Secondary objectives

To assess the influence of potential sources of heterogeneity on the diagnostic accuracy of symptoms and signs in the clinical recognition of *M. pneumoniae* in children and adolescents with community-acquired pneumonia.

Investigation of sources of heterogeneity

We investigated the use of other laboratory investigations (such as culture and PCR) alongside serology to diagnose *M. pneumoniae*.

METHODS

Criteria for considering studies for this review

Types of studies

Published peer-reviewed studies (any design) including prospectively and consecutively recruited cohorts of children with community-acquired pneumonia in any healthcare setting.

Participants

Participants aged 18 years or younger with no evidence of serious underlying comorbidity (e.g. cystic fibrosis, bronchiectasis, neoplasia) or immunocompromise (HIV-positive or on immunosuppressant medication), who have been diagnosed with community-acquired pneumonia based on clinical +/- radiological criteria.

Index tests

Clinical symptoms and signs reported in children and adolescents diagnosed with community-acquired pneumonia: cough, wheeze, coryza (nasal symptoms, including runny nose, nasal congestion and sneezing), crepitations (crackles audible on chest examination), fever (reported as a symptom or according to temperature threshold defined in study), rhonchi (wheeze audible on chest examination), shortness of breath, chest pain, diarrhea, myalgia (muscle aches) and headache.

Comparator tests

None.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Target conditions

M. pneumoniae infection in children and adolescents with community-acquired pneumonia.

Reference standards

Our reference standard was *M. pneumoniae* serology with or without the use of additional laboratory tests such as culture or PCR. *M. pneumoniae* serology is currently the most widely available diagnostic method. We defined a positive *M. pneumoniae* serology result as either a high antibody titre on a single serum sample or a significant rise in antibody titre between paired acute and convalescent sera, as defined by the manufacturers of the serology assay(s) being used in different studies.

Search methods for identification of studies

Electronic searches

We searched MEDLINE (January 1950 to 26 June 2012) and EMBASE (January 1980 to 26 June 2012) for suitable articles. Appendix 1 and Appendix 2 contain details of our electronic search strategies. We did not apply any language or publication restrictions to our search.

Searching other resources

We supplemented our electronic search by handsearching the reference lists of included studies and snowballing (i.e. reviewing full texts and reference lists of articles cited by previously identified publications). We also searched the Medion database (http://www.mediondatabase.nl) (25 June 2012), Database of Reviews of Effects 2012, Issue 6 (part of *T he Cochrane Library*, www.thecochranelibrary.com (accessed 25 June 2012) and the Cochrane Register of Diagnostic Test Accuracy studies (2 July 2012) to identify systematic reviews whose reference lists might provide additional references. We asked experts in the field to review our list of included studies for any obvious omissions.

Data collection and analysis

Selection of studies

We selected peer-reviewed published studies (any design) which included prospectively and consecutively recruited cohorts of children with community-acquired pneumonia in any healthcare setting and which reported data on clinical symptoms and signs in these children in sufficient detail for us to construct 2 x 2 tables. We excluded case reports, case series, systematic reviews and narrative reviews. We also excluded studies with unsuitable comparison groups (i.e. non-consecutively recruited *M. pneumoniae*-negative controls or participants with a different laboratory-confirmed microbial diagnosis) because assessments of the diagnostic value of symptoms and signs are likely to be distorted in these types of study populations.

We included studies which confirmed the diagnosis of *M. pneumoniae* using serology based on single serum samples or paired acute and convalescent sera with or without the use of additional laboratory methods such as culture or PCR (see Reference standards).

One review author (KW) scanned the titles of studies identified by our search to exclude any obviously irrelevant articles. Two review authors (KW, PG) independently scanned the titles and abstracts of the remaining studies and reviewed full-text versions of potentially relevant articles. We resolved any disagreements by discussion, if necessary with a third review author (DM or AH).

Data extraction and management

Two review authors (KW, PG) independently extracted data on study characteristics (study design, age and sex of participants, study inclusion and exclusion criteria, number of participants recruited, recruitment period, country(ies) where recruitment took place, healthcare setting, criteria for diagnosing community-acquired pneumonia, laboratory methods used to diagnose *M. pneumoniae*, number of participants diagnosed with *M. pneumoniae*) and clinical symptoms and signs. We constructed 2 x 2 tables for clinical symptoms and signs (see Statistical analysis and data synthesis section for further details). We resolved any discrepancies by discussion, if necessary with a third review author (RP).

Assessment of methodological quality

Two review authors (KW, PG) independently assessed the quality of included articles. We resolved any disagreements by consensus. Table 1 outlines details of our quality assessment tool and coding criteria based on the QUADAS tool (Reitsma 2009).

Statistical analysis and data synthesis

We constructed 2 x 2 tables for each study we included in our review, cross-classifying the absence or presence of *M. pneumoniae* with the absence or presence of clinical symptoms and signs. We used these tables to calculate study-specific values for sensitivity, specificity and positive and negative likelihood ratios. We also examined how the prevalence of *M. pneumoniae* in the study population influences the post-test probability of *M. pneumoniae* based on the absence or presence of different symptoms and signs (Van den Bruel 2010).

We calculated pooled sensitivities, specificities, positive and negative likelihood ratios with 95% confidence intervals (CIs) for clinical symptoms and signs where data were reported by at least four included studies, by fitting a bivariate normal model for the logit transforms of sensitivity and specificity (Leeflang 2008). We obtained estimates from these models using the command *metandi* (meta-analysis of diagnostic accuracy) in Stata version 11. We obtained summary estimates for positive and negative likelihood ratios directly from the summary estimates of sensitivity and specificity.

Investigations of heterogeneity

We planned to explore the following potential sources of heterogeneity by fitting bivariate models with covariates using multi-level mixed-effects logistic regression (*xtmelogit*) in Stata version 11:

1. Participant age group (preschool (up to four years of age) versus school age (five to 12 years of age) versus adolescents (13 to 18 years of age))*.
2. Healthcare setting (community versus hospital).
3. Method of diagnosing community-acquired pneumonia (based on clinical criteria only versus based on clinical and radiological criteria).

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

4. Serological method of diagnosing *M. pneumoniae* (high antibody titre on single serum sample versus significant rise in antibody titre between acute and convalescent sera).
5. Use of other laboratory investigations (such as culture or PCR) alongside serology to diagnose *M. pneumoniae*.

*We only planned to investigate heterogeneity if clinical symptoms and signs were reported in sufficient detail within studies to construct 2 x 2 tables in our specified age categories.

Sensitivity analyses

We used sensitivity analyses to explore the influence of negative classification of items 1 (representative spectrum) and 2 (acceptable reference standard) of our quality assessment tool (Table 1).

Assessment of reporting bias

We did not undertake any formal assessment of reporting bias in our review due to current uncertainty about how to assess reporting bias in diagnostic test accuracy reviews (Deeks 2005).

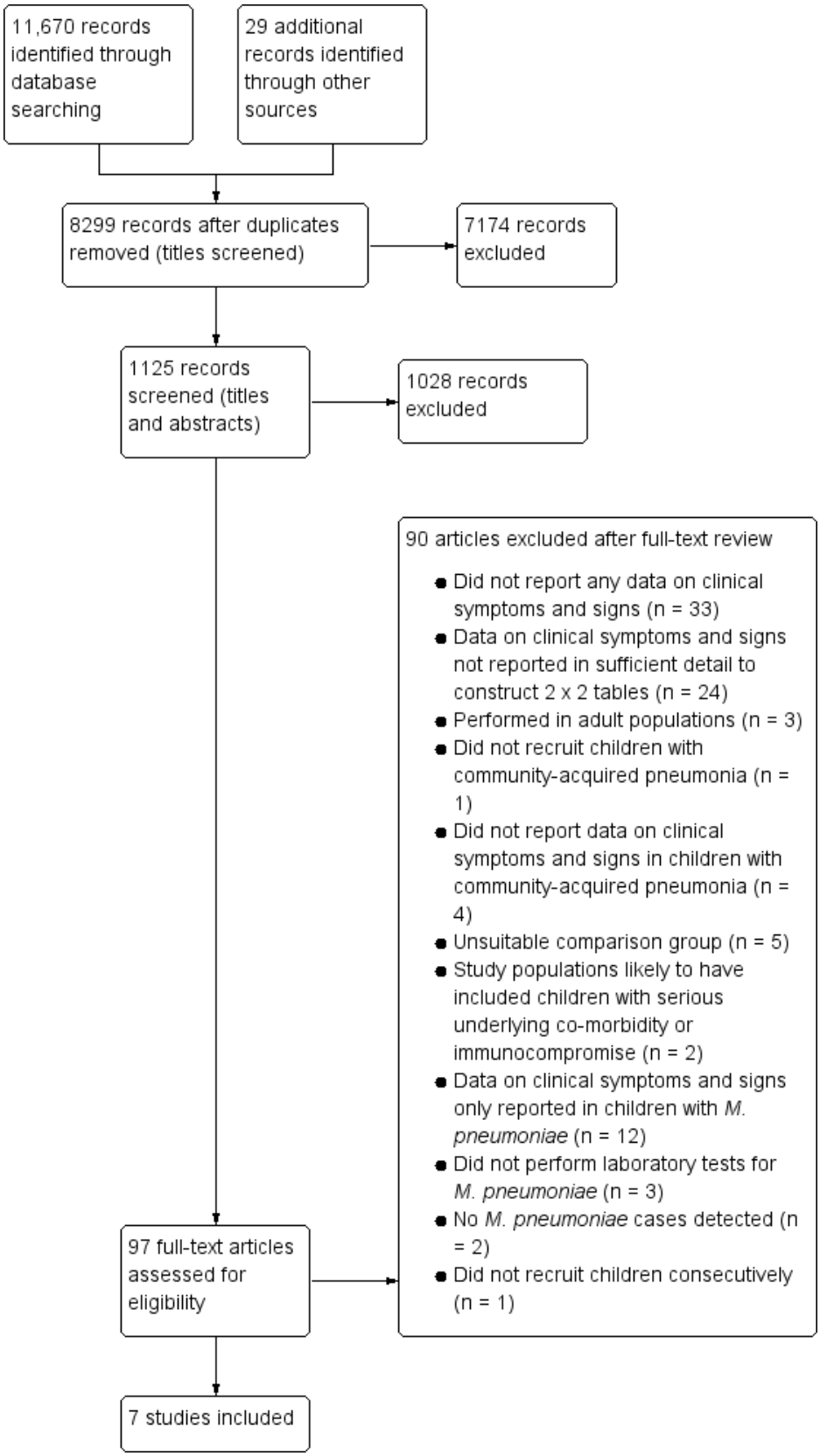
RESULTS

Results of the search

Figure 1 summarises the numbers of articles that we identified, screened and selected for this review. We identified 8299 articles (excluding duplicates) in the search, of which we excluded 7174 based on title alone. We excluded a further 1028 articles after reviewing their abstracts. We reviewed full-text versions of the remaining 97 articles. We included seven studies in our review. Agreement was very good based on title and abstract screening (% agreement = 97.2%; kappa = 0.84) and good based on full-text screening (% agreement = 93.8%; kappa = 0.67).

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 1. Study flow diagram.



Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Our Characteristics of excluded studies table lists the studies which we excluded after full-text screening and the reasons for excluding these studies. We excluded studies for four main reasons: unsuitable population, inadequate reporting of clinical symptoms and signs, lack of suitable comparator group or lack of laboratory testing for *M. pneumoniae*.

Unsuitable population: We excluded three studies performed in adult populations (De Roux 2006; Javier Alvarez 2001; Marrie 2005) and two studies whose populations we felt were highly likely to include children with serious underlying comorbidity or immunocompromise (Samransamruajkit 2008; Vervloet 2010). One study did not recruit children with community-acquired pneumonia (King 1991). Four studies recruited patients with different types of acute respiratory infections, including pneumonia, but did not report symptoms and signs in patients with community-acquired pneumonia specifically (Almasri 2011; Peng 2009; Pocheville Guruceta 1998; Shenoy 2005). One study did not recruit children consecutively; only children with community-acquired pneumonia in whom bacterial pathogens *M. pneumoniae* and *C. pneumoniae* were felt to be the causative organisms after clinical examination were included (Bamba 2006). In two studies, no *M. pneumoniae* cases were detected (Hortal 1994; Manfredi 1992).

Inadequate reporting of clinical symptoms and signs: We excluded 33 studies because they did not report any data on clinical symptoms or signs. We excluded a further 24 studies, which did report data on clinical symptoms and signs, but not in sufficient detail for us to be able to construct 2 x 2 tables.

Lack of suitable comparator group: Twelve studies were case series with no comparator group, which only reported data on clinical features in patients with *M. pneumoniae* (Broome 1980; Bunnag 2008; Defilippi 2008; Dular 1987; Gomez Campdera 2002; Guggenbichler 1977; Kurz 2011; Pereyre 2012; Putman 1975; Sakurai 1988; Touati 2010; Unay 2002). Five studies had unsuitable *M. pneumoniae*-negative comparison groups consisting of patients with *Chlamydia pneumoniae* (*C. pneumoniae)* (Esposito 2001; Kicinski 2011; Ouchi 1999; Sidal 2007) or other microbial diagnoses (Nakayama 2007).

Lack of laboratory testing for M. pneumoniae: Three studies did not perform laboratory tests for *M. pneumoniae* (Gimenez Sanchez 2007; Holmes 2001; Rahman 1990).

Summary of findings 1 gives an overview of the characteristics of studies included in this review. We included seven studies in our review which included a total of 1491 children with community-acquired pneumonia (Agarwal 2009; Chan 2001; Deerojanawong 2006; Kumar 2011; Maheshwari 2011; Principi 2001; Somer 2006). The prevalence of *M. pneumoniae* in these study populations ranged from 10% (Agarwal 2009) to 36% (Kumar 2011; Principi 2001). All of our included studies were prospective observational cohort studies conducted in hospital settings. Somer 2006 was nested within a larger prospective study evaluating the incidence of bacterial and atypical pathogens in hospitalised children with community-acquired pneumonia.

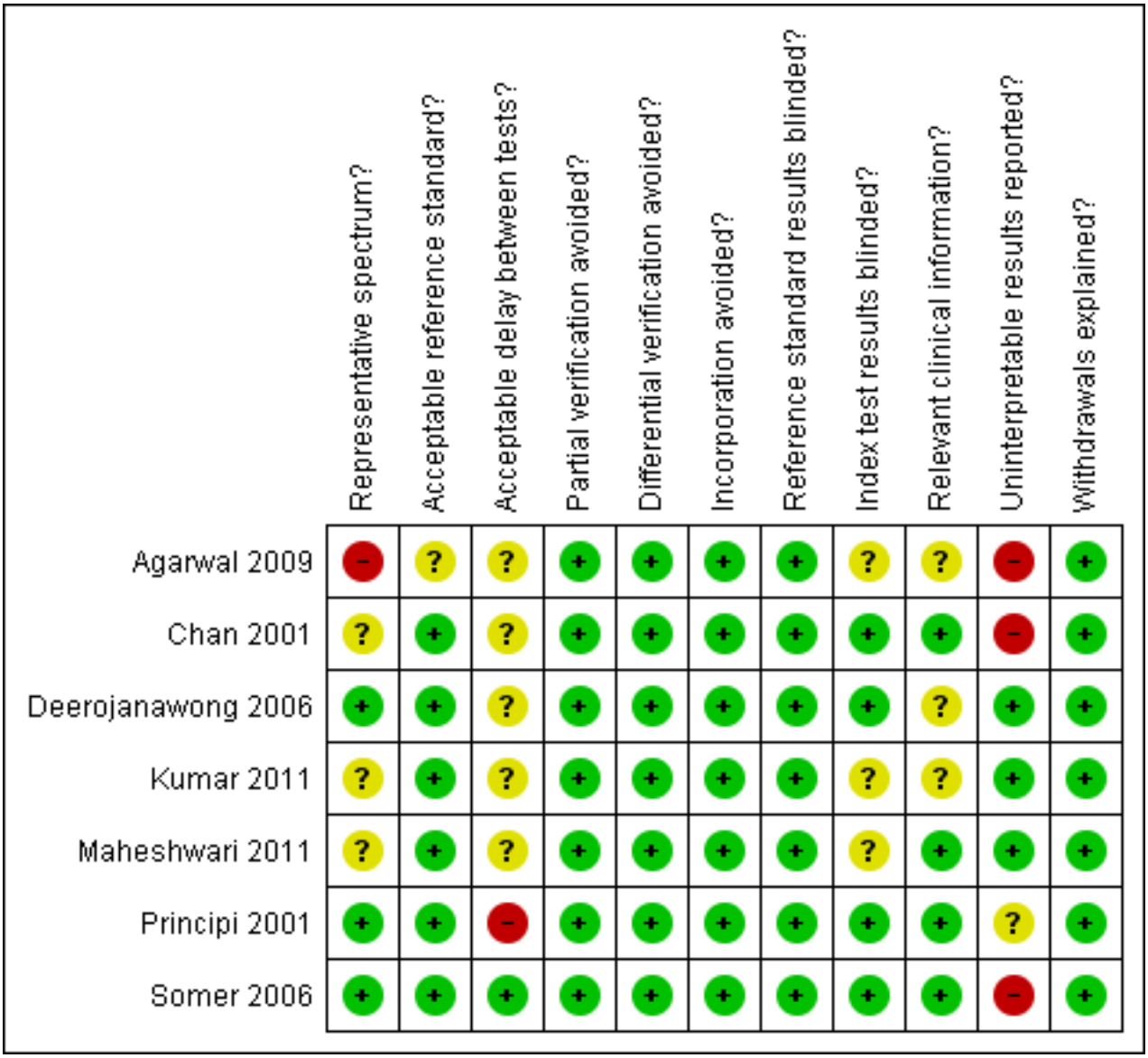
Agarwal 2009 recruited children with severe community-acquired pneumonia based on clinical features. Chan 2001 diagnosed children with community-acquired pneumonia based on the presence of respiratory symptoms and respiratory signs or chest radiograph changes. All other studies diagnosed children with community-acquired pneumonia based on both clinical and radiographic features. Two studies only used serology to diagnose *M. pneumoniae* (Chan 2001; Somer 2006). Four studies also used PCR of respiratory samples to detect *M. pneumoniae*. Maheshwari 2011 analyzed throat swabs, Kumar 2011 and Principi 2001 analyzed nasopharyngeal aspirates and Deerojanawong 2006 analyzed nasopharyngeal aspirates, sputum and throat swabs. Agarwal 2009 performed *M. pneumoniae* antigen detection in nasopharyngeal aspirate as well as serology. Only Agarwal 2009 diagnosed *M. pneumoniae* based on a single acute serum sample. All other included studies sought to obtain paired serum samples from participants.

Methodological quality of included studies

The methodological quality of included studies is summarised in Figure 2. Only two studies clearly reported that children with serious underlying co-morbidity or who were immunocompromised were excluded from the study population (Principi 2001; Somer 2006). One study included 51/245 children with asthma (21%) but only nine children (4%) with serious co-morbidities (seven children had congestive heart failure, one had hepatic disease and one had renal impairment) (Deerojanawong 2006). In three studies it was unclear whether or not a representative spectrum of patients had been recruited (Chan 2001; Kumar 2011; Maheshwari 2011). These studies did not state whether or not children with comorbid conditions were excluded, or report data on co-morbidities or clinical outcomes. One study only recruited children with severe community-acquired pneumonia based on World Health Organization (WHO) clinical criteria (Agarwal 2009); we therefore did not consider this study population to reflect a representative spectrum of children with community-acquired pneumonia.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



All except one of our included studies utilised acceptable reference standards for diagnosing *M. pneumoniae.* In two studies *M. pneumoniae* was diagnosed based on a single high antibody titre or a fourfold rise in antibody titre between acute and convalescent serum samples taken two to four weeks apart (Chan 2001; Somer 2006). Deerojanawong 2006 diagnosed *M. pneumoniae* based on a fourfold rise in antibody titre between acute and convalescent sera or a positive PCR result together with a persistently high antibody titre. Children with a positive PCR result in the absence of serological evidence of *M. pneumoniae* infection were considered to be carriers of *M. pneumoniae* and were therefore not categorised as having current *M. pneumoniae* infection.

In three studies children with positive PCR results were diagnosed with *M. pneumoniae* even in the absence of positive serology results (Kumar 2011; Maheshwari 2011; Principi 2001). However, the numbers of children who tested positive for *M. pneumoniae* on PCR but not on serology were low. In Kumar 2011 PCR was positive in 20 children of whom only three did not have serological evidence of *M. pneumoniae*. In Maheshwari 2011 PCR was positive in five children of whom only one did not have serological evidence of *M. pneumoniae*. Principi 2001 reported that 16 children with community-acquired lower respiratory tract infections (acute bronchitis, wheezing or pneumonia) had positive PCR results without serological evidence of acute infection. The study did not report how many of these children were in the pneumonia subgroup, of whom 36% (150/418) were diagnosed with *M. pneumoniae*. However, even if all 16 children had been in this subgroup, they would only have accounted for 11% of *M. pneumoniae* diagnoses in children with community-acquired pneumonia.

One study used antigen detection of *M. pneumoniae* in nasopharyngeal aspirate alongside serology as its reference

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

standard (Agarwal 2009). However, it was unclear whether or not this reference standard was acceptable, as no children tested positive for *M. pneumoniae* using both laboratory methods. Of the 24 children who were diagnosed with *M. pneumoniae*, 14 were positive by serology and 10 by antigen detection in nasopharyngeal aspirate.

All of our included studies avoided partial and differential verification. Deerojanawong 2006 obtained paired serum samples from 245/257 children; the 12 children from whom convalescent serum samples could not be obtained were excluded from the study population. Somer 2006 obtained paired serum samples from 140/159 children; the 19 children from whom convalescent serum samples could not be obtained were excluded from the study population. Maheshwari 2011 sought to obtain convalescent serum samples from all 75 children who entered the study, but only managed this in 45 children. Children from whom convalescent serum samples were not obtained were still included in the study population. Only 2/23 children in whom *M. pneumoniae* was detected were diagnosed on the basis of a fourfold rise in antibody titre alone.

Only one study clearly reported that acute serum samples were obtained within 24 hours of hospital admission, when clinical symptoms and signs were assessed (Somer 2006). We were unable to assess whether or not the delay between assessment of clinical symptoms and signs and obtaining samples for *M. pneumoniae* detection was acceptable in five studies, as these did not report the time interval between clinical assessment and sample-taking (Agarwal 2009; Chan 2001; Deerojanawong 2006; Kumar 2011; Maheshwari 2011). Principi 2001 reported that symptoms and signs were recorded at the time of hospital admission, whereas laboratory samples were taken at the time of enrolment into the study. The mean duration of hospitalisation ranged from 5.68 days in children with neither *M. pneumoniae* nor *C. pneumoniae* infection, to 6.63 days in children with both infections. We therefore considered that the delay between clinical assessment and laboratory sample taking was unacceptable in this study.

All of our included studies avoided incorporation bias, as *M. pneumoniae* was diagnosed based on laboratory test results and not on the absence or presence of clinical symptoms or signs. We also considered that blinding of the reference standard took place in our included studies. Somer 2006 reported that clinical assessment was performed at the time of hospital admission, when the results of convalescent serum samples would not have been available. Five other studies also sought convalescent serum samples from children, the results of which would not have been available during the acute community-acquired pneumonia illness episode, when clinical symptoms and signs were recorded (Chan 2001; Deerojanawong 2006; Kumar 2011; Maheshwari 2011; Principi 2001). Agarwal 2009 only obtained acute laboratory samples but the results of these would not have been available on admission, when clinical symptoms and signs were recorded.

No studies explicitly reported that interpretation of laboratory tests was performed blinded to knowledge about clinical symptoms and signs. However, in four studies, we felt that this is unlikely to have occurred, since clear laboratory criteria and antibody titre thresholds were specified as being diagnostic of *M. pneumoniae* (Chan 2001; Deerojanawong 2006; Principi 2001; Somer 2006). Blinding to clinical symptoms and signs was unclear in three studies, which did not report diagnostic antibody titre thresholds (Agarwal 2009; Kumar 2011; Maheshwari 2011). None of our included studies reported borderline or uninterpretable serology results. The five studies which used additional laboratory methods alongside serology to diagnose *M. pneumoniae* all reported data on participants with discrepant results on different tests (Agarwal 2009; Deerojanawong 2006; Kumar 2011; Maheshwari 2011; Principi 2001). However, Principi 2001 did not report the number of discrepant test results within the pneumonia subgroup.

Findings

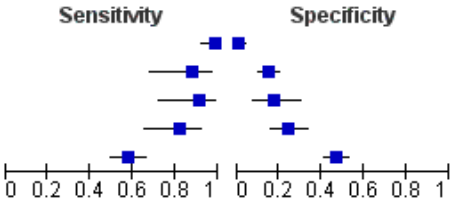
Figure 3 summarises study-specific values for the sensitivities and specificities of cough, wheeze, coryza, crepitations, fever, rhonchi, shortness of breath, chest pain, diarrhea and myalgia with 95% CIs. For cough, coryza, fever and rhonchi, sensitivity and specificity varied widely between different studies. In particular, the variation in study-specific specificity values was 20-fold for fever (0.02 to 0.43) and 50-fold for cough (0.01 to 0.47). There was a 10-fold variation in study-specific sensitivity for coryza (0.08 to 0.85).

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 3. Forest plot of tests: 1 Cough, 2 Wheeze, 3 Coryza, 4 Crepitations, 5 Fever, 6 Rhonchi, 7 Shortness of breath, 8 Headache, 9 Chest pain, 10 Diarrhoea, 11 Myalgia.

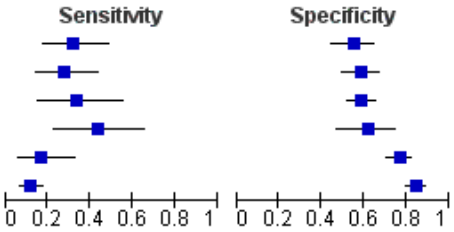
Cough

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kumar 2011	70	128	1	1	0.99 [0.92, 1.00]	0.01 [0.00, 0.04]
Agarwal 2009	21	186	3	33	0.88 [0.68, 0.97]	0.15 [0.11, 0.21]
Maheshwari 2011	21	43	2	9	0.91 [0.72, 0.99]	0.17 [0.08, 0.30]
Somer 2006	31	77	7	25	0.82 [0.66, 0.92]	0.25 [0.17, 0.34]
Principi 2001	87	142	63	126	0.58 [0.50, 0.66]	0.47 [0.41, 0.53]



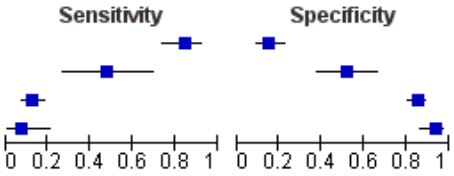
Wheeze

Study	TP	FP	FN	TN	Sensitivity	Specificity
Somer 2006	12	46	26	56	0.32 [0.18, 0.49]	0.55 [0.45, 0.65]
Chan 2001	11	54	29	76	0.28 [0.15, 0.44]	0.58 [0.49, 0.67]
Agarwal 2009	8	90	16	129	0.33 [0.16, 0.55]	0.59 [0.52, 0.65]
Maheshwari 2011	10	20	13	32	0.43 [0.23, 0.66]	0.62 [0.47, 0.75]
Deerojanawong 2006	6	49	30	160	0.17 [0.06, 0.33]	0.77 [0.70, 0.82]
Principi 2001	18	42	132	226	0.12 [0.07, 0.18]	0.84 [0.79, 0.88]



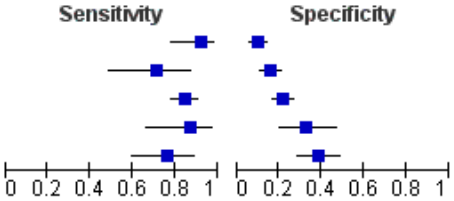
Coryza

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kumar 2011	60	109	11	20	0.85 [0.74, 0.92]	0.16 [0.10, 0.23]
Maheshwari 2011	11	25	12	27	0.48 [0.27, 0.69]	0.52 [0.38, 0.66]
Principi 2001	19	40	131	228	0.13 [0.08, 0.19]	0.85 [0.80, 0.89]
Somer 2006	3	7	35	95	0.08 [0.02, 0.21]	0.93 [0.86, 0.97]



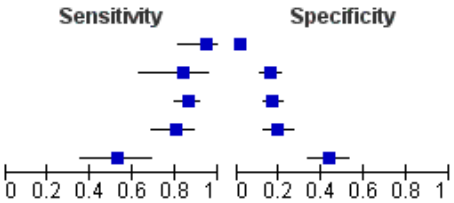
Crepitations

Study	TP	FP	FN	TN	Sensitivity	Specificity
Deerojanawong 2006	33	188	3	21	0.92 [0.78, 0.98]	0.10 [0.06, 0.15]
Agarwal 2009	17	184	7	35	0.71 [0.49, 0.87]	0.16 [0.11, 0.22]
Principi 2001	127	210	23	58	0.85 [0.78, 0.90]	0.22 [0.17, 0.27]
Maheshwari 2011	20	35	3	17	0.87 [0.66, 0.97]	0.33 [0.20, 0.47]
Somer 2006	29	63	9	39	0.76 [0.60, 0.89]	0.38 [0.29, 0.48]



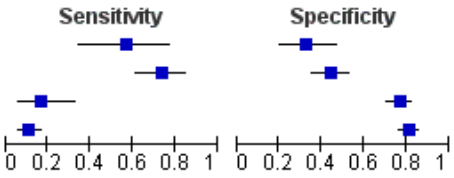
Fever

Study	TP	FP	FN	TN	Sensitivity	Specificity
Deerojanawong 2006	34	205	2	4	0.94 [0.81, 0.99]	0.02 [0.01, 0.05]
Agarwal 2009	20	184	4	35	0.83 [0.63, 0.95]	0.16 [0.11, 0.22]
Principi 2001	129	222	21	46	0.86 [0.79, 0.91]	0.17 [0.13, 0.22]
Kumar 2011	57	104	14	25	0.80 [0.69, 0.89]	0.19 [0.13, 0.27]
Somer 2006	20	58	18	44	0.53 [0.36, 0.69]	0.43 [0.33, 0.53]



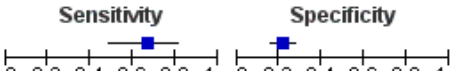
Rhonchi

Study	TP	FP	FN	TN	Sensitivity	Specificity
Maheshwari 2011	13	35	10	17	0.57 [0.34, 0.77]	0.33 [0.20, 0.47]
Kumar 2011	45	72	16	57	0.74 [0.61, 0.84]	0.44 [0.35, 0.53]
Deerojanawong 2006	6	49	30	160	0.17 [0.06, 0.33]	0.77 [0.70, 0.82]
Principi 2001	16	50	134	218	0.11 [0.06, 0.17]	0.81 [0.76, 0.86]



Shortness of breath

Study	TP	FP	FN	TN	Sensitivity	Specificity
Deerojanawong 2006	24	164	12	45	0.67 [0.49, 0.81]	0.22 [0.16, 0.28]



Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 3. (Continued)

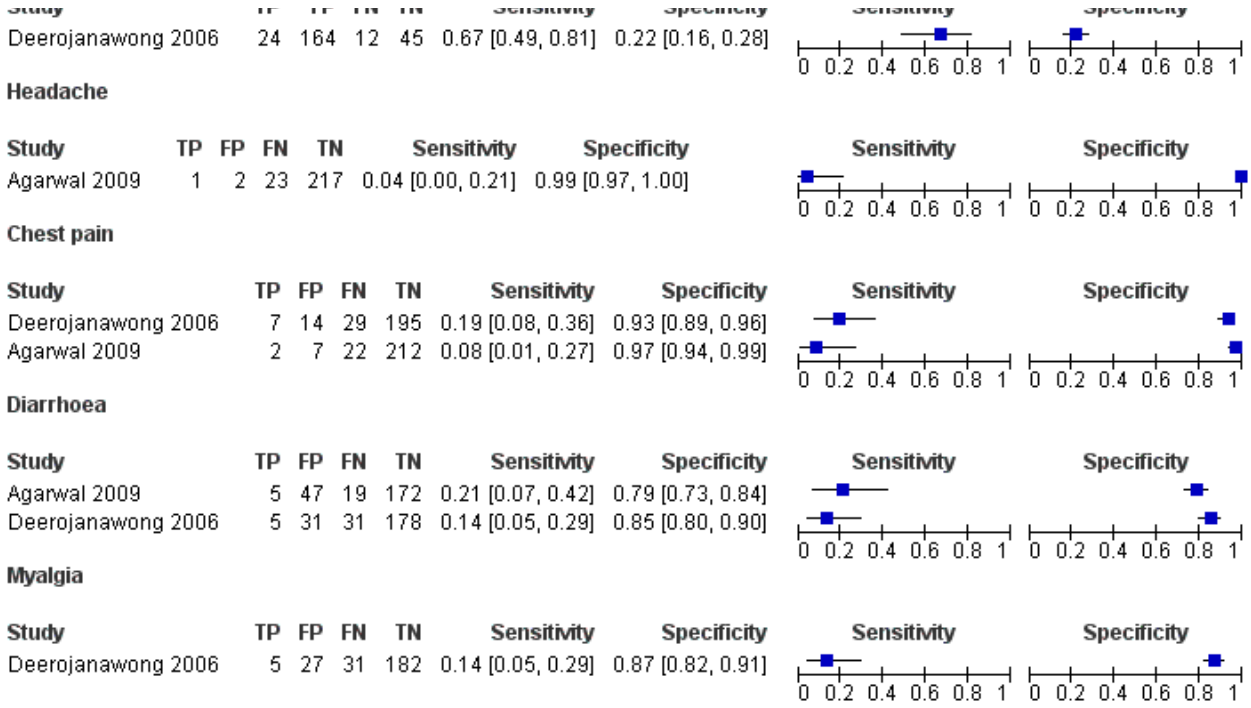


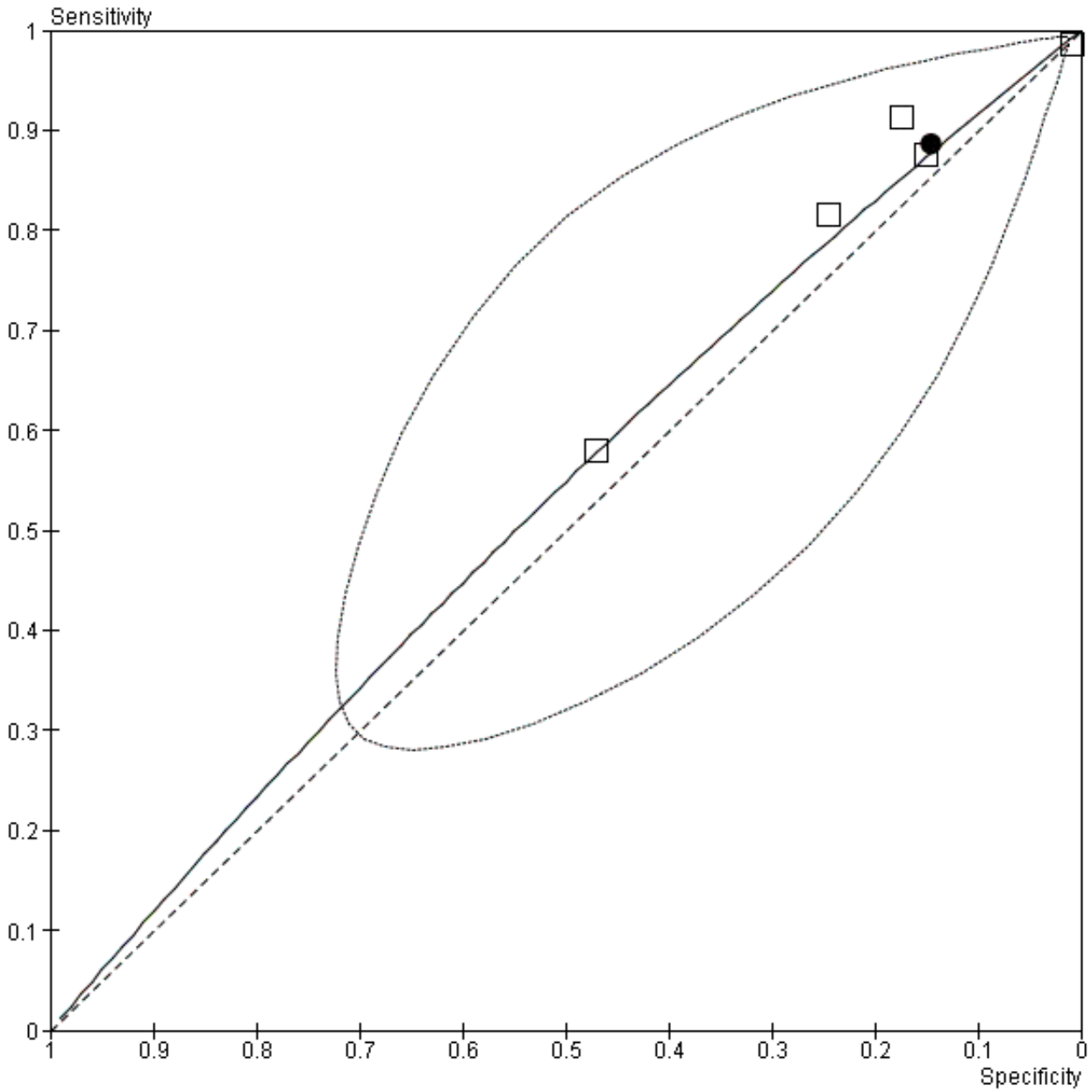
Table 2 shows that rhonchi were 32% more likely to be present in children with *M. pneumoniae* in one study (pooled positive likelihood ratio (LR+) 1.32, 95% confidence interval (CI) 1.07 to 1.64; pooled negative likelihood ratio (LR-) 0.59, 95% CI 0.37 to 0.94) (Kumar 2011) but 10% more likely to be absent in children with *M. pneumoniae* in another study (LR+ 0.57, 95% CI 0.34 to 0.97; LR- 1.10, 95% CI 1.01 to 1.19) (Principi 2001). Table 2 also shows that in two studies the presence of chest pain more than doubled the probability of *M. pneumoniae* in children with community-acquired pneumonia (Agarwal 2009, Deerojanawong 2006). The presence of chest pain increased the probability of *M. pneumoniae* from 10% to 22% in one study (Agarwal 2009) and from 15% to 33% in the other study (Deerojanawong 2006).

We were able to obtain pooled estimates for cough, wheeze, coryza and crepitations (Summary of findings 2). Five studies reported data on cough (Agarwal 2009; Kumar 2011; Maheshwari 2011; Principi 2001; Somer 2006), six studies on wheeze (Agarwal 2009; Chan 2001; Deerojanawong 2006; Maheshwari 2011; Principi 2001; Somer 2006), four studies on coryza (Kumar 2011; Maheshwari 2011; Principi 2001; Somer 2006) and five studies on crepitations (Agarwal 2009; Deerojanawong 2006; Maheshwari 2011; Principi 2001; Somer 2006).

Cough (Figure 4) and crepitations (Figure 5) were sensitive but poorly specific indicators of *M. pneumoniae* (Cough: pooled sensitivity 0.89, 95% confidence interval (CI) 0.67 to 0.97; pooled specificity 0.15, 95% CI 0.05 to 0.37. Crepitations: pooled sensitivity 0.84, 95% CI 0.78 to 0.88; pooled specificity 0.22, 95% CI 0.14 to 0.32). The performance of coryza as a diagnostic indicator was no better than chance (Figure 6; pooled sensitivity 0.32, 95% CI 0.08 to 0.72; pooled specificity 0.66, 95% CI 0.28 to 0.91). Wheeze had poor sensitivity but moderate specificity (pooled sensitivity 0.25, 95% CI 0.17 to 0.36; pooled specificity 0.67, 95% CI 0.56 to 0.76). The summary curve for wheeze was below the diagonal, indicating that absence, rather than presence, of wheeze may indicate *M. pneumoniae* infection (Figure 7).

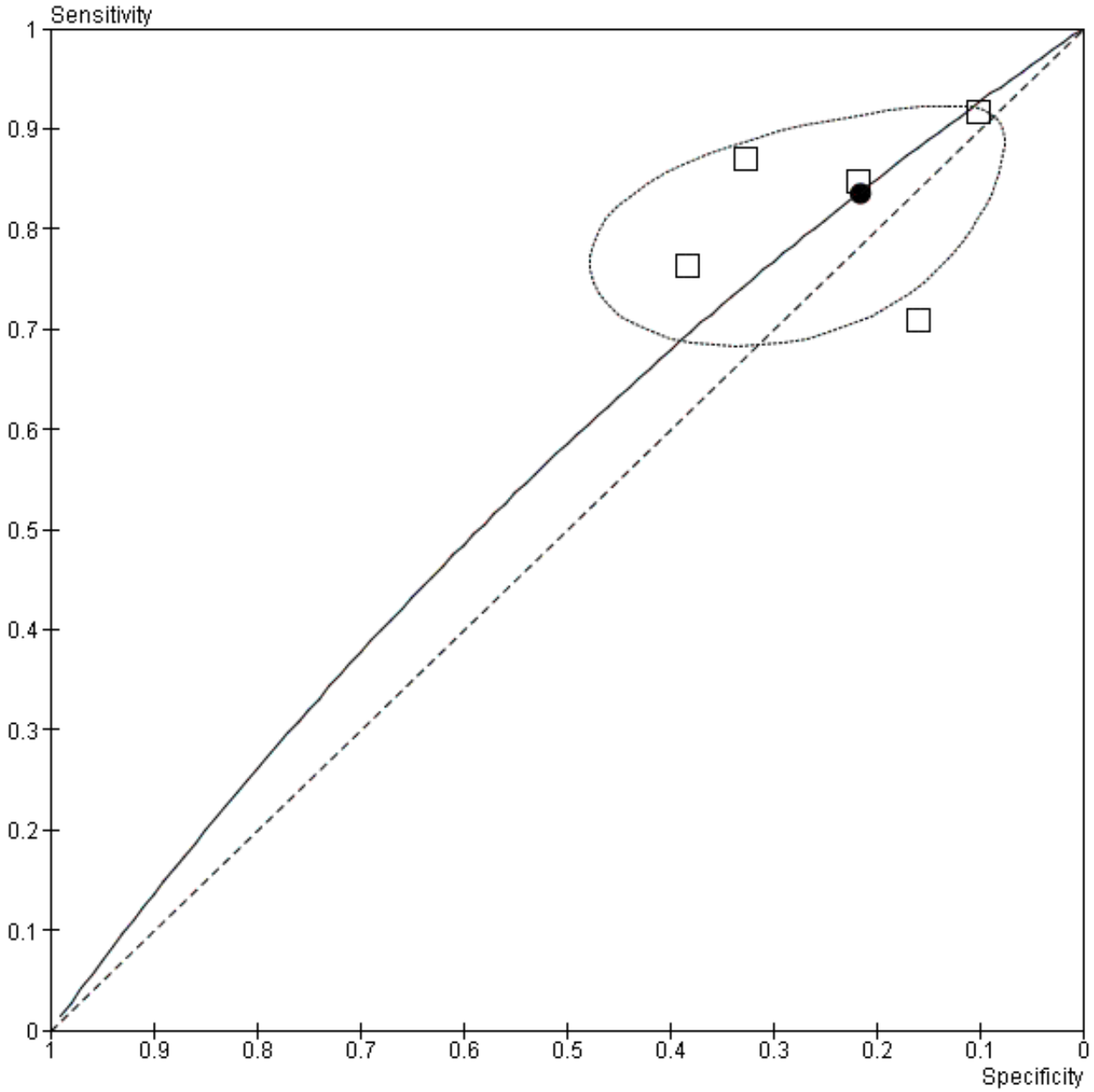
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 4. Summary ROC plot of cough (black dot - summary point; black dotted line - 95% confidence region for summary point; black solid line - summary ROC curve)



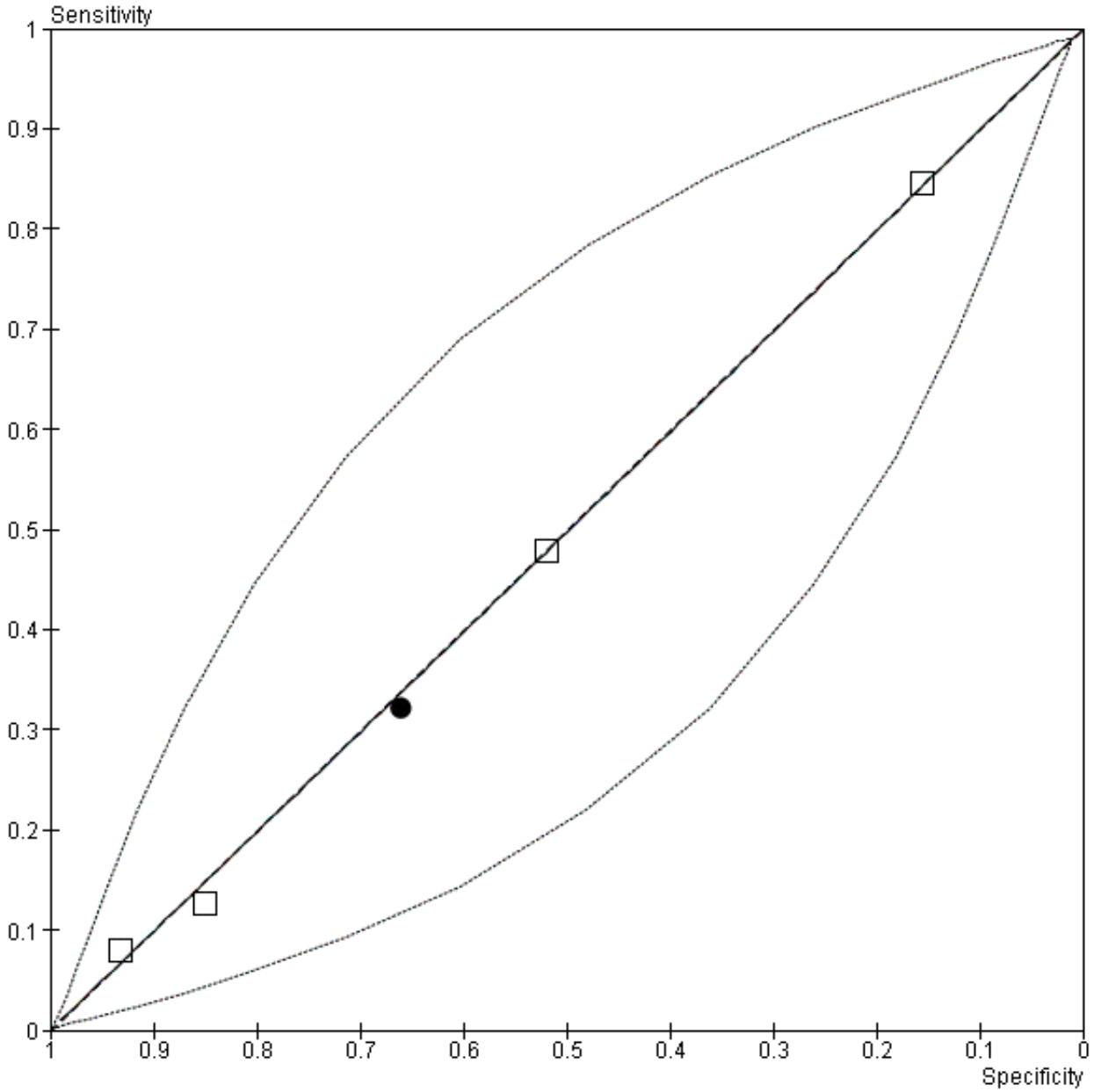
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 5. Summary ROC plot of crepitations (black dot - summary point; black dotted line - 95% confidence region for summary point; black solid line - summary ROC curve)



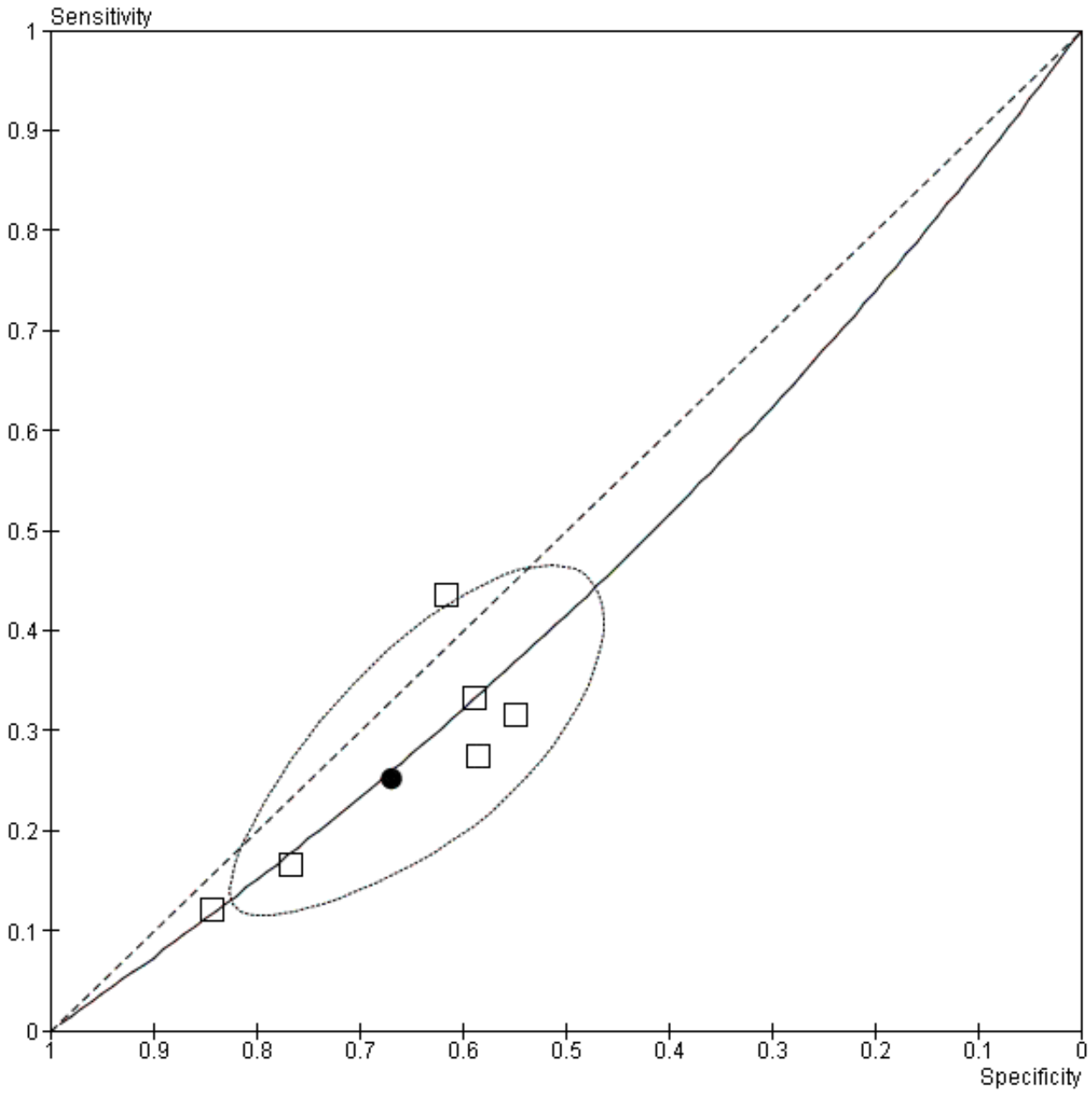
Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 6. Summary ROC plot of coryza (black dot - summary point; black dotted line - 95% confidence region for summary point; black solid line - summary ROC curve)



Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 7. Summary ROC Plot of Wheeze (black dot - summary point; black dotted line - 95% confidence region for summary point; black solid line - summary ROC curve)



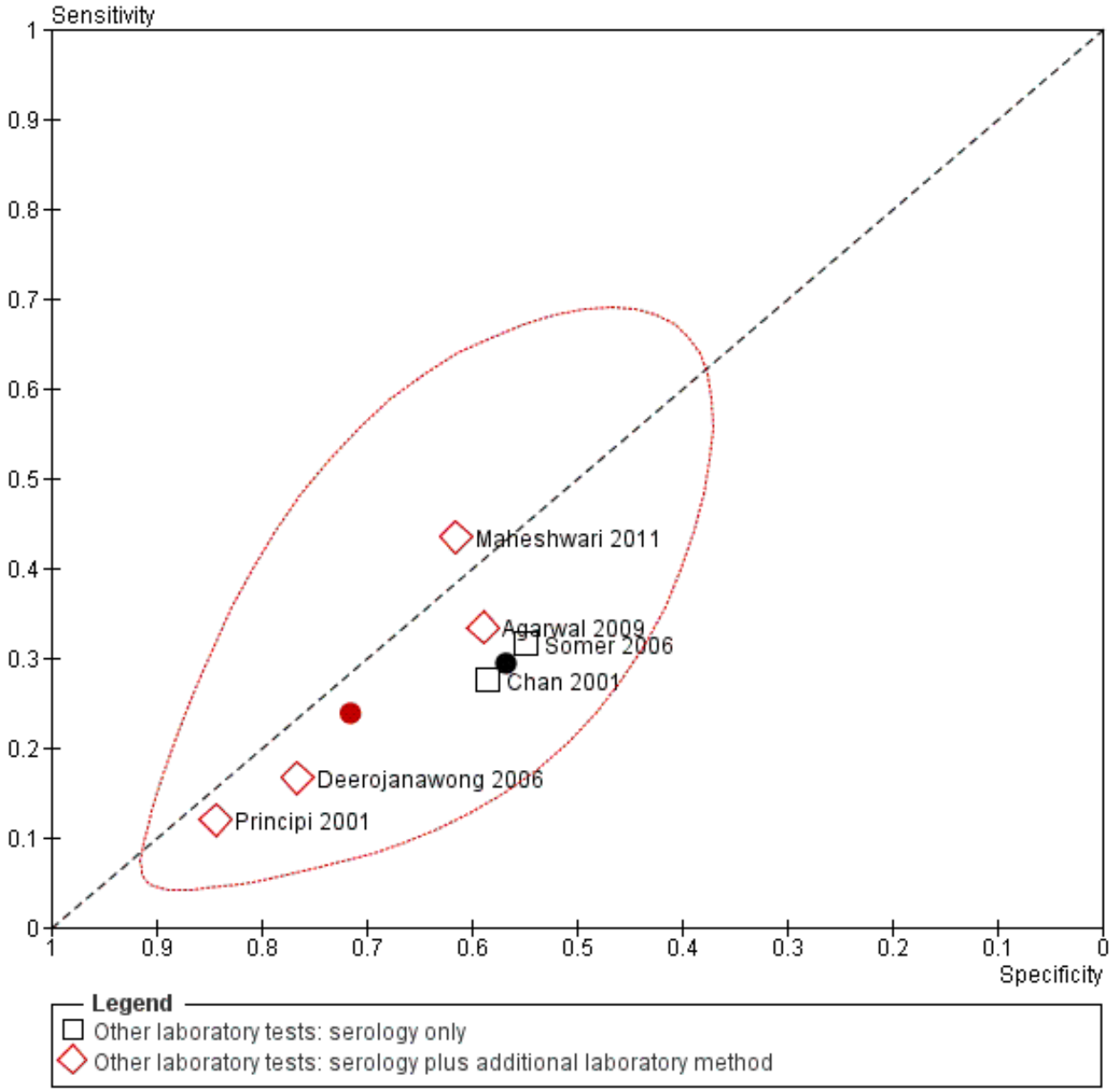
Although four studies reported data on rhonchi (Deerojanawong 2006; Kumar 2011; Maheshwari 2011; Principi 2001), the model failed to converge to a summary estimate. This failure to converge could have been due to the small number of studies combined with the data reported for the individual studies and is a well-known problem in these models (Macaskill 2010).

Wheeze was 12% more likely to be absent in children with *M. pneumoniae* (pooled LR+ 0.76, 95% CI 0.60 to 0.97; pooled LR- 1.12, 95% CI 1.02 to 1.23). We performed a sensitivity analysis excluding Agarwal 2009 because we did not feel that this study recruited a representative spectrum of patients (only children with severe community-acquired pneumonia included) and had concerns about the acceptability of the reference standard (no children tested positive for *M. pneumoniae* on both IgM serology and antigen detection in nasopharyngeal aspirate). However, this sensitivity analysis did not change our findings (pooled LR+ 0.75, 95% CI 0.58 to 0.98; pooled LR- 1.11, 95% CI 1.01 to 1.23). Our findings also did not change when we analyzed data from studies in which *M. pneumoniae* was diagnosed using serology only (pooled LR+ 0.68, 95% CI 0.50 to 0.92; pooled LR- 1.24, 95% 1.03 to 1.51) (Chan 2001; Somer 2006). However, wheeze was not a statistically significant diagnostic indicator based on data from studies which used other laboratory tests alongside serology to diagnose *M. pneumoniae* (pooled LR+ 0.84, 95% CI 0.63 to 1.12; pooled LR- 1.06, 95% CI 0.96 to 1.18) (Agarwal 2009; Deerojanawong 2006;

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Maheshwari 2011; Principi 2001). Figure 8 summarises individual and pooled sensitivity and specificity values for wheeze based on data from studies which diagnosed *M. pneumoniae* using serology only versus other laboratory tests alongside serology.

Figure 8. Summary ROC plot of wheeze including summary points (black dot - summary point for studies which diagnosed *M. pneumoniae* using serology only; red dot - summary point for studies which diagnosed *M. pneumoniae* using serology plus additional laboratory methods; red dotted line - 95% confidence region for summary point calculated using data from studies which diagnosed *M. pneumoniae* using serology plus additional laboratory methods).



We did not investigate the influence of methods of diagnosing community-acquired pneumonia or serological methods of diagnosing *M. pneumoniae* since Agarwal 2009 was the only study reporting data on wheeze which diagnosed community-acquired pneumonia based on clinical criteria only and diagnosed *M. pneumoniae* using a single high antibody titre; we had already excluded data from Agarwal 2009 during our sensitivity analysis.

Data were not sufficient to perform investigations of heterogeneity for any other clinical symptoms or signs apart from wheeze. It was not possible to explore the influence of healthcare setting or participant age group because all the studies included in this review were conducted in hospital settings and did not report data stratified according to our age groups of interest.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

The presence of crepitations was not a statistically significant indicator of *M. pneumoniae* (pooled LR+ 1.06, 95% CI 0.96 to 1.18; pooled LR- 0.77, 95% CI 0.52 to 1.12). However, when we performed a sensitivity analysis excluding data from Agarwal 2009 we found that the presence of crepitations was a diagnostic indicator of *M. pneumoniae*, although this finding was only of borderline statistical significance (pooled LR+ 1.10, 95% CI 0.99 to 1.23; pooled LR- 0.66, 95% CI 0.46 to 0.96).

Five studies reported data on fever (Agarwal 2009; Deerojanawong 2006; Kumar 2011; Principi 2001; Somer 2006). However, we were only able fit a bivariate model when we performed a sensitivity analysis excluding data from Agarwal 2009 as the model did not converge when all five studies were included. Fever had high sensitivity (pooled sensitivity 0.85, 95% CI 0.63 to 0.95) but poor specificity (pooled specificity 0.15, 95% CI 0.05 to 0.38). Overall, fever was not a useful diagnostic indicator (pooled LR+ 1.00, 95% CI 0.94 to 1.07; pooled LR- 1.00, 95% CI 0.70 to 1.44).

Coryza and cough were not useful diagnostic indicators of *M. pneumoniae* (coryza: pooled LR+ 0.95, 95% CI 0.71 to 1.26; pooled LR- 1.03, 95% CI 0.90 to 1.17. Cough: pooled LR+ 1.04, 95% CI 0.95 to 1.13; pooled LR- 0.78, 95% CI 0.44 to 1.39). We attempted to perform a sensitivity analysis of data on cough excluding Agarwal 2009. However, we were unable to obtain a summary measure from the four remaining studies using the bivariate model as the algorithm failed to converge.

DISCUSSION

Summary of main results

There is a paucity of high quality data relating to the diagnostic value of symptoms and signs in the clinical recognition of *M. pneumoniae* in children and adolescents with community-acquired pneumonia. Based on currently available data, the absence or presence of individual clinical symptoms or signs cannot be used to help clinicians accurately diagnose *M. pneumoniae*. The absence of wheeze is a statistically significant diagnostic indicator of *M. pneumoniae.* However, its clinical utility is limited, since absence of wheeze is only 12% more likely in children with *M. pneumoniae* versus children without *M. pneumoniae*. However, this review did find preliminary evidence from two studies to suggest that the presence of chest pain approximately doubles the probability of *M. pneumoniae* in children with community-acquired pneumonia. Chest pain may therefore be a useful clinical indicator of *M. pneumoniae*, whose diagnostic value should be evaluated further in future studies.

Strengths and weaknesses of the review

We used a systematic and comprehensive search strategy to identify articles for our review. We analyzed full-text versions of any articles felt to be potentially relevant, including studies relating to community-acquired pneumonia or respiratory tract infections generally, even if *M. pneumoniae* was not specifically mentioned in the title or abstract. We did not apply any language restrictions to our search. Two review authors independently screened abstracts and full-text articles as well as extracted data from and assessed methodological quality of included studies. In order to assess the validity and robustness of our findings, we performed sensitivity analyses excluding data from one study (Agarwal 2009) because we had concerns that this study had recruited an unrepresentative spectrum of patients and were unclear about the reliability of the reference standard used to diagnose *M. pneumoniae*.

Since there is currently no 'gold standard' for the laboratory diagnosis of *M. pneumoniae*, we also assessed the impact on our findings of using other laboratory methods in addition to serology to detect *M. pneumoniae*. In this review, we selected serology as our reference standard because it is currently the most widely available test for *M. pneumoniae*. However, a combination of serological and polymerase chain reaction (PCR) methods is considered to be optimal for detecting *M. pneumoniae* in patients with community-acquired pneumonia (Thurman 2009). PCR is a more sensitive method of detecting *M. pneumoniae* than serology during the first two weeks after symptom onset (Nilsson 2008). Although Nilsson 2008 found that *M. pneumoniae* DNA could persist in the oropharynx for up to seven months, a more recent study has demonstrated that *M. pneumoniae* carriage among asymptomatic individuals is rare (1/428 subjects, 0.2%) (Chalker 2011). Similarly, *M. pneumoniae* immunoglobulin (IgM) antibodies are detected in only 0.3% of healthy patients and patients with positive PCR results (sputum or other respiratory secretions) have similar clinical and demographic characteristics to patients with positive IgM serology (Von Baum 2009).

Our main limitations in this review were paucity of data and considerable heterogeneity in the findings of our included studies, particularly in relation to cough, coryza, fever and rhonchi. We only had sufficient data to obtain pooled estimates for cough, wheeze, coryza and crepitations. We were only able to obtain pooled estimates for fever after excluding data from Agarwal 2009 during our sensitivity analysis. We were also only able to investigate the use of additional laboratory tests alongside serology as a potential source of heterogeneity for one symptom (wheeze). We did not have sufficient data to investigate several other potential sources of heterogeneity, including age and healthcare setting (primary versus secondary care). No studies reported data on combinations of clinical symptoms and signs in children with and without *M. pneumoniae*.

There were also inconsistencies in the reporting of clinical symptoms and signs across different studies. Coryzal symptoms were described as coryza (Kumar 2011), rhinorrhoea (Maheshwari 2011), rhinitis (Principi 2001) or runny nose (Somer 2006). Rales rather than crepitations were described in four studies (Deerojanawong 2006; Maheshwari 2011; Principi 2001; Somer 2006). Although two studies reported data on chest pain (Agarwal 2009; Deerojanawong 2006) no further details were given about its character. In one study, data on the clinical features of two participants with concurrent *M. pneumoniae* and *C. pneumoniae* infections were not reported separately (Somer 2006). We therefore analyzed the data conservatively, assuming that the clinical features being studied were absent in both participants.

Applicability of findings to the review question

Based on currently published data, the absence or presence of individual clinical symptoms and signs should not be used to guide clinical decisions about empirical macrolide antibiotic prescribing for suspected *M. pneumoniae* infections. In two studies (Agarwal 2009; Deerojanawong 2006) the presence of chest pain more than doubled the probability of *M. pneumoniae*, but these findings were only based on small numbers of participants. The absence of wheeze is the only statistically significant diagnostic indicator,

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

but has only limited clinical utility, since it is only 12% more likely in *M. pneumoniae*-positive children with community-acquired pneumonia.

Based on our pooled sensitivity estimate for wheeze, 25% of children with *M. pneumoniae* have wheeze as a clinical symptom. Therefore, a policy of empirical macrolide antibiotic treatment in children without wheeze would result in antibiotics being withheld from 25% of children with *M. pneumoniae*. More importantly, a high percentage of children receiving empirical antibiotic treatment would be *M. pneumoniae*-negative and therefore be receiving antibiotics unnecessarily. Assuming that the specificity of wheeze is 67% (based on our pooled specificity estimate), the percentage of children receiving antibiotics unnecessarily would range from 61% if *M. pneumoniae* prevalence was 36% (the highest prevalence estimate among our included studies) to 89% if *M. pneumoniae* prevalence was 10% (the lowest prevalence estimate among our included studies).

The diagnostic value of clinical symptoms and signs may vary between children of different ages. Two case series found that coryza, tachypnoea, diarrhea and vomiting were more common in preschool than in older children with *M. pneumoniae* (Defilippi 2008; Othman 2005). In addition, our findings may not be applicable to children presenting in primary care with community-acquired pneumonia because all of our included studies were conducted in hospital settings. Children admitted to hospital with community-acquired pneumonia are likely to represent a narrower and more severe spectrum of illness than children who present in primary care. At the moment, the relationship between illness severity and clinical presentation of *M. pneumoniae* is uncertain. Greater variation in presenting symptoms and a higher prevalence of certain clinical features (including rhinorrhoea, headache and chest pain) during epidemic outbreaks have previously been observed (Gomez Campdera 2006) and may reflect a wider spectrum of disease severity when *M. pneumoniae* prevalence is high. Our findings may also have limited applicability in developed countries, since all our included studies except one (Principi 2001) were conducted in developing countries.

Population-level data on *M. pneumoniae* incidence are likely to play an important role in helping clinicians to interpret the diagnostic value of clinical symptoms and signs. The performance of a clinical decision model for pertussis in infants has been shown to improve with the incorporation of local disease incidence data (Fine 2010). Clinicians should also take previous antibiotic use into account when considering possible microbial aetiology in children with community-acquired pneumonia. Treatment with beta-lactam antibiotics up to 14 days before admission to hospital with community-acquired pneumonia is reported to be associated with a threefold increased chance of infection with atypical pathogens (including *M. pneumoniae*) and a threefold decreased probability of pneumococcal infection (Van de Garde 2008). Somer 2006 excluded children who had received antibiotics up to 10 days before admission and Principi 2001 excluded children who had received antibiotics within the last 48 hours.

The diagnostic value of wheeze may vary according to the prevalence of other respiratory pathogens, particularly respiratory viruses. Evidence of viral infection has previously been detected in 33% of acute asthma exacerbations in children, whereas evidence of *M. pneumoniae* infection was only detected in 2% (Freymuth 1999). The high prevalence of viral infections in children presenting with acute wheezing episodes is well established (Heymann 2004; Jartti 2004). One study found that *M. pneumoniae* was only present in 5% of children with acute wheezing episodes of proven viral aetiology (Lehtinen 2006). We may therefore have found that wheeze is less likely in children with *M. pneumoniae* because of the relatively infrequent association between *M. pneumoniae* and viral infections.

Based on scarce preliminary data, chest pain may be a useful indicator of *M. pneumoniae* in children who present with community-acquired pneumonia in outpatient settings. Among adults with community-acquired pneumonia, 41.8% of outpatients report pleuritic chest pain compared to 29.3% of inpatients (Wattanathum 2003). Wattanathum 2003 also reported a significantly higher prevalence of *M. pneumoniae* in outpatients (29.6%) than in inpatients (6.8%; $P < 0.001$). However, establishing the absence or presence of subjective symptoms, such as chest pain, may be difficult in preschool children (Hay 2002). Moreover, further research is needed to substantiate the diagnostic value of chest pain in the clinical recognition of *M. pneumoniae*.

AUTHORS' CONCLUSIONS

Implications for practice

This review has found that *M. pneumoniae* cannot be reliably diagnosed in children and adolescents with community-acquired pneumonia based on the absence or presence of individual clinical symptoms and signs. Although the absence of wheeze is a statistically significant diagnostic indicator, it does not have sufficient diagnostic value to guide empirical macrolide antibiotic treatment in children with community-acquired pneumonia. Data from two studies suggest that the presence of chest pain more than doubles the probability of *M. pneumoniae*. However, further research is needed to substantiate this finding. No data on the diagnostic value of combinations of clinical symptoms and signs has yet been published. Clinicians should therefore consider other factors, including previous antibiotic use and population-based data on *M. pneumoniae* incidence, to help them estimate the likelihood of *M. pneumoniae* infection in the context of a clinical consultation.

Implications for research

More high quality, large-scale studies are needed to help develop prediction rules based on epidemiological data as well as clinical and baseline patient characteristics, which clinicians can use to help them diagnose *M. pneumoniae* during clinical consultations. These studies should also consider a wider range of extra-pulmonary clinical features, such as headache, diarrhea and myalgia. In particular, more studies conducted in primary care settings are needed. Given that there is no gold standard for *M. pneumoniae* diagnosis, greater consistency in the laboratory methods used across different studies is needed to ensure that acute *M. pneumoniae* infections are reliably detected. The development of rapid point of care tests for the diagnosis of *M. pneumoniae* is also an important area for further research. The ability to diagnose *M. pneumoniae* more accurately will not only help inform more appropriate clinical decisions, but will also facilitate the design and conduct of more definitive research to determine the efficacy of antibiotics in the treatment of community-acquired pneumonia and other respiratory tract infections caused by *M. pneumoniae* (Mulholland 2010).

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ACKNOWLEDGEMENTS

We would like to thank Nia Roberts and Sarah Thorning for assisting us with preparing our search strategy, performing our searches and retrieving articles for this review. We thank Yemisi Takwoingi for her advice on statistical analysis. We wish to thank Paul Glasziou and Inge Axelsson for commenting on drafts of the protocol and full review. We also wish to thank Chanpen Choprapawon, Anne Lyddiatt and Amita Jain for commenting on the draft protocol and Rakesh Lodha, Elizabeth Ayres and Conor Teljeur for commenting on the draft of the full review. Kay Wang's post is funded by the National Institute for Health Research and this review is part of a wider programme of research.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

REFERENCES

References to studies included in this review

Agarwal 2009 *{published data only}*

Agarwal J, Awasthi S, Rajput A, Tiwari M. Atypical bacterial pathogens in community-acquired pneumonia in children: a hospital based study. *Tropical Doctor* 2009;**39**:109-11.

Chan 2001 *{published data only}*

Chan PWK, Lum LCS, Ngeow YF, Yasim MY. Mycoplasma pneumoniae infection in Malaysian children admitted with community acquired pneumonia. *Southeast Asian Journal of Tropical Medicine and Public Health* 2001;**32**:397-401.

Deerojanawong 2006 *{published data only}*

Deerojanawong J, Prapphal N, Suwanjutha S, Lochindarat S, Chantarojanasiri T, Kunakorn M, et al. Prevalence and clinical features of Mycoplasma pneumoniae in Thai children. *Journal of the Medical Association of Thailand* 2006;**89**:1641-7.

Kumar 2011 *{published data only}*

Kumar S, Saigal SR, Sethi GR. Rapid diagnosis of Mycoplasma pneumoniae by polymerase chain reaction in community-acquired lower respiratory tract infections. *Tropical Doctor* 2011;**41**:160-2.

Maheshwari 2011 *{published data only}*

Maheshwari M, Kumar S, Sethi GR, Bhalla P. Detection of Mycoplasma pneumoniae in children with lower respiratory tract infections. *Tropical Doctor* 2011;**41**:40-2.

Principi 2001 *{published data only}*

Principi N, Esposito S, Blasi F, Allegra L: Mowgli Study Group. Role of Mycoplasma pneumoniae and Chlamydia pneumoniae in children with community-acquired lower respiratory tract infections. *Clinical Infectious Diseases* 2001;**32**:1281-9.

Somer 2006 *{published data only}*

Somer A, Salman N, Yalcin I, Agacfidan A. Role of Mycoplasma pneumoniae and Chlamydia pneumoniae in children with community-acquired pneumonia in Istanbul, Turkey. *Journal of Tropical Paediatrics* 2006;**52**:173-7.

References to studies excluded from this review

Almasri 2011 *{published data only}*

Almasri M, Diza E, Papa A, Eboriadou M, Souliou E. Mycoplasma pneumoniae respiratory tract infections among Greek children. *Hippokratia* 2011;**15**:147-52.

Al-Moyed 2003 *{published data only}*

Al-Moyed KA, Al-Shamahy HA. Mycoplasma pneumoniae infection in Yemen: incidence, presentation and antibiotic susceptibility. Eastern Mediterranean Health Journal 2003; Vol. 9, issue 3:279-90.

Al-Rashed 1998 *{published data only}*

Al-Rashed A. Role of Mycoplasma pneumoniae in acute respiratory-tract infections in Saudi paediatric patients. Annals of Tropical Medicine and Parasitology 1998; Vol. 92, issue 5:595-601.

Angadi 1980 *{published data only}*

Angadi SA, Mukerji S, Nimbkar YS, Merchant SM. Serological study of acute respiratory tract infection in children with reference to Mycoplasma pneumoniae complement fixing and cold hemagglutinating antibodies. Indian Journal of Pathology and Microbiology 1980; Vol. 23, issue 1:65-8.

Antonelli 2009 *{published data only}*

Antonelli F, De Brasi D, Siani P. Appropriateness of hospitalization for CAP-affected pediatric patients: report from a Southern Italy General Hospital. Italian Journal of Pediatrics 2009; Vol. 35, issue 1:26.

Baer 2003 *{published data only}*

Baer G, Engelcke G, Abele-Horn M, Schaad UB, Heininger U. Role of Chlamydia pneumoniae and Mycoplasma pneumoniae as causative agents of community-acquired pneumonia in hospitalised children and adolescents. European Journal of Clinical Microbiology and Infectious Diseases 2003; Vol. 22, issue 12:742-5.

Bamba 2006 *{published data only}*

Bamba M, Jozaki K, Sugaya N, Tamai S, Ishihara J, Kori T, et al. Prospective surveillance for atypical pathogens in children with community-acquired pneumonia in Japan. Journal of Infection and Chemotherapy 2006; Vol. 12, issue 1:36-41.

Bii 2002 *{published data only}*

Bii CC, Yamaguchi H, Kai M, Nagai K, Sugiura Y, Taguchi H, et al. Mycoplasma pneumoniae in children with pneumonia at Mbagathi District Hospital, Nairobi. East African Medical Journal 2002; Vol. 79, issue 6:317-22.

Block 1995 *{published data only}*

Block S, Hedrick J, Hammerschlag MR, Cassell GH, Craft JC. Mycoplasma pneumoniae and Chlamydia pneumoniae in pediatric community-acquired pneumonia: comparative efficacy and safety of clarithromycin vs. erythromycin ethylsuccinate. Pediatric Infectious Disease Journal 1995; Vol. 14, issue 6:471-7.

Broome 1980 *{published data only}*

Broome CV, LaVenture M, Kaye HS, Davis AT, White H, Plikaytis BD, et al. An explosive outbreak of Mycoplasma pneumoniae infection in a summer camp. Pediatrics 1980; Vol. 66, issue 6:884-8.

Bunnag 2008 *{published data only}*

Bunnag T, Lochindarat S, Srisan P, Jetanachai P. Mycoplasma pneumonia in young children, 2-5 years of age. Journal of the Medical Association of Thailand 2008; Vol. 91 Suppl 3:124-7.

Butun 2006 *{published data only}*

Butun Y, Kose S, Babayigit A, Olmez D, Anal O, Uzuner N, et al. Chlamydia and Mycoplasma serology in respiratory tract

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

infections of children. Tuberkuloz ve Toraks 2006; Vol. 54, issue 3:254-8.

Chaudhry 1998 *{published data only}*

Chaudhry R, Nazima N, Dhawan B, Kabra SK. Prevalence of Mycoplasma pneumoniae and Chlamydia pneumoniae in children with community acquired pneumonia. [Erratum appears in Indian J Pediatr 1998 Nov-Dec;65(6):866]. Indian Journal of Pediatrics 1998; Vol. 65, issue 5:717-21.

Chkhaidze 2006 *{published data only}*

Chkhaidze I, Manjavidze N, Nemsadze K. Serodiagnosis of acute respiratory infections in children in Georgia. Indian Journal of Pediatrics 2006; Vol. 73, issue 7:569-72.

Defilippi 2008 *{published data only}*

Defilippi A, Silvestri M, Tacchella A, Giacchino R, Melioli G, Di Marco E, et al. Epidemiology and clinical features of Mycoplasma pneumoniae infection in children. Respiratory Medicine 2008; Vol. 102, issue 12:1762-8.

De Roux 2006 *{published data only}*

De Roux A, Ewig S, Garcia E, Marcos MA, Mensa J, Lode H, et al. Mixed community-acquired pneumonia in hospitalised patients. European Respiratory Journal 2006; Vol. 27, issue 4:795-800.

Dowdle 1967 *{published data only}*

Dowdle WR, Stewart JA, Heyward JT, Robinson RQ. Mycoplasma pneumoniae infections in a children's population: a five-year study. American Journal of Epidemiology 1967; Vol. 85:137-45.

Drummond 2000 *{published data only}*

Drummond P, Clark J, Wheeler J, Galloway A, Freeman R, Cant A. Community acquired pneumonia - a prospective UK study. Archives of Disease in Childhood 2000; Vol. 83, issue 5:408-12.

Dular 1987 *{published data only}*

Dular R, Lambert M, Bruce BW, Phipps PH, Rossier E, Kasatiya S. Mycoplasma pneumoniae infections in a rural setting in Canada. Canadian Medical Association Journal 1987; Vol. 136, issue 12:1271-3.

Elkholy 2009 *{published data only}*

Elkholy A, Elkaraksy H, Fattouh A, Bazaraa H, Hegazy R, Abdelhalim M. Acute lower respiratory tract infection due to Chlamydia and Mycoplasma spp. in Egyptian children under 5 years of age. Journal of Tropical Pediatrics 2009; Vol. 55, issue 3:195-7.

Esposito 2001 *{published data only}*

Esposito S, Blasi F, Bellini F, Allegra L, Principi N. Mycoplasma pneumoniae and Chlamydia pneumoniae infections in children with pneumonia. European Respiratory Journal 2001; Vol. 17, issue 2:241-5.

Ferwerda 2001 *{published data only}*

Ferwerda A, Moll HA, Hop WCJ, Kouwenberg JM, Tjon Pian CV, Robben SGF, et al. Efficacy, safety and tolerability of 3-day azithromycin versus 10-day co-amoxiclav in the treatment of children with acute lower respiratory tract infections. Journal of Antimicrobial Chemotherapy 2001; Vol. 47:441-6.

Fischer 2002 *{published data only}*

Fischer JE, Steiner F, Zucol F, Berger C, Martignon L, Bossart W, et al. Use of simple heuristics to target macrolide prescription in children with community-acquired pneumonia. Archives of Pediatrics and Adolescent Medicine 2002; Vol. 156, issue 10:1005-8.

Forgie 1991 *{published data only}*

Forgie IM, O'Neill KP, Lloyd-Evans N, Leinonen M, Campbell H, Whittle HC, et al. Etiology of acute lower respiratory tract infections in Gambian children: II. Acute lower respiratory tract infection in children ages one to nine years presenting at the hospital. Pediatric Infectious Disease Journal 1991; Vol. 10, issue 1:42-7.

Gendrel 1997 *{published data only}*

Gendrel D, Raymond J, Moulin F, Iniguez JL, Ravilly S, Habib F, et al. Etiology and response to antibiotic therapy of community-acquired pneumonia in French children. European Journal of Clinical Microbiology and Infectious Diseases 1997; Vol. 16, issue 5:388-91.

Gimenez Sanchez 2007 *{published data only}*

Gimenez Sanchez F, Sanchez Marenco A, Battles Garrido JM, Lopez Soler JA, Sanchez-Solis Querol M. Clinicoepidemiological characteristics of community-acquired pneumonia in children aged less than 6 years old. Anales de Pediatria 2007; Vol. 66, issue 6:578-84.

Gomez Campdera 2002 *{published data only}*

Gomez Campdera JA, Rodriquez Fernandez R, Megias Montijano A, Gonzalez Sanchez MI, Navarro Gomez M, Ruiz Magro P. Mycoplasma pneumoniae in patients under three years of age. Acta Pediatrica Espanola 2002; Vol. 60, issue 7:343-7.

Guggenbichler 1977 *{published data only}*

Guggenbichler JP, Berger H. Mycoplasma pneumonias in childhood (author's transl). Padiatrie und Padologie 1977; Vol. 12, issue 1:10-8.

Gutierrez 2005 *{published data only}*

Gutierrez F, Masia M, Rodriguez JC, Mirete C, Soldan B, Padilla S, et al. Community-acquired pneumonia of mixed etiology: prevalence, clinical characteristics, and outcome. European Journal of Clinical Microbiology and Infectious Diseases 2005; Vol. 24, issue 6:377-83.

Harris 1998 *{published data only}*

Harris J-AS, Kolokathis A, Campbell M, Cassell G, Hammerschlag M. Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children. Pediatric Infectious Disease Journal 1998; Vol. 17:865-71.

Heinz 1983 *{published data only}*

Heinz F, Januska J, Raszka J, Cervenka P, Mlynkova H, Kupec V. Contribution to the problem of sporadic acute respiratory infections (ARI) caused by RS viruses and Mycoplasma pneumoniae in preschool-age children and adults. Ceskoslovenska Epidemiologie, Mikrobiologie, Imunologie 1983; Vol. 32, issue 4:197-203.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Heiskanen-Kosma 1998 *{published data only}*

Heiskanen-Kosma T, Korppi M, Jokinen C, Kurki S, Heiskanen L, Juvonen H, et al. Etiology of childhood pneumonia: serologic results of a prospective, population-based study. Pediatric Infectious Disease Journal 1998; Vol. 17:986-91.

Holmes 2001 *{published data only}*

Holmes WF, Macfarlane JT, Macfarlane RM, Hubbard R. Symptoms, signs, and prescribing for acute lower respiratory tract illness. British Journal of General Practice 2001; Vol. 51:177-81.

Hortal 1994 *{published data only}*

Hortal M, Suarez A, Deleon C, Estevan M, Mogdasy MC, Russi JC, et al. Etiology and severity of community acquired pneumonia in children from Uruguay: a 4-year study. Revista do Instituto de Medicina Tropical de Sao Paulo 1994; Vol. 36, issue 3:255-64.

Javier Alvarez 2001 *{published data only}*

Javier Alvarez Gutierrez F, Del Castillo Otero D, Garcia Fernandez A, Romero Romero B, Jose Del Rey Perez J, Soto Campos G, et al. Prospective study of 221 community acquired pneumonias followed up in an outpatient clinic. Etiology and clinical-radiological progression. Medicina Clinica 2001; Vol. 116:161-6.

Jensen 1967 *{published data only}*

Jensen KJ, Senterfit LB, Scully WE, Conway TJ, West RF, Drummy WW. Mycoplasma pneumoniae infections in children. An epidemiologic appraisal in families treated with oxytetracycline. American Journal of Epidemiology 1967; Vol. 86:419-32.

Jokinen 1993 *{published data only}*

Jokinen C, Heiskanen L, Juvonen H, Kallinen S, Karkola K, Korppi M, et al. Incidence of community-acquired pneumonia in the population of four municipalities in Eastern Finland. American Journal of Epidemiology 1993; Vol. 137:977-88.

Juven 2000 *{published data only}*

Juven T, Mertsola J, Waris M, Leinonen M, Meurman O, Roivainen M, et al. Etiology of community-acquired pneumonia in 254 hospitalized children. Pediatric Infectious Disease Journal 2000; Vol. 19, issue 4:293-8.

Kapellerova 2007 *{published data only}*

Kapellerova A, Zlocha J, Kukova Z, Luptakova M, Tarhini A. Mycoplasmal pneumonia in childhood [Slovak]. Cesko-Slovenska Pediatrie 2007; Vol. 62, issue 1:16-24.

Kicinski 2011 *{published data only}*

Kicinski P, Wisniewska-Ligier M, Wozniakowska-Gesicka T. Pneumonia caused by Mycoplasma pneumoniae and Chlamydophila pneumoniae in children - comparative analysis of clinical picture. Advances in Medical Sciences 2011; Vol. 56, issue 1:56-63.

King 1991 *{published data only}*

King DE, Muncie HL. High prevalence of Mycoplasma pneumoniae in patients with respiratory tract symptoms: a rapid detection method. Journal of Family Practice 1991; Vol. 32, issue 5:529-31.

Kogan 2003 *{published data only}*

Kogan R, Martinez MA, Rubilar L, Paya E, Quevedo I, Puppo H, et al. Comparative randomized trial of azithromycin versus erythromycin and amoxicillin for treatment of community-acquired pneumonia in children. Pediatric Pulmonology 2003; Vol. 35, issue 2:91-8.

Korppi 2004 *{published data only}*

Korppi M, Heiskanen-Kosma T, Kleemola M. Incidence of community-acquired pneumonia in children caused by Mycoplasma pneumoniae: serological results of a prospective, population-based study in primary health care. Respirology 2004; Vol. 9, issue 1:109-14.

Kurz 2011 *{published data only}*

Kurz H, Göpfrich H. Epidemiology and morbidity of mycoplasma as causative agent for community-acquired pneumonia in hospitalized children in a community hospital in Vienna. *Wiener Medizinische Wochenschrift* 2011;**161**:180-3.

Lagerstrom 2003 *{published data only}*

Lagerstrom F, Bader M, Foldevi M, Fredlund H, Nordin-Olsson I, Holmberg H. Microbiological etiology in clinically diagnosed community-acquired pneumonia in primary care in Orebro Sweden. Clinical Microbiology and Infection 2003; Vol. 9, issue 7:645-52.

Lassmann 2008 *{published data only}*

Lassmann B, Poetschke M, Ninteretse B, Issifou S, Winkler S, Kremsner PG, et al. Community-acquired pneumonia in children in Lambarene, Gabon. American Journal of Tropical Medicine and Hygiene 2008; Vol. 79, issue 1:109-14.

Lee 2008 *{published data only}*

Lee P-I, Wu M-H, Huang L-M, Chen J-M, Lee C-Y. An open, randomized, comparative study of clarithromycin and erythromycin in the treatment of children with community-acquired pneumonia. Journal of Microbiology, Immunology and Infection 2008; Vol. 41, issue 1:54-61.

Liam 2001 *{published data only}*

Liam CK, Lim KH, Wong CM. Community-acquired pneumonia in patients requiring hospitalization. Respirology 2001; Vol. 6, issue 3:259-64.

Lochindarat 2007 *{published data only}*

Lochindarat S, Suwanjutha S, Prapphal N, Chantarojanasiri T, Bunnag T, Deerojanawong J, et al. Mycoplasma pneumoniae and Chlamydophila pneumoniae in children with community-acquired pneumonia in Thailand. International Journal of Tuberculosis and Lung Disease 2007; Vol. 11, issue 7:814-9.

Maltezou 2004 *{published data only}*

Maltezou HC, La-Scola B, Astra H, Constantopoulou I, Vlahou V, Kafetzis DA, et al. Mycoplasma pneumoniae and Legionella pneumophila in community-acquired lower respiratory tract infections among hospitalized children: diagnosis by real time

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

PCR. Scandinavian Journal of Infectious Diseases 2004; Vol. 36, issue 9:639-42.

Manfredi 1992 *{published data only}*

Manfredi R, Jannuzzi C, Mantero E, Longo L, Schiavone R, Tempesta A, et al. Clinical comparative study of azithromycin versus erythromycin in the treatment of acute respiratory tract infections in children. Journal of Chemotherapy 1992; Vol. 4, issue 6:364-70.

Marrie 1996 *{published data only}*

Marrie TJ, Peeling RW, Fine MJ, Singer DE, Coley CM, Kapoor WN. Ambulatory patients with community-acquired pneumonia: the frequency of atypical agents and clinical course. American Journal of Medicine 1996; Vol. 101:508-15.

Marrie 2005 *{published data only}*

Marrie TJ, Poulin-Costello M, Beecroft MD, Herman-Gnjidi Z. Etiology of community-acquired pneumonia treated in an ambulatory setting. Respiratory Medicine 2005; Vol. 99:60-5.

Masia 2006 *{published data only}*

Masia M, Gutierrez F, Padilla S, Soldian B, Mirete C, Shum C, et al. Clinical characterisation of pneumonia caused by atypical pathogens combining classic and novel predictors. Clinical Microbiology and Infection 2006; Vol. 13, issue 2:153-61.

Matute 2006 *{published data only}*

Matute AJ, Brouwer WP, Hak E, Delgado E, Alonso E, Hoepelman IM. Aetiology and resistance patterns of community-acquired pneumonia in Leon, Nicaragua. International Journal of Antimicrobial Agents 2006; Vol. 28, issue 5:423-7.

Michelow 2004 *{published data only}*

Michelow IC, Olsen K, Lozano J, Rollins NK, Duffy LB, Ziegler T, et al. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 2004; Vol. 113, issue 4:701-7.

Murphy 1981 *{published data only}*

Murphy TF, Henderson FW, Clyde Jr WA, Collier AM, Denny FW. Pneumonia: an eleven-year study in a pediatric practice. American Journal of Epidemiology 1981; Vol. 113:12-21.

Nagalingam 2004 *{published data only}*

Nagalingam NA, Adesiyun AA, Swanston WH, Bartholomew M. Prevalence of Mycoplasma pneumoniae and Chlamydia pneumoniae in pneumonia patients in four major hospitals in Trinidad. New Microbiologica 2004; Vol. 27, issue 4:345-51.

Nagayama 1988 *{published data only}*

Nagayama Y, Sakurai N, Yamamoto K, Honda A, Makuta M, Suzuki R. Isolation of Mycoplasma pneumoniae from children with lower-respiratory-tract infections. Journal of Infectious Diseases 1988; Vol. 157, issue 5:911-7.

Nagayama 1990 *{published data only}*

Nagayama Y, Sakurai N, Yamamoto K. Clinical observations of children with pleuropneumonia due to Mycoplasma pneumoniae. Pediatric Pulmonology 1990; Vol. 8:182-7.

Nakayama 2007 *{published data only}*

Nakayama E, Hasegawa K, Morozumi M, Kobayashi R, Chiba N, Iitsuka T, et al. Rapid optimization of antimicrobial chemotherapy given to pediatric patients with community-acquired pneumonia using PCR techniques with serology and standard culture. Journal of Infection and Chemotherapy 2007; Vol. 13, issue 5:305-13.

Ngeow 2005 *{published data only}*

Ngeow Y-F, Suwanjutha S, Chantarojanasriri T, Wang F, Saniel M, Alejandria M, et al. An Asian study on the prevalence of atypical respiratory pathogens in community-acquired pneumonia. International Journal of Infectious Diseases 2005; Vol. 9, issue 3:144-53.

Ouchi 1999 *{published data only}*

Ouchi K, Komura H, Fujii M, Matsushima H, Maki T, Hasegawa K, et al. Chlamydia pneumoniae infection and Mycoplasma pneumoniae infection in pediatric patients. Kansenshogaku Zasshi - Journal of the Japanese Association for Infectious Diseases 1999; Vol. 73, issue 12:1177-82.

Pandey 2000 *{published data only}*

Pandey A, Chaudhry R, Nisar N, Kabra SK. Acute respiratory tract infections in Indian children with special reference to Mycoplasma pneumoniae. Journal of Tropical Pediatrics 2000; Vol. 46, issue 6:371-4.

Peng 2009 *{published data only}*

Peng D, Zhao D, Liu J, Wang X, Yang K, Xicheng H, et al. Multipathogen infections in hospitalized children with acute respiratory infections. Virology Journal 2009; Vol. 6:155.

Pereyre 2012 *{published data only}*

Pereyre S, Renaudin H, Charron A, Bebear C. Clonal spread of Mycoplasma pneumoniae in primary school, Bordeaux, France. *Emerging Infectious Diseases* 2012;**18**:343-5.

Pocheville Guruceta 1998 *{published data only}*

Pocheville Guruceta I, Angulo Barrena P, Ortiz Andres A, Fernandez Fernandez B, Vazquez Ronco MA, Garea Ibanez C, et al. Clinical and epidemiological spectrum of Mycoplasma pneumoniae infections at a pediatric hospital. Anales Espanoles de Pediatria 1998; Vol. 48, issue 2:127-31.

Prapphal 2006 *{published data only}*

Prapphal N, Suwanjutha S, Durongkaveroj P, Lochindarat S, Kunakorn M, Deerojanawong J, et al. Prevalence and clinical presentations of atypical pathogens infection in community acquired pneumonia in Thailand. Journal of the Medical Association of Thailand 2006; Vol. 89, issue 9:1412-9.

Putman 1975 *{published data only}*

Putman CE, Curtis AM, Simeone JF, Jensen P. Mycoplasma pneumonia. Clinical and roentgenographic patterns. American Journal of Roentgenology, Radium Therapy and Nuclear Medicine 1975; Vol. 124:417-22.

Rahman 1990 *{published data only}*

Rahman M, Huq F, Sack DA, Butler T, Azad AK, Alam A, et al. Acute lower respiratory tract infections in hospitalized patients

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

with diarrhea in Dhaka, Bangladesh. Reviews of Infectious Diseases 1990; Vol. 12, issue Suppl 8:899-906.

Sakurai 1988 *{published data only}*

Sakurai N, Nagayama Y. The clinical observation of M. pneumoniae infections among children in Asahi General Hospital with special reference to mixed viral infections. Acta Paediatrica Japonica (Overseas Edition) 1988; Vol. 30, issue 3:267-75.

Sakurai 1988a *{published data only}*

Sakurai N, Nagayama Y, Honda A, Makuta M, Yamamoto K, Kojima S. Mycoplasma pneumoniae and other pathogens in the aetiology of lower respiratory tract infections among Japanese children. Journal of Infection 1988; Vol. 16, issue 3:253-61.

Samransamruajkit 2008 *{published data only}*

Samransamruajkit R, Jitchaiwat S, Wachirapaes W, Deerojanawong J, Sritippayawan S, Prapphal N. Prevalence of Mycoplasma and Chlamydia pneumonia in severe community-acquired pneumonia among hospitalized children in Thailand. Japanese Journal of Infectious Diseases 2008; Vol. 61, issue 1:36-9.

Shenoy 2005 *{published data only}*

Shenoy VD, Upadhyaya SA, Rao SP, Shobha KL. Mycoplasma pneumoniae infection in children with acute respiratory infection. Journal of Tropical Pediatrics 2005; Vol. 51, issue 4:232-5.

Sidal 2007 *{published data only}*

Sidal M, Kilic A, Unuvar E, Oguz F, Onel M, Agacfidan A, et al. Frequency of Chlamydia pneumoniae and Mycoplasma pneumoniae infections in children. Journal of Tropical Pediatrics 2007; Vol. 53, issue 4:225-31.

Stawarski 2001 *{published data only}*

Stawarski A, Choroszy-Krol I, Iwanczak B, Ruczkowska J, Iwanczak F. Epidemiology of atypical pneumonia caused by Mycoplasma pneumoniae and Chlamydia sp. in children. Advances in Clinical and Experimental Medicine 2001; Vol. 10, issue 1:37-44.

Szabo 1977 *{published data only}*

Szabo N, Loos T, Szabo I, Martha I. Illness due to Mycoplasma pneumoniae in childhood. Zeitschrift fur Erkrankungen der Atmungsorgane 1977; Vol. 148, issue 3:307-11.

Tajima 2006 *{published data only}*

Tajima T, Nakayama E, Kondo Y, Hirai F, Ito H, Iitsuka T, et al. Etiology and clinical study of community-acquired pneumonia in 157 hospitalized children. Journal of Infection and Chemotherapy 2006; Vol. 12, issue 6:372-9.

Tinsa 2009 *{published data only}*

Tinsa F, Boussetta K, Gharbi A, Bousnina D, Abdelaziz R, Brini I, et al. Community acquired pneumonia in children. Tunisie Medicale 2009; Vol. 87, issue 12:851-6.

Touati 2010 *{published data only}*

Touati A, Pereyre S, Bouziri A, Achour W, Khaldi A, Ben Jaballah N, et al. Prevalence of Mycoplasma pneumoniae-associated respiratory tract infections in hospitalized children: results of a 4-year prospective study in Tunis. Diagnostic Microbiology and Infectious Disease 2010; Vol. 68, issue 2:103-9.

Tsolia 2004 *{published data only}*

Tsolia MN, Psarras S, Bossios A, Audi H, Paldanius M, Gourgiotis D, et al. Etiology of community-acquired pneumonia in hospitalized school-age children: evidence for high prevalence of viral infections. Clinical Infectious Diseases 2004; Vol. 39, issue 5:681-6.

Unay 2002 *{published data only}*

Unay B, Kismet E, Guney C, Akin R, Ozcan O. The frequency and treatment of childhood pneumonia due to Mycoplasma pneumoniae [Turkish]. Gulhane Medical Journal 2002; Vol. 44, issue 2:125-8.

Van der Straeten 1976 *{published data only}*

Van der Straeten M, De Vos M, Druyts E. Hospital treatment and diagnosis of Mycoplasma pneumoniae pneumonia. Infection 1976; Vol. 4, issue Suppl 1:55-7.

Vervloet 2010 *{published data only}*

Vervloet LA, Camargos PAM, Soares DRF, De Oliveira GA, De Oliveira JN. Clinical, radiographic and hematological characteristics of Mycoplasma pneumoniae pneumonia. Jornal de Pediatria 2010; Vol. 86, issue 6:480-7.

Virkki 2002 *{published data only}*

Virkki R, Juven T, Rikalainen H, Svedström E, Mertsola J, Ruuskanen O. Differentiation of bacterial and viral pneumonia in children. Thorax 2002; Vol. 57:438-41.

Woodhead 1987 *{published data only}*

Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. Lancet 1987; Vol. 1, issue 8534:671-4.

Wubbel 1999 *{published data only}*

Wubbel L, Muniz L, Ahmed A, Trujillo M, Carubelli C, McCoig C, et al. Etiology and treatment of community-acquired pneumonia in ambulatory children. Pediatric Infectious Disease Journal 1999; Vol. 18:98-104.

Yang 2001 *{published data only}*

Yang Y, Shen X, Vuori-Holopainen E, Leboulleux D, Wang YJ, Leinonen M, et al. Seroetiology of acute lower respiratory infections among hospitalized children in Beijing. Pediatric Infectious Disease Journal 2001; Vol. 20, issue 1:52-8.

Yin 2003 *{published data only}*

Yin CC, Huah LW, Lin JTP, Goh A, Ling H, Moh CO. Lower respiratory tract infection in hospitalized children. Respirology 2003; Vol. 8:83-9.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Zoricic-Letoja 1995 *{published data only}*

Zoricic-Letoja I, Basic-Grbac M, Mikulic Z, Krstic-Buric M. Pneumonia in school children and adolescents - the clinical and etiological aspects [Serbian]. Paediatria Croatica 1995; Vol. 39, issue 3:175-8.

Additional references

Averbuch 2011

Averbuch D, Hidalgo-Grass C, Moses AE, Engelhard D, Nir-Paz R. Macrolide resistance in Mycoplasma pneumoniae, Israel, 2010. *Emerging Infectious Diseases* 2011;**17**:1079-82.

BTS 2011

British Thoracic Society Community Acquired Pneumonia in Children Guideline Group. Guidelines for the management of community acquired pneumonia in children: update 2011. *Thorax* 2011;**66**:ii1-ii23.

Butler 2004

Butler C, Rollnick S, Kinnersley P, Tapper-Jones L, Houston H. Communicating about expected course and re-consultation for respiratory tract infections in children: an exploratory study. *British Journal of General Practice* 2004;**54**:536-8.

Chalker 2011

Chalker VJ, Stocki T, Mentasti M, Fleming D, Sadler C, Ellis J, et al. *Mycoplasma pneumoniae* infection in primary care investigated by real-time PCR in England and Wales. *European Journal of Clinical Microbiology and Infectious Diseases* 2011;**30**:915-21.

Chung 2007

Chung A, Perera R, Brueggemann AB, Elamin AE, Harnden A, Mayon-White R, et al. Effect of antibiotic prescribing on antibiotic resistance in individual children in primary care: prospective cohort study. *BMJ* 2007;**335**:429.

Deeks 2005

Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *Journal of Clinical Epidemiology* 2005;**58**:882-93.

Don 2005

Don M, Fasoli L, Paldanius M, Vainionpaa R, Kleemola M, Raty R, et al. Aetiology of community-acquired pneumonia: serological results of a paediatric survey. *Scandinavian Journal of Infectious Diseases* 2005;**37**(11-2):806-12.

Dumke 2010

Dumke R, Von Baum H, Lück PC, Jacobs E. Occurrence of macrolide-resistant Mycoplasma pneumoniae strains in Germany. *Clinical Microbiology and Infection* 2010;**16**:613-6.

Fine 2010

Fine AM, Reis BY, Nigrovic LE, Goldmann DA, LaPorte TN, Olson KL, et al. Use of population health data to refine diagnostic decision-making for pertussis. *Journal of American Medical Informatics Association* 2010;**17**(1):85-90.

Freymuth 1999

Freymuth F, Vabret A, Brouard J, Toutain F, Verdon R, Petitjean J, et al. Detection of viral, Chlamydia pneumoniae and Mycoplasma pneumoniae infections in exacerbations of asthma in children. *Journal of Clinical Virology* 1999;**13**(3):131-9.

Gomez Campdera 2006

Gomez Campdera JA, Rodriguez Fernandez R, Navarro Gomez ML, Gonzalez Sanchez MI, Megias Montijano A. Mycoplasma pneumoniae: endemic or epidemic disease. *Acta Pediatrica Espanola* 2006;**64**(11):536-44.

Goossens 2005

Goossens H, Ferech M, Stichele RV, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;**365**:579-87.

Gulliford 2009

Gulliford M, Latinovic R, Charlton J, Little P, Van Staa T, Ashworth M. Selective decrease in consultations and antibiotic prescribing for acute respiratory tract infections in UK primary care up to 2006. *Journal of Public Health (Oxford)* 2009;**31**:512-20.

Hammerschlag 2001

Hammerschlag MR. Mycoplasma pneumoniae infections. *Current Opinion in Infectious Diseases* 2001;**14**:181-6.

Hay 2002

Hay AD, Wilson AD. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. *British Journal of General Practice* 2002;**52**:401-9.

Heymann 2004

Heymann PW, Carper HT, Murphy DM, Platts-Mills TAE, Patrie J, McLaughlin AP, et al. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. *Journal of Allergy and Clinical Immunology* 2004;**114**:239-47.

Hsieh 2007

Hsieh S-C, Kuo Y-T, Chern M-S, Chen C-Y, Chan W-P, Yu C. Mycoplasma pneumonia: clinical and radiographic features in 39 children. *Pediatrics International* 2007;**49**:363-7.

Jartti 2004

Jartti T, Lehtinen P, Vuorinen T, Osterback R, Van den Hoogen B, Osterhaus AD, et al. Respiratory picornaviruses and respiratory syncytial virus as causative agents of acute expiratory wheezing in children. *Emerging Infectious Diseases* 2004;**10**(6):1095-101.

Leeflang 2008

Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM, Cochrane Diagnostic Test Accuracy Working Group. Systematic reviews of diagnostic test accuracy. *Annals of Internal Medicine* 2008;**149**:889-97.

Lehtinen 2006

Lehtinen P, Jartti T, Virkki R, Vuorinen T, Leinonen M, Peltola V, et al. Bacterial coinfections in children with viral wheezing.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

European Journal of Clinical Microbiology and Infectious Diseases 2006;**25**(7):463-9.

Loens 2010

Loens K, Goossens H, Ieven M. Acute respiratory infection due to Mycoplasma pneumoniae: current status of diagnostic methods. *European Journal of Clinical Microbiology and Infectious Diseases* 2010;**29**:1055-69.

Macaskill 2010

Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and presenting results. In: Deeks JJ, Bossuyt PM, Gatsonis C editor(s). Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0. Chichester: Wiley-Blackwell, 2010.

Morozumi 2008

Morozumi M, Iwata S, Hasegawa K, Chiba N, Takayanagi R, Matsubara K, et al. Increased macrolide resistance of Mycoplasma pneumoniae in pediatric patients with community-acquired pneumonia. *Antimicrobial Agents and Chemotherapy* 2008;**52**:348-50.

Mulholland 2010

Mulholland S, Gavranich JB, Chang AB. Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children. *Cochrane Database of Systematic Reviews* 2010, Issue 7. [DOI: 10.1002/14651858.CD004875.pub3]

NICE 2008

National Institute for Health and Clinical Excellence. Respiratory tract infections - antibiotic prescribing. Clinical Guideline 69 2008.

Nilsson 2008

Nilsson AC, Bjorkman P, Persson K. Polymerase chain reaction is superior to serology for the diagnosis of acute Mycoplasma pneumoniae infection and reveals a high rate of persistent infection. *BMC Microbiology* 2008;**8**:93.

Othman 2005

Othman N, Isaacs D, Kesson A. Mycoplasma pneumoniae infections in Australian children. *Journal of Paediatrics and Child Health* 2005;**41**:671-6.

Pereyre 2007

Pereyre S, Charron A, Renaudin H, Bebear C, Bebear CM. First report of macrolide-resistant strains and description of a novel nucleotide sequence variation in the P1 adhesin gene in Mycoplasma pneumoniae clinical strains isolated in France over 12 years. *Journal of Clinical Microbiology* 2007;**45**:3534-9.

Reitsma 2009

Reitsma JB, Whiting P, Vlassov VV, Leeflang MMG, Deeks JJ. Chapter 9: Assessing methodological quality. In: Deeks JJ, Bossuyt PM, Gatsonis C editor(s). Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0. The Cochrane Collaboration. Available from http://srdta.cochrane.org/. Chichester: Wiley-Blackwell, 2011.

Sopena 1999

Sopena N. Prospective study of community-acquired pneumonia of bacterial etiology in adults. *European Journal of Clinical Microbiology and Infectious Diseases* 1999;**18**:852-8.

Stevens 1978

Stevens D, Swift PGF, Johnston PGB, Kearney PJ, Corner BD, Burman D. Mycoplasma pneumoniae infections in children. *Archives of Disease in Childhood* 1978;**53**:38-42.

Thurman 2009

Thurman KA, Walter ND, Schwartz SB, Mitchell SL, Dillon MT, Baughman AL, et al. Comparison of laboratory diagnostic procedures for detection of *Mycoplasma pneumoniae* in community outbreaks. *Clinical Infectious Diseases* 2009;**48**:1244-9.

Van de Garde 2008

Van de Garde EMW, Endeman H, Van Hemert RN, Voorn GPR, Deneer VHM, Leufkens HGM, et al. Prior outpatient antibiotic use as predictor for microbial aetiology of community-acquired pneumonia: hospital-based study. *European Journal of Clinical Pharmacology* 2008;**64**(4):405-10.

Van den Bruel 2010

Van den Bruel A, Haj-Hassan T, Thompson M, Buntinx F, Mant D, European Research Network on Recognising Serious Infection investigators. Diagnostic value of clinical features at presentation to identify serious infection in children in developed countries: a systematic review. *Lancet* 2010;**375**:834-45.

Von Baum 2009

Von Baum H, Welte T, Marre R, Suttorp N, Lück C, Ewig S. *Mycoplasma pneumoniae* pneumonia revisited within the German Competence Network for Community-acquired pneumonia (CAPNETZ). *BMC Infectious Diseases* 2009;**9**:62.

Wattanathum 2003

Wattanathum A, Chaoprasong C, Nunthapisud P, Chantaratchada S, Limpairojn N, Jatakanon A, et al. Community-acquired pneumonia in Southeast Asia. The microbial differences between ambulatory and hospitalized patients. *Chest* 2003;**123**:1512-9.

Zhao 2012

Zhao F, Lv M, Tao X, Huang H, Zhang B, Zhang Z, et al. Antibiotic sensitivity of 40 Mycoplasma pneumoniae isolates and molecular analysis of macrolide-resistant isolages from Beijing, China. *Antimicrobial Agents and Chemotherapy* 2012;**56**:1108-9.

CHARACTERISTICS OF STUDIES

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

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Agarwal 2009

Clinical features and settings	Hospital setting (Chhatrapati Shahuji Mahraj Medical University, India) Clinical features for study inclusion: cough or difficulty in breathing (an increased respiratory rate or chest indrawing)
Participants	Children aged 1 to 59 months admitted with clinical diagnosis of WHO-defined severe pneumonia Number of participants: 243 Male participants: 160, (65.8%) Number of participants with *M. pneumoniae:* 24, (9.9%)
Study design	Prospective observational cohort study
Target condition and reference standard(s)	*M. pneumoniae* detected using: 1. IgM serology on single blood sample (ELISA, i.e. enzyme-linked immunoadsorbent assay) 2. antigen detection in nasopharyngeal aspirate sample (ELISA) Presence of *M. pneumoniae* infection was defined as *M. pneumoniae* detected using either laboratory method
Index and comparator tests	Symptoms: fever, cough, headache, chills, vomiting, chest pain, diarrhea, wheeze, sore throat, sinus pain Signs: temperature > 100 °F, central cyanosis, nasal flaring, altered sensorium, crepitations, respiratory rate > 40 breaths per minute, inability to feed
Follow-up	Symptoms and signs recorded at the time of admission. Blood and nasopharyngeal aspirate samples obtained at the same time, but timing in relation to admission not stated
Notes	Mean duration of hospital stay in children with *M. pneumoniae* was 8.74 days (standard deviation 6.52), which was not significantly different from that in children with other infections. No children tested positive for *M. pneumoniae* on both serology and antigen detection in nasopharyngeal aspirate

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	No	Participants were children with severe community-acquired pneumonia based on WHO clinical criteria. The study population therefore only represented a limited part of the spectrum of disease severity among children admitted with community-acquired pneumonia. Co-morbidities in study population were not reported
Acceptable reference standard? All tests	Unclear	No children were positive for *M. pneumoniae* on both types of laboratory testing; 14 children had *M. pneumoniae* based on IgM serology and 10 based on antigen detection in nasopharyngeal aspirate. Timing of sample taking in relation to symptom onset was not reported
Acceptable delay between tests? All tests	Unclear	Symptoms and signs recorded on admission, but timing of sample taking in relation to admission was not reported
Partial verification avoided? All tests	Yes	All study participants were subjected to the same laboratory tests

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Agarwal 2009 *(Continued)*

Differential verification avoided? All tests	Yes	All study participants were subjected to the same laboratory tests
Incorporation avoided? All tests	Yes	The diagnosis of *M. pneumoniae* was based on laboratory test results only
Reference standard results blinded? All tests	Yes	Clinical symptoms and signs likely to have been recorded on study entry, since only children meeting WHO clinical criteria for severe community-acquired pneumonia were eligible to take part in this study. Laboratory test results would therefore not have been available at the time that clinical assessment took place
Index test results blinded? All tests	Unclear	Diagnostic antibody titre for *M. pneumoniae* detection not reported
Relevant clinical information? All tests	Unclear	Baseline data on participant age, sex, weight and height were recorded. Baseline data were also collected on antibiotic intake, previous hospitalisation and oxygen administration during the preceding 6 days. Unclear whether data on duration of illness were collected
Uninterpretable results reported? All tests	No	No intermediate or borderline test results reported. Study did not report definitions of intermediate or borderline results for either type of ELISA test
Withdrawals explained? All tests	Yes	Data reported for all 243 participants, no withdrawals

Chan 2001

Clinical features and settings	Hospital setting (University of Malaya Medical Center, Malaysia) Clinical features for study inclusion: fever > 37.5 °C with respiratory symptoms and chest signs or chest radiograph changes compatible with a diagnosis of pneumonia
Participants	Children aged 1 month to 15 years with community-acquired pneumonia Number of participants: 170 Male participants: 112, (65.9%) Number of participants with *M. pneumoniae*: 40 (23.5%)
Study design	Prospective observational cohort study
Target condition and reference standard(s)	*M. pneumoniae* detected based on serological testing of acute and convalescent blood samples taken 2 to 4 weeks apart (passive particle agglutination test). Presence of *M. pneumoniae* infection defined as single antibody titre of more than 1:160 or a fourfold or greater rise in antibody titre between acute and convalescent samples. The antibody titre threshold used to diagnose *M. pneumoniae* on a single serum sample was adjusted from 1:40 (manufacturer's recommendation) to 1:160. A titre of 1:40 was considered too low, as this was found in 45% of healthy blood donors. However, a titre of 1:160 was only found in 10% of the healthy population
Index and comparator tests	Wheeze

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Chan 2001 *(Continued)*

Follow-up	Children followed up during admission. Duration between admission and recording of clinical features/initial sample taking was not reported
Notes	Extra-pulmonary complications were encountered in 3 children with *M. pneumoniae*. Two children had elevated liver enzymes which normalised after a week and one died from multi-organ failure on day 15 of illness

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Unclear	Co-morbidities in study population were not reported. Did not state whether or not children with co-morbidities were excluded
Acceptable reference standard? All tests	Yes	*M. pneumoniae* detected based on serological testing of acute and convalescent blood samples taken 2 to 4 weeks apart
Acceptable delay between tests? All tests	Unclear	Timing of collection of acute blood sample in relation to recording of clinical features was not reported
Partial verification avoided? All tests	Yes	All study participants were subjected to the same laboratory tests
Differential verification avoided? All tests	Yes	All study participants were subjected to the same laboratory tests
Incorporation avoided? All tests	Yes	Clear thresholds for positive serological diagnosis of *M. pneumoniae* reported
Reference standard results blinded? All tests	Yes	Clinical symptoms and signs were recorded during the acute community-acquired pneumonia illness episode, when the results of convalescent serum samples would not have been available
Index test results blinded? All tests	Yes	Clear thresholds for positive serological diagnosis of *M. pneumoniae* reported
Relevant clinical information? All tests	Yes	Baseline data were collected from participants on age, sex, ethnicity and duration of illness
Uninterpretable results reported? All tests	No	No intermediate or borderline serology results reported. Study did not provide definition of intermediate or borderline serology result
Withdrawals explained? All tests	Yes	Data reported for all 170 participants; no withdrawals

Deerojanawong 2006

Clinical features and settings	Multicentre study performed at 3 hospitals in Bangkok, Thailand (Queen Sirkit National Insititute of Health, King Chulalongkorn Memorial Hospital, Ramathibodi Hospital)

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Deerojanawong 2006 *(Continued)*

	Clinical features for study inclusion: clinical and radiological diagnosis of community-acquired pneumonia, defined as new infiltrates or consolidation on chest X-ray that could not be attributed to other aetiology and the presence of 3 or more of: cough, acute change in quality of sputum, fever or hypothermia (> 38 °C or < 36.1 °C) within the preceding 24 hours, rales or evidence of pulmonary consolidation, leukocytosis, malaise/myalgia or gastrointestinal symptoms
Participants	Children aged 2 to 15 years with community-acquired pneumonia Children were excluded if they had evidence or history of tuberculosis, nosocomial pneumonia, aspiration pneumonia or bronchiectasis. Children were also excluded if they were HIV-positive or had been hospitalised within 2 weeks prior to consultation Number of participants: 257 Number of participants who underwent testing for *M. pneumoniae*: 245 Male participants: 135, (55.1%) Number of participants with *M. pneumoniae*: 36, (14.7%)
Study design	Prospective observational cohort study
Target condition and reference standard(s)	*M. pneumoniae* detected using: 1. serological testing of acute and convalescent blood samples taken 2 to 4 weeks apart (particle agglutination test) 2. PCR analysis of respiratory secretion samples (throat swabs, sputum or nasopharyngeal aspirate). Presence of current *M. pneumoniae* infection was defined as a fourfold or greater rise in antibody titres between paired acute and convalescent sera or high antibody titres (>= 1:160) in both serum samples together with the presence of positive PCR for *M. pneumoniae* in respiratory secretions Results of single serum samples were excluded from the analysis. The presence of positive PCR for *M. pneumoniae* in the absence of a positive serologic response was interpreted as possible carriage
Index and comparator tests	Symptoms: cough, fever, chill, chest pain, dyspnoea, malaise, myalgia, diarrhea, wheezing Signs: rales, rhonchi, bronchial breath sounds
Follow-up	Children followed up during admission. Duration between admission and recording of clinical features/initial sample taking was not reported
Notes	In total, 199 children (81%) were treated in hospitals and 3 children (1%) required treatment in the intensive care unit

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Inclusion criteria not based on indicators of disease severity. Co-morbidities in study population: asthma (n = 51), congestive heart failure (n = 7), hepatic disease (n = 1), renal impairment (n = 1)
Acceptable reference standard? All tests	Yes	In total 36 children met laboratory diagnostic criteria for current *M. pneumoniae* infection; 24 children were diagnosed by a fourfold or greater increase in antibody titre between acute and convalescent sera and 12 were diagnosed by positive PCR with persistent high antibody titre. 16 children with a 4-fold or greater increase in antibody titre were also positive by PCR
Acceptable delay between tests?	Unclear	Timing of nasopharyngeal aspirate and acute blood sample collection in relation to recording of clinical features was not reported

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Deerojanawong 2006 *(Continued)*

All tests		
Partial verification avoided? All tests	Yes	Of the 257 children enrolled in the study with a diagnosis of community-acquired pneumonia, paired sera could only be obtained from 245 children
Differential verification avoided? All tests	Yes	All study participants were subjected to the same laboratory tests
Incorporation avoided? All tests	Yes	The diagnosis of *M. pneumoniae* was based on laboratory test results only
Reference standard results blinded? All tests	Yes	Clinical symptoms and signs were recorded during the acute community-acquired pneumonia illness episode, when the results of convalescent serum samples would not have been available
Index test results blinded? All tests	Yes	Clear laboratory criteria for laboratory diagnosis of *M. pneumoniae* were reported
Relevant clinical information? All tests	Unclear	Baseline data on participant age, sex and co-morbidity were recorded. However, unclear whether data on duration of illness were collected at the time of study entry
Uninterpretable results reported? All tests	Yes	Six children had positive PCR results without serological evidence of *M. pneumoniae* infection. These children were considered to be carriers of *M. pneumoniae* and were hence not classified as having current *M. pneumoniae* infection
Withdrawals explained? All tests	Yes	Explained that they were only able to obtain paired sera from 245/257 children. The 12 children from whom convalescent serum samples could not be obtained were excluded from the study population

Kumar 2011

Clinical features and settings	Hospital setting (Lok Nayak Hospital, India) Clinical features for study inclusion: cough and fever with breathlessness of less than 30 days duration, increased respiratory rate on examination, signs of consolidation or bronchopneumonia with or without wheeze on auscultation, radiological findings suggestive of consolidation, bronchopneumonia or interstitial infiltrates with or without hyperinflation
Participants	Children aged 2 months to 12 years admitted to hospital with lower respiratory tract infections Number of participants: 200 Male participants: 127 (63.5%) Number of participants with *M. pneumoniae*: 71 (35.5%)
Study design	Prospective observational cohort study
Target condition and reference standard(s)	*M. pneumoniae* detected using: 1. serological testing of acute and convalescent blood samples (ELISA for IgM and IgG antibodies to *M. pneumoniae*). Serological evidence of *M. pneumoniae* infection was defined as presence of *M. pneumoniae*-specific IgM or IgG or fourfold rise in IgG titre between acute and convalescent sera 2. PCR analysis of nasopharyngeal aspirates

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Kumar 2011 *(Continued)*

	Presence of *M. pneumoniae* infection was defined as *M. pneumoniae* detected using either or both laboratory methods
Index and comparator tests	Symptoms: cough, coryza, afebrile Signs: wheeze audible on auscultation
Follow-up	Duration of follow-up not reported
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Unclear	Co-morbidities in study population were not reported. Did not state whether or not children with co-morbidities were excluded
Acceptable reference standard? All tests	Yes	Children with positive PCR results but negative serology results were still diagnosed with *M. pneumoniae*. However, there was good agreement between PCR and serology results; 20 children had positive PCR results of whom only 3 did not also have serological evidence of *M. pneumoniae* infection
Acceptable delay between tests? All tests	Unclear	Timing of nasopharyngeal aspirate and acute blood sample collection in relation to recording of clinical features was not reported
Partial verification avoided? All tests	Yes	All study participants were subjected to the same laboratory tests
Differential verification avoided? All tests	Yes	All study participants were subjected to the same laboratory tests
Incorporation avoided? All tests	Yes	The diagnosis of *M. pneumoniae* was based on laboratory test results only
Reference standard results blinded? All tests	Yes	Clinical symptoms and signs were recorded during the acute community-acquired pneumonia illness episode, when the results of convalescent serum samples would not have been available
Index test results blinded? All tests	Unclear	Laboratory criteria/thresholds for serological diagnosis of *M. pneumoniae* detection were not reported
Relevant clinical information? All tests	Unclear	Baseline data on participant age and sex were collected. However, unclear whether data on duration of illness were collected at the time of study entry
Uninterpretable results reported? All tests	Yes	Three children had positive PCR results without serological evidence of *M. pneumoniae* infection
Withdrawals explained? All tests	Yes	Data reported for all 200 participants; no withdrawals reported

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Maheshwari 2011

Clinical features and settings	Hospital setting (Maulana Azad Medical College, India) Clinical features for study inclusion: presence of cough and fever with breathlessness of less than 30 days duration, tachypnoea and presence of radiological features of lower respiratory tract infections
Participants	Children aged 6 months to 12 years with clinically suspected lower respiratory tract infections Number of participants: 75 Male participants: 42, (56.0%) Number of participants with *M. pneumoniae*: 23, (30.7%)
Study design	Prospective observational cohort study
Target condition and reference standard(s)	*M. pneumoniae* detected using: 1. serological testing of acute and convalescent blood samples (ELISA for IgM and IgG antibodies to *M. pneumoniae*) 2. PCR analysis of throat swabs Presence of *M. pneumoniae* infection was defined as *M. pneumoniae* detected using either or both laboratory methods
Index and comparator tests	Symptoms: rhinorrhoea, wheezing, dry cough Signs: rales, rhonchi
Follow-up	Duration of follow-up not reported
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Unclear	Co-morbidities in study population were not reported. Did not state whether or not children with co-morbidities were excluded
Acceptable reference standard? All tests	Yes	Children with positive PCR results but negative serology results were still diagnosed with *M. pneumoniae*. However, there was good agreement between PCR and serology results; 5 children had positive PCR results of whom only 1 did not also have serological evidence of *M. pneumoniae* infection
Acceptable delay between tests? All tests	Unclear	Timing of throat swab and acute blood sample collection in relation to recording of clinical features was not reported
Partial verification avoided? All tests	Yes	Tried to obtain convalescent blood samples from all 75 children, but only managed to obtain samples in 45 children
Differential verification avoided? All tests	Yes	Tried to obtain convalescent blood samples from all 75 children, but only managed to obtain samples in 45 children
Incorporation avoided? All tests	Yes	The diagnosis of *M. pneumoniae* was based on laboratory test results only

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Maheshwari 2011 *(Continued)*

Reference standard results blinded? All tests	Yes	Clinical symptoms and signs were recorded during the acute community-acquired pneumonia illness episode, when the results of convalescent serum samples would not have been available
Index test results blinded? All tests	Unclear	Laboratory criteria/thresholds for serological diagnosis of *M. pneumoniae* detection were not reported
Relevant clinical information? All tests	Yes	A detailed history and clinical examination were performed for all participants
Uninterpretable results reported? All tests	Yes	One child had a positive PCR result without serological evidence of *M. pneumoniae* infection
Withdrawals explained? All tests	Yes	Data were presented for all 75 participants. Reported that only managed to obtain convalescent serum samples from 45/75 participants

Principi 2001

Clinical features and settings	Multicentre study performed at 21 centres in Italy (hospital setting) Children were classified into 3 groups based on clinical and radiological findings: 1. acute bronchitis (cough and/or rhonchi with a normal chest radiograph) 2. wheezing (cough and/or dyspnoea with expiratory rales and/or wheezes unrelated to any known specific sensitisation, with a normal chest radiograph or hyperinflation 3. pneumonia (diffuse or lobar pulmonary infiltration evident on chest radiograph)
Participants	Previously healthy children aged 2 to 14 years who had been hospitalised for signs and/or symptoms of community-acquired lower respiratory tract infection Exclusion criteria: severe concomitant diseases (neoplasia, kidney or liver disease, immunodepression, cardiovascular disease, malabsorption syndrome), nosocomial infections, use of antibiotics during the last 48 hours Total number of participants: 613 Male participants: 310 (50.6%) Number of participants with pneumonia: 418 Number of participants with *M. pneumoniae*: 150 (35.9%)
Study design	Prospective observational cohort study
Target condition and reference standard(s)	Acute *M. pneumoniae* infection defined as significant antibody response on paired serum samples (IgM specific antibody >= 1:100; IgG specific antibody >= 1:400 or 4-fold increase in IgG antibody titre) and/or nasopharyngeal aspirate positive for *M. pneumoniae* on PCR analysis Past *M. pneumoniae* infection defined as IgG antibody titre >= 1:100 but < 1:400 without a fourfold increase in paired serum samples and/or nasopharyngeal aspirate positive for *M. pneumoniae* on PCR analysis Convalescent serum samples were obtained 4 to 6 weeks after acute serum samples
Index and comparator tests	Symptoms: cough, rhinitis, tachypnoea, wheezing

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Principi 2001 *(Continued)*

	Signs: fever (temperature >= 37.8 °C), rales, rhonchi
Follow-up	Clinical features (medical history and physical examination) were recorded for each child at the time of admission. Acute serum samples and nasopharyngeal aspirates were obtained at the time of study entry. Children were re-evaluated 4 to 6 weeks after study entry, when convalescent serum samples were obtained
Notes	

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Clearly reported that children with severe concomitant diseases, nosocomial infections and who had received antibiotics within the last 48 hours were excluded from the study
Acceptable reference standard? All tests	Yes	16 children with community-acquired lower respiratory tract infections (acute bronchitis, wheezing or pneumonia) had positive PCR results without serological evidence of acute *M. pneumoniae* infection. The study did not report how many of these children were in the pneumonia subgroup. However, even if all 16 children had been in this subgroup, they would only have represented 11% of the 150 children with pneumonia who were diagnosed with *M. pneumoniae*
Acceptable delay between tests? All tests	No	Clinical symptoms and signs were recorded on admission. Acute serum samples and nasopharyngeal aspirates were taken on enrolment into the study. Mean duration of hospitalisation at time of enrolment ranged from 5.68 days in children with neither *M. pneumoniae* nor *C. pneumoniae* infections to 6.63 days in children with both infections
Partial verification avoided? All tests	Yes	Acute and convalescent serum samples were obtained from all children
Differential verification avoided? All tests	Yes	The same laboratory methods were used to detect *M. pneumoniae* in all children
Incorporation avoided? All tests	Yes	The diagnosis of *M. pneumoniae* was based on laboratory test results only
Reference standard results blinded? All tests	Yes	Clinical symptoms and signs were recorded during the acute community-acquired pneumonia illness episode, when the results of convalescent serum samples would not have been available
Index test results blinded? All tests	Yes	Clear laboratory criteria for diagnosis of acute and past *M. pneumoniae* infection were reported
Relevant clinical information? All tests	Yes	At the time of admission, systematic recordings were made of each patient's medical history, including the date of onset of illness, the underlying respiratory symptoms and the presence of fever (temperature >= 37.8 °C)
Uninterpretable results reported? All tests	Unclear	Sixteen children with community-acquired lower respiratory tract infections had positive PCR results without serological evidence of acute *M. pneumoniae* infection. However, the study did not report how many of these were in the pneumonia subgroup

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Principi 2001 *(Continued)*

Withdrawals explained? All tests	Yes	Data were reported for all 418 children with pneumonia; no withdrawals were reported

Somer 2006

Clinical features and settings	Hospital setting (Istanbul, Turkey) Clinical features for study inclusion: combination of acute respiratory symptoms (tachypnoea, dyspnoea, cough, difficulty in breathing, chest indrawing and nasal flaring or with non specific symptoms such as lethargy, fever and rigours) and chest radiographic findings compatible with pneumonia
Participants	Previously healthy children aged 2 months to 15 years hospitalised because of a diagnosis of community-acquired pneumonia Exclusion criteria: active tuberculosis, malignancy, hospital-acquired pneumonia, underlying pulmonary or immunological disease. This study was undertaken as part of a larger prospective study evaluating the incidence of bacterial and atypical pathogens in hospitalised children with community-acquired pneumonia. As a result of the protocol of this larger study, children who had received antibiotics during the 10 days before admission were excluded Number of participants: 140 Male participants: 85 (60.7%) Number of participants with *M. pneumoniae*: 38 (27%)
Study design	Nested prospective observational cohort study
Target condition and reference standard(s)	*M. pneumoniae* detected based on serological testing of acute and convalescent serum samples (ELISA). Evidence of infection was defined as either a single positive serum IgM titre (>= 1:10) at any visit or a fourfold increase in IgG titres at visit 2
Index and comparator tests	Symptoms: cough, chest indrawing, nasal flaring, fever, wheeze, sputum, runny nose Signs: cyanosis, crepitations, expiration prolonged
Follow-up	A convalescent serum sample was obtained from each child 2 to 4 weeks after the acute serum sample
Notes	A total of 206 children were admitted with community-acquired pneumonia during the study period of whom 47 did not meet the study inclusion criteria (pulmonary tuberculosis, n = 12; congenital immunodeficiency, n = 10; chronic pulmonary disease, n = 9; malignancy, n = 8; antibiotic use in the 10 days before admission, n = 8) All patients were treated with antimicrobials, mostly ampicillin, clarithromycin or cefuroxime

Table of Methodological Quality

Item	Authors' judgement	Description
Representative spectrum? All tests	Yes	Previously healthy children admitted with a diagnosis of community-acquired pneumonia based on clinical and radiological criteria
Acceptable reference standard? All tests	Yes	Serological testing of acute and convalescent serum samples
Acceptable delay between tests?	Yes	Acute serum was obtained within 24 hours of admission and convalescent serum was obtained 2 to 4 weeks later

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Somer 2006 *(Continued)*
All tests

Partial verification avoided? All tests	Yes	Convalescent serum was not obtained from 19 patients who did not return for follow-up appointments. Paired serum samples were obtained from all 140 participants
Differential verification avoided? All tests	Yes	Paired serum samples were obtained from all 140 participants
Incorporation avoided? All tests	Yes	The diagnosis of *M. pneumoniae* was based on laboratory test results only
Reference standard results blinded? All tests	Yes	Data on clinical symptoms and signs were recorded at the time of admission, when laboratory test results would not have been available
Index test results blinded? All tests	Yes	Clear laboratory criteria for diagnosis of *M. pneumoniae* infection were reported
Relevant clinical information? All tests	Yes	A thorough medical history was obtained at admission
Uninterpretable results reported? All tests	No	No intermediate or borderline serology results were reported. Study did not provide definition of intermediate or borderline serology result
Withdrawals explained? All tests	Yes	Convalescent serum was not obtained from 19 patients who did not return for follow-up appointments. These patients were excluded from the study population

ELISA: enzyme-linked immunoadsorbent assay
IgG: immunoglobulin G
IgM: immunoglobulin M
PCR: polymerase chain reaction
WHO: World Health Organization

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

Study	Reason for exclusion
Al-Moyed 2003	Study population consisted of participants aged 10 to 60 years with clinically and radiographically diagnosed lower respiratory tract infections. Reported data on clinical symptoms and signs in all participants according to whether or not *M. pneumoniae* was detected, but did not report these data in children specifically
Al-Rashed 1998	Did not report any data on clinical symptoms or signs
Almasri 2011	Reported data on clinical symptoms and signs in children with community-acquired respiratory tract infections (pneumonia, pharyngitis or tracheobronchitis) in relation to whether or not *M. pneumoniae* was detected. However, these data were not reported specifically in the subgroup of children with community-acquired pneumonia
Angadi 1980	Did not report any data on clinical symptoms or signs

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Antonelli 2009	Reported data on clinical symptoms and signs but not in relation to whether or not *M. pneumoniae* was detected
Baer 2003	Did not report any data on clinical symptoms or signs
Bamba 2006	Did not recruit children with community-acquired pneumonia consecutively. Only recruited children in whom bacterial pathogens, *M. pneumoniae* and *Chlamydia pneumoniae* were felt to be the causative organisms after clinical examination
Bii 2002	Did not report any data on clinical symptoms or signs
Block 1995	Did not report any data on clinical symptoms or signs
Broome 1980	Only reported data on clinical symptoms and signs in children with *M. pneumoniae*
Bunnag 2008	Only reported data on clinical symptoms and signs in children with *M. pneumoniae*
Butun 2006	Reported data on clinical symptoms and signs but not in relation to whether or not *M. pneumoniae* was detected
Chaudhry 1998	Did not report any data on clinical symptoms or signs
Chkhaidze 2006	Did not report any data on clinical symptoms or signs
De Roux 2006	Study was performed in an adult population
Defilippi 2008	Only reported data on clinical symptoms and signs in children with *M. pneumoniae*
Dowdle 1967	Did not report any data on clinical symptoms or signs
Drummond 2000	Did not report any data on clinical symptoms or signs
Dular 1987	Only reported clinical symptoms and signs in children with *M. pneumoniae*
Elkholy 2009	Did not report any data on clinical symptoms or signs
Esposito 2001	Unsuitable comparison group (children with *C. pneumoniae* infection)
Ferwerda 2001	Double-blind, randomised, comparative trial comparing the efficacy of a 3-day course of azithromycin with a 10-day course of co-amoxiclav in the treatment of lower respiratory tract infections in children. Provided data on clinical symptoms and signs according to treatment arm. Did not provide laboratory confirmation of *M. pneumoniae*
Fischer 2002	Reported longer duration of fever as a significant predictor of *M. pneumoniae*, but did not report data on absence or presence or fever or any other clinical features
Forgie 1991	Reported data on clinical symptoms and signs but not in relation to whether or not *M. pneumoniae* was detected
Gendrel 1997	Did not report any data on clinical symptoms or signs
Gimenez Sanchez 2007	Did not perform laboratory tests to detect *M. pneumoniae*
Gomez Campdera 2002	Only reported data on clinical symptoms and signs in children with *M. pneumoniae*

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Guggenbichler 1977	Only reported data on clinical symptoms and signs in children with *M. pneumoniae*
Gutierrez 2005	Did not report any data on clinical symptoms or signs
Harris 1998	Double-blind, randomised, comparative trial comparing the safety and efficacy of azithromycin with amoxicillin/clavulanate or erythromycin for the treatment of community-acquired pneumonia, including atypical pneumonia caused by *M. pneumoniae* and *C. pneumoniae*. Data on clinical symptoms and signs were reported according to treatment arm but according to whether or not *M. pneumoniae* infection was detected
Heinz 1983	Did not report any data on clinical symptoms or signs
Heiskanen-Kosma 1998	Did not report any data on clinical symptoms or signs
Holmes 2001	Did not perform laboratory tests to detect *M. pneumoniae*
Hortal 1994	No *M. pneumoniae*-positive cases detected
Javier Alvarez 2001	Study was performed in an adult population
Jensen 1967	Did not report any data on clinical symptoms or signs
Jokinen 1993	Did not report any data on clinical symptoms or signs
Juven 2000	Did not report any data on clinical symptoms or signs
Kapellerova 2007	Reported complications in children with *M. pneumoniae*. Did not report data on clinical symptoms or signs
Kicinski 2011	Unsuitable comparison group (children with *C. pneumoniae* infection)
King 1991	Did not recruit children with community-acquired pneumonia (recruited children who had not been treated with antibiotics during the previous 7 days whether or not they had respiratory symptoms)
Kogan 2003	Comparative randomised trial to determine the efficacy of azithromycin versus erythromycin and amoxicillin in the treatment of presumed bacterial community-acquired pneumonia in ambulatory children. Children were tested for *M. pneumoniae* (serology and PCR) but data on clinical symptoms and signs were reported according to treatment arm and not according to whether or not *M. pneumoniae* was detected
Korppi 2004	Did not report any data on clinical symptoms or signs
Kurz 2011	Only reported data on clinical symptoms and signs in children with *M. pneumoniae*
Lagerstrom 2003	Study population included children and adults (patients with community-acquired pneumonia aged 10 years and over). Data on clinical symptoms and signs reported but not in relation to whether or not *M. pneumoniae* was detected. Data in children not reported separately
Lassmann 2008	Reported data on clinical symptoms and signs in relation to whether or not atypical infections (*Bordetella pertussis*, *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*) were detected
Lee 2008	Reported data on clinical symptoms and signs but not in relation to whether or not *M. pneumoniae* was detected
Liam 2001	Did not report any data on clinical symptoms or signs

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Lochindarat 2007	Reported data on clinical symptoms and signs in relation to whether or not atypical infections (*M. pneumoniae* or *C. pneumoniae*) were detected
Maltezou 2004	Did not report any data on clinical symptoms or signs
Manfredi 1992	No *M. pneumoniae*-positive cases detected
Marrie 1996	Reported data on clinical symptoms and signs in relation to whether or not atypical infections (*M. pneumoniae*, *C. pneumoniae*, *Legionella* species or respiratory viruses) were detected
Marrie 2005	Study was performed in an adult population
Masia 2006	Reported data on clinical symptoms and signs in relation to whether or not atypical infections (*M. pneumoniae*, *Legionella pneumophila*, *Chlamydophila* species or *Coxiella burnetti*) were detected
Matute 2006	Reported data on clinical symptoms and signs in relation to whether or not pneumococcus was detected
Michelow 2004	Reported data on clinical symptoms and signs in relation to whether or not atypical infections (*M. pneumoniae* or *C. pneumoniae*) were detected
Murphy 1981	Did not report any data on clinical symptoms or signs
Nagalingam 2004	Reported that several symptoms (abdominal pain, chest pain, chills, diarrhea, difficulty breathing, fever, ear pains, headache, hoarseness, muscle pains, productive cough, vomiting/nausea, wheezing and mental confusion) did not significantly affect the prevalence of *M. pneumoniae* in patients with pneumonia but did not report absence or presence of these symptoms in children with or without *M. pneumoniae*
Nagayama 1988	Study population was divided into 3 groups (pneumonia, fever and wheezing). Prevalence of *M. pneumoniae* was estimated in each group but clinical symptoms and signs not reported in relation to whether or not *M. pneumoniae* was detected
Nagayama 1990	Study reported clinical manifestations in children with pleuropneumonia versus children with pneumonia without pleural effusion
Nakayama 2007	Unsuitable comparison group (children in whom other viral and/or bacterial infections were detected)
Ngeow 2005	Reported data on clinical symptoms and signs but not in relation to whether or not *M. pneumoniae* was detected
Ouchi 1999	Unsuitable comparison group (children with *C. pneumoniae* infection)
Pandey 2000	Reported data on clinical symptoms and signs but not in relation to whether or not *M. pneumoniae* was detected
Peng 2009	Recruited children hospitalised with acute respiratory infections but not community-acquired pneumonia specifically. Also excluded children with signs of bacterial infections
Pereyre 2012	Only reported data on clinical symptoms and signs in children with *M. pneumoniae*
Pocheville Guruceta 1998	Recruited patients with wide range of presentations, including respiratory disease, arthritis or skin disease. Only performed *M. pneumoniae* serology on children with clinical features felt to be compatible with *M. pneumoniae* infection

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Study	Reason for exclusion
Prapphal 2006	Reported data on clinical symptoms and signs in relation to whether or not atypical infections (*M. pneumoniae*, *C. pneumoniae* or *Legionella pneumoniae*) were detected
Putman 1975	Case series (children and adults). Only reported data on clinical features in patients with *M. pneumoniae*
Rahman 1990	Did not perform laboratory tests to detect *M. pneumoniae*. Recruited patients with cough and diarrhea
Sakurai 1988	Only reported data on clinical symptoms and signs in children with *M. pneumoniae*
Sakurai 1988a	Did not report any data on clinical symptoms or signs
Samransamruajkit 2008	Clinical outcome data suggest that study population likely to include a high proportion of children with severe underlying comorbidity and/or immunocompromise (mean duration of hospitalisation was 18.8 days and 25% of children developed respiratory failure)
Shenoy 2005	Recruited children with upper and lower acute respiratory tract infections, not community-acquired pneumonia specifically. Age range of study population was not defined
Sidal 2007	Unsuitable comparison group (children with *C. pneumoniae* infection)
Stawarski 2001	Did not report any data on clinical symptoms or signs
Szabo 1977	Did not report any data on clinical symptoms or signs
Tajima 2006	Did not report any data on clinical symptoms or signs
Tinsa 2009	Reported data on clinical symptoms and signs but not in relation to whether or not *M. pneumoniae* was detected
Touati 2010	Only reported clinical symptoms and signs in children with *M. pneumoniae*
Tsolia 2004	Did not report any data on clinical symptoms or signs
Unay 2002	Only reported clinical symptoms and signs in children with *M. pneumoniae*
Van der Straeten 1976	Did not report any data on clinical symptoms or signs
Vervloet 2010	Clinical outcome data suggest that study population likely to include a high proportion of children with severe underlying comorbidity and/or immunocompromise (23% of children with *M. pneumoniae* and 17% without *M. pneumoniae* required mechanical ventilation)
Virkki 2002	Did not report any data on clinical symptoms or signs
Woodhead 1987	Did not report any data on clinical symptoms and signs
Wubbel 1999	Did not report any data on clinical symptoms or signs
Yang 2001	Reported data on clinical symptoms and signs in relation to whether or not atypical infections (*M. pneumoniae* or *C. pneumoniae*) were detected
Yin 2003	Did not report any data on clinical symptoms or signs
Zoricic-Letoja 1995	Did not report any data on clinical symptoms or signs

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

PCR: polymerase chain reaction

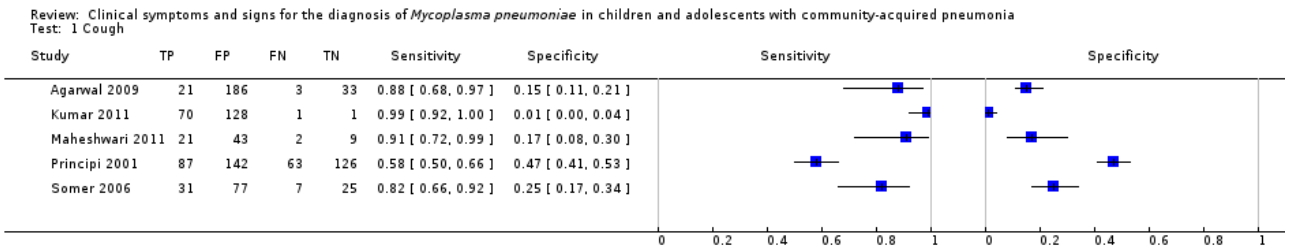
D A T A

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

Test	No. of studies	No. of participants
1 Cough	5	1076
2 Wheeze	6	1291
3 Coryza	4	833
4 Crepitations	5	1121
5 Fever	5	1246
6 Rhonchi	4	928
7 Shortness of breath	1	245
8 Headache	1	243
9 Chest pain	2	488
10 Diarrhoea	2	488
11 Myalgia	1	245

Test 1. Cough.

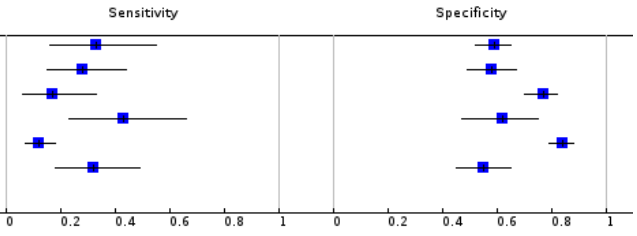


Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Test 2. Wheeze.

Review: Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia
Test: 2 Wheeze

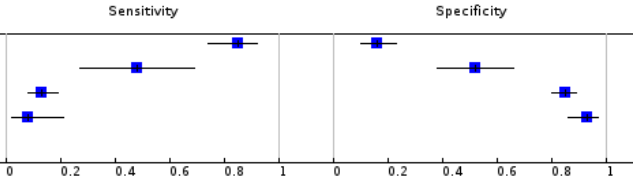
Study	TP	FP	FN	TN	Sensitivity	Specificity
Agarwal 2009	8	90	16	129	0.33 [0.16, 0.55]	0.59 [0.52, 0.65]
Chan 2001	11	54	29	76	0.28 [0.15, 0.44]	0.58 [0.49, 0.67]
Deerojanawong 2006	6	49	30	160	0.17 [0.06, 0.33]	0.77 [0.70, 0.82]
Maheshwari 2011	10	20	13	32	0.43 [0.23, 0.66]	0.62 [0.47, 0.75]
Principi 2001	18	42	132	226	0.12 [0.07, 0.18]	0.84 [0.79, 0.88]
Somer 2006	12	46	26	56	0.32 [0.18, 0.49]	0.55 [0.45, 0.65]



Test 3. Coryza.

Review: Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia
Test: 3 Coryza

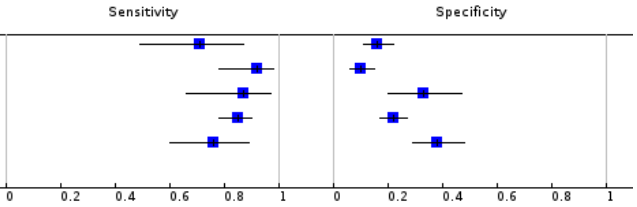
Study	TP	FP	FN	TN	Sensitivity	Specificity
Kumar 2011	60	109	11	20	0.85 [0.74, 0.92]	0.16 [0.10, 0.23]
Maheshwari 2011	11	25	12	27	0.48 [0.27, 0.69]	0.52 [0.38, 0.66]
Principi 2001	19	40	131	228	0.13 [0.08, 0.19]	0.85 [0.80, 0.89]
Somer 2006	3	7	35	95	0.08 [0.02, 0.21]	0.93 [0.86, 0.97]



Test 4. Crepitations.

Review: Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia
Test: 4 Crepitations

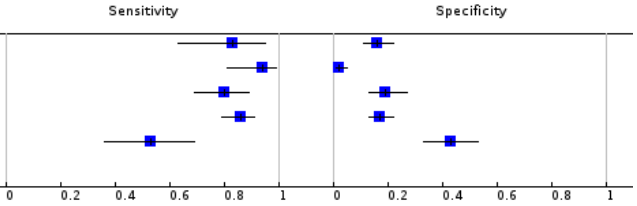
Study	TP	FP	FN	TN	Sensitivity	Specificity
Agarwal 2009	17	184	7	35	0.71 [0.49, 0.87]	0.16 [0.11, 0.22]
Deerojanawong 2006	23	188	3	21	0.92 [0.78, 0.98]	0.10 [0.06, 0.15]
Maheshwari 2011	20	35	3	17	0.87 [0.66, 0.97]	0.33 [0.20, 0.47]
Principi 2001	127	210	23	58	0.85 [0.78, 0.90]	0.22 [0.17, 0.27]
Somer 2006	29	63	9	39	0.76 [0.60, 0.89]	0.38 [0.29, 0.48]



Test 5. Fever.

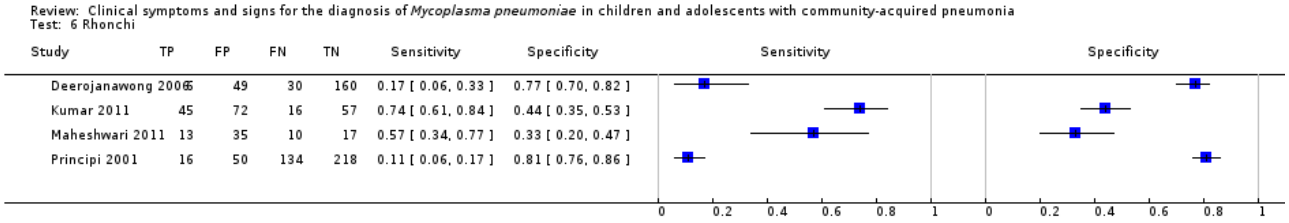
Review: Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia
Test: 5 Fever

Study	TP	FP	FN	TN	Sensitivity	Specificity
Agarwal 2009	20	184	4	35	0.83 [0.63, 0.95]	0.16 [0.11, 0.22]
Deerojanawong 2006	54	205	2	4	0.94 [0.81, 0.99]	0.02 [0.01, 0.05]
Kumar 2011	57	104	14	25	0.80 [0.69, 0.89]	0.19 [0.13, 0.27]
Principi 2001	129	222	21	46	0.86 [0.79, 0.91]	0.17 [0.13, 0.22]
Somer 2006	20	58	18	44	0.53 [0.36, 0.69]	0.43 [0.33, 0.53]

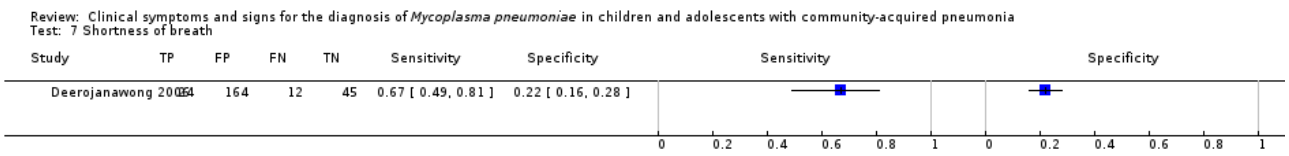


Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

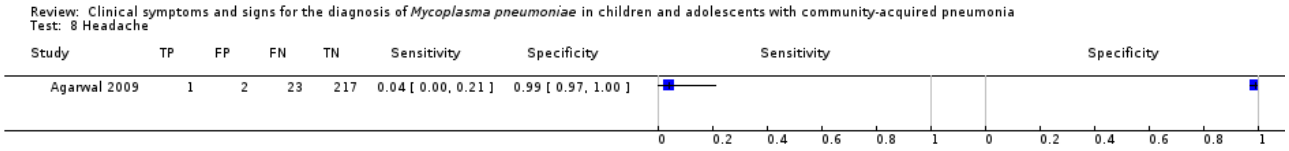
Test 6. Rhonchi.



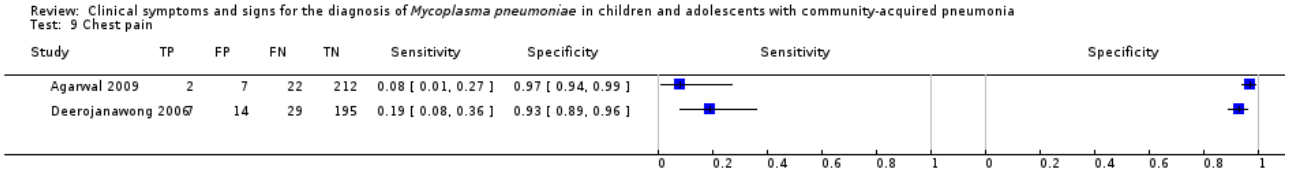
Test 7. Shortness of breath.



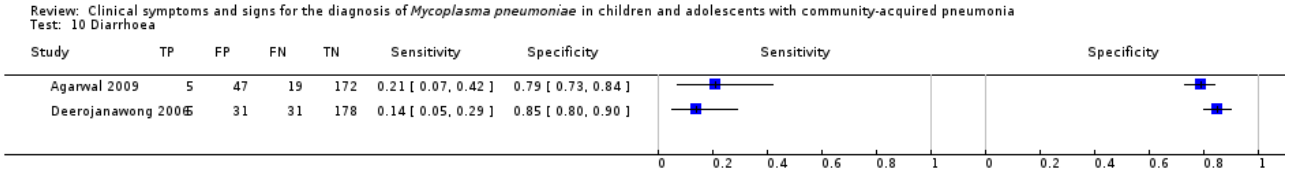
Test 8. Headache.



Test 9. Chest pain.

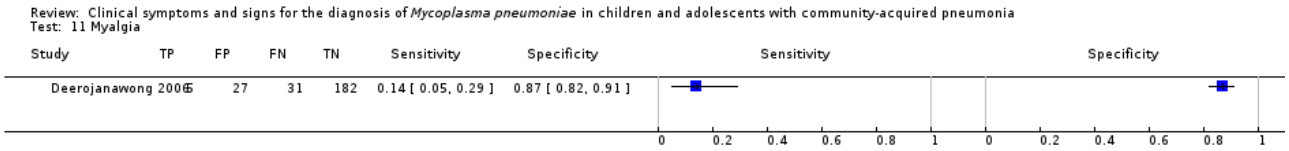


Test 10. Diarrhoea.



Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Test 11. Myalgia.



ADDITIONAL TABLES

Table 1. Quality assessment tool and coding criteria

Item	Yes	No	Unclear
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	• Participants recruited prospectively and consecutively from any healthcare setting • Participants diagnosed with community-acquired pneumonia based on clinical +/- radiological criteria • Characteristics of participants: aged 18 years or younger, no serious underlying co-morbidity (e.g. cystic fibrosis, bronchiectasis, neoplasia) or immunocompromise (HIV-positive or on immunosuppressant medication)	• Participants not recruited prospectively or consecutively • Participants only recruited from limited spectrum of disease severity within the healthcare setting in which the study was conducted • Participants not diagnosed with community-acquired pneumonia • Characteristics of participants: over 18 years of age, serious underlying co-morbidity (e.g. cystic fibrosis, bronchiectasis, neoplasia) or immunocompromise (HIV-positive or on immunosuppressant medication)	• Insufficient information on recruitment method, criteria for diagnosis of community-acquired pneumonia and participant characteristics (age, co-morbidity)
2. Is the reference standard likely to classify the target condition correctly?	• Positive *M. pneumoniae* serology result defined as a significant rise in antibody titre between paired acute and convalescent sera or a high antibody titre on a single serum sample, as per instructions from the manufacturers of the serology assay(s) being used in the study • +/- use of additional laboratory tests alongside serology (e.g. PCR, culture)	• Diagnosis of *M. pneumoniae* not confirmed by laboratory tests • Laboratory confirmation of *M. pneumoniae* does not include serology	• Insufficient information on method of confirming infection with *M. pneumoniae* • Discrepant results between serology and other laboratory tests among participants diagnosed with *M. pneumoniae*
3. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	• Initial serum sample obtained within 24 hours of presentation • Convalescent serum samples obtained 2 to 4 weeks after initial serum samples (in studies where these were taken)	• Criteria for 'Yes' not met	• Insufficient information on timing of sample collection
4. Did the whole sample or a ran-	• Attempted to obtain and test acute serum samples or both acute and convalescent	• Attempted to obtain and test serum samples from	• Insufficient information on the number and char-

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Quality assessment tool and coding criteria *(Continued)*

dom selection of the sample, receive verification using the intended reference standard?	serum samples from all study participants as per instructions from the manufacturers of the serology assay(s) being used in the study	a non random selection of study participants defined by criteria other than those specified by the manufacturers of the serology assay(s) being used in the study	acteristics of participants from whom serum samples were obtained and tested
5. Did patients receive the same reference standard irrespective of the index test result?	• Method of laboratory testing for *M. pneumoniae* was the same for all study participants	• Choice of method of laboratory testing for *M. pneumoniae* related to participants' clinical symptoms and signs	• Insufficient information on whether or not choice of method of laboratory testing for *M. pneumoniae* was related to participants' clinical symptoms and signs
6. Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	• Diagnosis of *M. pneumoniae* based on laboratory test results only	• Diagnosis of *M. pneumoniae* based on laboratory test results and absence or presence of clinical symptoms and signs	• Insufficient information about whether diagnosis of *M. pneumoniae* was made based on laboratory test results only or on absence or presence of clinical symptoms and signs in addition to laboratory test results
7. Were the reference standard results interpreted without knowledge of the results of the index test? (index test results blinded)	• Laboratory results interpreted without knowledge of clinical symptoms and signs	• Laboratory results interpreted with knowledge of clinical symptoms and signs	• Insufficient information about whether laboratory results were interpreted with or without knowledge of clinical symptoms and signs
8. Were the index test results interpreted without knowledge of the results of the reference standard?	• Clinical symptoms and signs reported without knowledge of *M. pneumoniae* laboratory test results	• Clinical symptoms and signs reported with knowledge of *M. pneumoniae* laboratory test results	• Insufficient information about whether clinical features were reported with or without knowledge of *M. pneumoniae* laboratory test results
9. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	• Data on baseline participant characteristics (age, sex, duration of illness) available when data on symptoms and signs were collected • Radiological findings not available to clinician when data on symptoms and signs were collected	• Data on baseline participants characteristics (age, sex, duration of illness) not available when data on symptoms and signs were collected • Radiological findings available to clinician when data on symptoms and signs were collected	• Insufficient information to be able to assess whether or not data on baseline participant characteristics (age, sex, duration of illness) or radiological findings were available when data on symptoms and signs were collected
10. Were uninterpretable/intermediate test results reported?	• Number of participants with intermediate or borderline serology results reported and/or number of participants with discrepant results on serological testing versus other methods of laboratory testing reported	• Study does not report information on numbers of participants with intermediate, borderline and discrepant test results or how these were managed during data analysis	• Insufficient information on numbers of participants with intermediate, borderline and discrepant test results and how these were managed during data analysis

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 1. Quality assessment tool and coding criteria *(Continued)*

	• Description of how the above results were managed during data analysis, or • Absence of intermediate, borderline or discrepant test results reported and definitions of intermediate or borderline results provided		
11. Were withdrawals from the study explained?	• Number of children who were withdrawn from the study reported together with reasons for withdrawal	• Number of children who were withdrawn from the study not reported or explained	• Insufficient information about number of children withdrawn from study and reasons for withdrawal
12. Did the study provide a clear definition of what was considered to be a positive result?	• Criteria for diagnosis of *M. pneumoniae* clearly described for each laboratory test used in study • If more than one laboratory test was used (e.g. serology and PCR), authors provided a clear description of how a diagnosis of *M. pneumoniae* was defined based on the results of each of these tests	• Definition of positive *M. pneumoniae* result not provided	• Insufficient information on definition of positive *M. pneumoniae* result according to result(s) of laboratory test(s) used

Based on recommended quality criteria derived from the QUADAS tool (Reitsma 2009).
PCR: polymerase chain reaction

Table 2. Pre-/post-test probabilities and likelihood ratios with 95% confidence intervals

Symptom/sign	Study	Pre-test probability	Post-test probability (symptom/sign positive)	Post-test probability (symptom/sign negative)	Positive likelihood ratio	Negative likelihood ratio
Cough	Agarwal 2009	0.10 (0.06 to 0.14)	0.10 (0.06 to 0.15)	0.08 (0.02 to 0.22)	1.03 (0.88 to 1.21)	0.83 (0.28 to 2.50)
	Kumar 2011	0.36 (0.29 to 0.43)	0.35 (0.29 to 0.42)	0.50 (0.01 to 0.99)	0.99 (0.96 to 1.03)	1.82 (0.12 to 28.6)
	Maheshwari 2011	0.31 (0.21 to 0.42)	0.33 (0.22 to 0.46)	0.18 (0.02 to 0.52)	1.10 (0.93 to 1.32)	0.50 (0.12 to 2.15)
	Principi 2001	0.36 (0.31 to 0.41)	0.38 (0.32 to 0.45)	0.33 (0.27 to 0.41)	1.09 (0.92 to 1.31)	0.89 (0.71 to 1.12)
	Somer 2006	0.27 (0.20 to 0.35)	0.29 (0.20 to 0.38)	0.22 (0.09 to 0.40)	1.08 (0.90 to 1.30)	0.75 (0.36 to 1.60)
Wheeze	Agarwal 2009	0.10 (0.06 to 0.14)	0.08 (0.04 to 0.15)	0.11 (0.06 to 0.17)	0.81 (0.45 to 1.46)	1.13 (0.84 to 1.53)
	Chan 2001	0.24 (0.17 to 0.31)	0.17 (0.90 to 0.28)	0.28 (0.16 to 0.55)	0.66 (0.39 to 1.14)	1.24 (0.98 to 1.58)
	Deerojanawong 2006	0.15 (0.11 to 0.20)	0.11 (0.04 to 0.22)	0.16 (0.11 to 0.22)	0.71 (0.33 to 1.54)	1.09 (0.92 to 1.28)
	Maheshwari 2011	0.31 (0.21 to 0.42)	0.33 (0.17 to 0.53)	0.29 (0.16 to 0.44)	1.13 (0.63 to 2.02)	0.92 (0.61 to 1.40)

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 2. Pre-/post-test probabilities and likelihood ratios with 95% confidence intervals *(Continued)*

	Principi 2001	0.36 (0.31 to 0.41)	0.30 (0.19 to 0.43)	0.37 (0.32 to 0.42)	0.77 (0.46 to 1.28)	1.04 (0.97 to 1.13)
	Somer 2006	0.27 (0.20 to 0.35)	0.21 (0.11 to 0.33)	0.32 (0.22 to 0.43)	0.70 (0.42 to 1.17)	1.25 (0.94 to 1.65)
Coryza	Kumar 2011	0.36 (0.29 to 0.43)	0.36 (0.28 to 0.43)	0.35 (0.19 to 0.55)	1.00 (0.88 to 1.13)	1.00 (0.51 to 1.97)
	Mahesh-wari 2011	0.31 (0.21 to 0.42)	0.31 (0.16 to 0.48)	0.31 (0.17 to 0.48)	0.99 (0.60 to 1.66)	1.00 (0.51 to 1.97)
	Principi 2001	0.36 (0.31 to 0.41)	0.32 (0.21 to 0.46)	0.36 (0.32 to 0.42)	0.85 (0.51 to 1.41)	1.03 (0.95 to 1.11)
	Somer 2006	0.27 (0.20 to 0.35)	0.30 (0.07 to 0.65)	0.27 (0.20 to 0.35)	1.15 (0.31 to 4.22)	0.99 (0.89 to 1.10)
Crepita-tions	Agarwal 2009	0.10 (0.06 to 0.14)	0.08 (0.05 to 0.13)	0.17 (0.07 to 0.31)	0.84 (0.65 to 1.10)	1.83 (0.91 to 3.65)
	Deerojana-wong 2006	0.15 (0.11 to 0.20)	0.15 (0.11 to 0.20)	0.13 (0.03 to 0.32)	1.02 (0.91 to 1.14)	0.83 (0.26 to 2.64)
	Mahesh-wari 2011	0.31 (0.21 to 0.42)	0.36 (0.24 to 0.50)	0.15 (0.03 to 0.38)	1.29 (1.01 to 1.65)	0.40 (0.13 to 1.23)
	Principi 2001	0.36 (0.31 to 0.41)	0.38 (0.32 to 0.43)	0.28 (0.19 to 0.40)	1.08 (0.99 to 1.19)	0.71 (0.46 to 1.1)
	Somer 2006	0.27 (0.20 to 0.35)	0.32 (0.22 to 0.42)	0.19 (0.09 to 0.33)	1.24 (0.98 to 1.56)	0.62 (0.33 to 1.15)
Fever	Agarwal 2009	0.10 (0.06 to 0.14)	0.10 (0.06 to 0.15)	0.10 (0.03 to 0.24)	0.99 (0.82 to 1.20)	1.04 (0.41 to 2.68)
	Deerojana-wong 2006	0.15 (0.11 to 0.20)	0.14 (0.10 to 0.19)	0.33 (0.04 to 0.78)	0.96 (0.89 to 1.05)	2.90 (0.55 to 15.27)
	Kumar 2011	0.36 (0.29 to 0.43)	0.35 (0.28 to 0.43)	0.36 (0.21 to 0.53)	1.00 (0.86 to 1.15)	1.02 (0.57 to 1.83)
	Principi 2001	0.36 (0.31 to 0.41)	0.37 (0.32 to 0.42)	0.31 (0.21 to 0.44)	1.04 (0.95 to 1.13)	0.82 (0.51 to 1.31)
	Somer 2006	0.27 (0.20 to 0.35)	0.26 (0.16 to 0.37)	0.29 (0.18 to 0.42)	0.93 (0.66 to 1.31)	1.10 (0.73 to 1.64)
Rhonchi	Deerojana-wong 2006	0.15 (0.11 to 0.20)	0.11 (0.04 to 0.22)	0.16 (0.11 to 0.22)	0.71 (0.33 to 1.54)	1.09 (0.92 to 1.28)
	Kumar 2011	0.36 (0.29 to 0.43)	0.38 (0.30 to 0.48)	0.22 (0.13 to 0.33)	1.32 (1.07 to 1.64)	0.59 (0.37 to 0.94)
	Mahesh-wari 2011	0.31 (0.21 to 0.42)	0.27 (0.15 to 0.42)	0.37 (0.19 to 0.58)	0.84 (0.56 to 1.26)	1.33 (0.72 to 2.44)

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Table 2. Pre-/post-test probabilities and likelihood ratios with 95% confidence intervals *(Continued)*

	Principi 2001	0.36 (0.31 to 0.41)	0.24 (0.15 to 0.36)	0.38 (0.33 to 0.43)	0.57 (0.34 to 0.97)	1.10 (1.01 to 1.19)
Shortness of breath	Deerojana-wong 2006	0.15 (0.11 to 0.20)	0.13 (0.08 to 0.18)	0.21 (0.11 to 0.34)	0.85 (0.67 to 1.08)	1.55 (0.91 to 2.63)
Headache	Agarwal 2009	0.10 (0.06 to 0.14)	0.04 (0.00 to 0.21)	0.01 (0.00 to 0.03)	4.56 (0.43 to 48.48)	0.97 (0.89 to 1.05)
Chest pain	Agarwal 2009	0.10 (0.06 to 0.14)	0.22 (0.03 to 0.60)	0.09 (0.06 to 0.14)	2.61 (0.57 to 11.85)	0.95 (0.84 to 1.07)
	Deerojana-wong 2006	0.15 (0.11 to 0.20)	0.33 (0.15 to 0.57)	0.13 (0.09 to 0.18)	2.90 (1.26 to 6.69)	0.86 (0.73 to 1.02)
Diarrhoea	Agarwal 2009	0.10 (0.06 to 0.14)	0.10 (0.03 to 0.21)	0.10 (0.06 to 0.15)	0.97 (0.43 to 2.20)	1.01 (0.81 to 1.25)
	Deerojana-wong 2006	0.15 (0.11 to 0.20)	0.14 (0.05 to 0.29)	0.15 (0.10 to 0.20)	0.94 (0.39 to 2.25)	1.01 (0.88 to 1.17)
Myalgia	Deerojana-wong 2006	0.15 (0.11 to 0.20)	0.16 (0.05 to 0.33)	0.15 (0.10 to 0.20)	1.08 (0.44 to 2.61)	0.99 (0.86 to 1.14)

APPENDICES

Appendix 1. MEDLINE search strategy

1. Pneumonia/
2. Pneumonia, Bacterial/
3. Pneumonia, Mycoplasma/
4. mycoplasma pneumon*.tw.
5. "m. pneumoniae".tw.
6. (community-acquired pneumon* or community acquired pneumon*).tw.
7. or/1-6
8. Cough/
9. cough*.tw.
10. wheez*.tw.
11. "shortness of breath".tw.
12. sore throat*.tw.
13. coryza.tw.
14. "chest pain".tw.
15. crepitation*.tw.
16. Fever/
17. fever*.tw.
18. Exanthema/
19. (rash or rashes).tw.
20. exp Diarrhea/
21. (diarrhoea or diarrhea).tw.
22. myalgia.tw.
23. Headache/
24. headache*.tw.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

25.clinical assessment*.tw.
26.clinical feature*.tw.
27.(symptom* or sign* or characteristic* or manifestation*).tw.
28.or/8-27
29.7 and 28
30.exp Infant/
31.(infant* or infancy or newborn* or baby* or babies or neonat* or preterm* or prematur*).tw.
32.exp Child/
33.(child* or schoolchild* or school age* or preschool* or kid or kids or toddler*).tw.
34.Adolescent/
35.(adoles* or teen* or boy* or girl*).tw.
36.Minors/
37.Puberty/
38.(minor* or pubert* or pubescen*).tw.
39.exp Pediatrics/
40.(pediatric* or paediatric*).tw.
41.exp Schools/
42.(nursery school* or kindergar* or primary school* or secondary school* or elementary school* or high school* or highschool*).tw.
43.or/30-42
44.29 and 43
45.Pneumonia, Mycoplasma/di [Diagnosis]
46.Pneumonia, Bacterial/di [Diagnosis]
47.45 or 46
48.43 and 47
49.44 or 48

Appendix 2. EMBASE search strategy

1. *PNEUMONIA/
2. bacterial pneumonia/ or infectious pneumonia/
3. Mycoplasma pneumonia/
4. COMMUNITY ACQUIRED PNEUMONIA/
5. mycoplasma pneumon*.tw.
6. "m. pneumoniae".tw.
7. (community-acquired pneumon* or community acquired pneumon*).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. coughing/ or wheezing/
10. cough*.tw.
11. wheez*.tw.
12. "short of breath*".tw.
13. "shortness of breath".tw.
14. sore throat*.tw.
15. coryza.tw.
16. "chest pain".tw.
17. crepitation*.tw.
18. fever/
19. (fever* or febrile).tw.
20. exp rash/
21. (rash or rashes).tw.
22. diarrhea/
23. (diarrhoea* or diarrhea*).tw.
24. myalgia.tw.
25. HEADACHE/
26. (headache* or head ache*).tw.
27. clinical feature/
28. clinical assessment*.tw.
29. clinical feature*.tw.
30. (symptom* or sign* or characteristic* or manifestation*).tw.

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

31. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. 8 and 31
33. exp infant/
34. (infant* or infancy or newborn* or baby* or babies or neonat* or preterm* or prematur*).tw.
35. child/ or boy/ or girl/ or preschool child/ or school child/ or toddler/
36. (child* or schoolchild* or school age* or preschool* or kid or kids or toddler*).tw.
37. adolescent/
38. (adoles* or teen* or boy* or girl*).tw.
39. juvenile/
40. Puberty/
41. (minor* or pubert* or pubescen*).tw.
42. pediatrics/
43. (pediatric* or paediatric*).tw.
44. school/ or high school/ or kindergarten/ or middle school/ or nursery school/ or primary school/
45. (nursery school* or kindergar* or primary school* or secondary school* or elementary school* or high school* or highschool*).tw.
46. 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47. 32 and 46

CONTRIBUTIONS OF AUTHORS

KW, AH and DM developed the scope of the protocol.
RP developed the data analysis plan.
KW, PG, AT, DM and AH developed the search strategy and criteria for quality assessment of articles.
All authors were involved in writing the protocol.
KW and PG screened articles, assessed methodological quality and extracted data from included studies.
KW and RP performed the data analysis.
KW wrote the first draft of the review.
All authors contributed towards the final manuscript.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- Department of Primary Care Health Sciences, University of Oxford, UK.

External sources

- National Institute for Health Research, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had intended to assess the diagnostic value of both individual and combinations of clinical symptoms and signs. However, we were only able to analyze individual clinical features because none of our included studies reported data on combinations of clinical symptoms and signs. In our protocol we had proposed to extract and analyze data on rash and sore throat. However, data on rash were not reported in our included studies. One study presented data on sore throat, but this was not present in any children within the study population (Agarwal 2009). We summarised study-specific sensitivity and specificity values with 95% CIs using forest plots. We also calculated 95% CIs for post-test probabilities based on the absence or presence of each clinical feature studied.

In our protocol, we stated that we would add an item to our quality assessment tool (item 12) on whether a study provided a clear definition of what was considered to be a positive *M. pneumoniae* result. However, we decided not to include this item in our review because, having extracted data from our included studies, we felt that items 1 (representative spectrum) and 2 (acceptability of the reference standard) would be more appropriate factors on which to base our sensitivity analysis. We included an additional criterion to item 1 (representative spectrum) stating that we would not consider a study which only recruited participants from a limited spectrum of disease severity within that study's chosen healthcare setting to have included a representative spectrum of patients. We had planned to perform sensitivity analyses based on items 10 (reporting of uninterpretable or intermediate test results) and 11 (explanation of withdrawals) of our quality assessment tool but did not have sufficient data to do so.

We had also planned to explore several factors as potential sources of heterogeneity: participant age group (preschool (up to four years) versus school age (five to 12 years) versus adolescents (13 to 18 years)), healthcare setting (community versus hospital), method of diagnosing community-acquired pneumonia (based on clinical criteria only or on clinical and radiological criteria), serological methods of

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

diagnosing *M. pneumoniae* (high antibody titre on single serum sample versus significant rise in antibody titre) and use of other laboratory methods alongside serology to diagnose *M. pneumoniae*. However, in this review, we only had sufficient data to explore the use of other laboratory methods alongside serology as a potential source of heterogeneity in our analysis of wheeze. Among the six studies which reported data on wheeze, only one study (Agarwal 2009) diagnosed community-acquired pneumonia based on clinical criteria only and diagnosed *M. pneumoniae* based on a single high antibody titre. We therefore did not investigate these factors as potential sources of heterogeneity, since we had already performed sensitivity analyses excluding data from Agarwal 2009. We did not have sufficient data to perform investigations of heterogeneity for any of the other clinical symptoms or signs studied in this review. We were unable to explore healthcare setting as a potential source of heterogeneity because all of our included studies were conducted in hospital settings. We were also unable to explore participant age group as a potential source of heterogeneity because our included studies did not report data stratified according to our age groups of interest.

INDEX TERMS

Medical Subject Headings (MeSH)

*Mycoplasma pneumoniae; Community-Acquired Infections [diagnosis] [microbiology]; Pneumonia, Mycoplasma [*diagnosis]; Randomized Controlled Trials as Topic; Respiratory Sounds; Symptom Assessment [*methods]

MeSH check words

Adolescent; Child; Humans

Copyright © 2012 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.