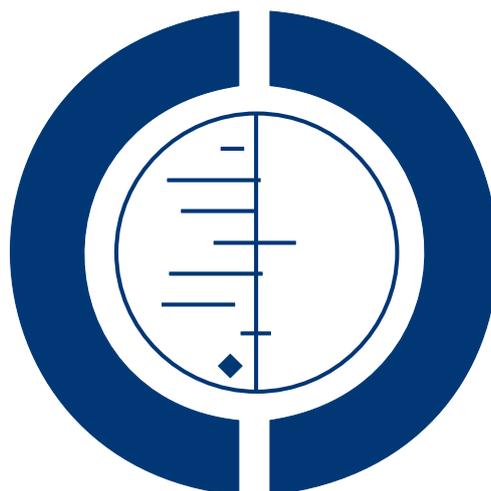


# Antibiotics for community-acquired lower respiratory tract infections secondary to *Mycoplasma pneumoniae* in children (Review)

Mulholland S, Gavranich JB, Chang AB



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[Intervention Review]

# Antibiotics for community-acquired lower respiratory tract infections secondary to *Mycoplasma pneumoniae* in children

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## ABSTRACT

### Background

*Mycoplasma pneumoniae* (*M. pneumoniae*) is widely recognised as an important cause of community-acquired lower respiratory tract infection (LRTI) in children. Pulmonary manifestations are typically tracheobronchitis or pneumonia but *M. pneumoniae* is also implicated in wheezing episodes in both asthmatic and non-asthmatic individuals. Although antibiotics are used to treat LRTI, a review of several major textbooks offers conflicting advice for using antibiotics in the management of *M. pneumoniae* LRTI in children.

### Objectives

To determine whether antibiotics are effective in the treatment of childhood LRTI secondary to *M. pneumoniae* infections acquired in the community.

### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 1), which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to February 2010) and EMBASE (1980 to February 2010).

### Selection criteria

Randomised controlled trials (RCTs) comparing antibiotics commonly used for treating *M. pneumoniae* (i.e. macrolide, tetracycline or quinolone classes) versus placebo, or antibiotics from any other class in the treatment of children under 18 years of age with community-acquired LRTI secondary to *M. pneumoniae*.

### Data collection and analysis

The review authors independently selected trials for inclusion and assessed methodological quality. We extracted and analysed relevant data separately. Disagreements were resolved by consensus.

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## Main results

A total of 1912 children were enrolled from seven studies. Data interpretation was limited by the inability to extract data that referred to children with *M. pneumoniae*. In most studies, clinical response did not differ between children randomised to a macrolide antibiotic and children randomised to a non-macrolide antibiotic. In one controlled study (of children with recurrent respiratory infections, whose acute LRTI was associated with *Mycoplasma*, *Chlamydia* or both by polymerase chain reaction, and/or paired sera) 100% of children treated with azithromycin had clinical resolution of their illness compared to 77% not treated with azithromycin at one month.

## Authors' conclusions

There is insufficient evidence to draw any specific conclusions about the efficacy of antibiotics for this condition in children (although one trial suggests macrolides may be efficacious in some children with LRTI secondary to *Mycoplasma*). The use of antibiotics has to be balanced with possible adverse events. There is still a need for high quality, double-blinded RCTs to assess the efficacy and safety of antibiotics for LRTI secondary to *M. pneumoniae* in children.

## PLAIN LANGUAGE SUMMARY

### Antibiotics to treat community-acquired lower respiratory tract infections secondary to *Mycoplasma pneumoniae* in children

*Mycoplasma pneumoniae* (*M. pneumoniae*) is a bacterial infection often responsible for lower respiratory tract infections (LRTI) in children. The infection can present in a number of different ways and the most common respiratory manifestations are acute bronchitis, pneumonia or wheezing. The illness is generally self-limiting with symptoms that can last several weeks but may (occasionally) also cause severe pneumonia. Antibiotics are often given to children with *M. pneumoniae* LRTI. We found seven studies (1912 children) but could not extract relevant data relating to efficacy or adverse events. Thus there is still insufficient evidence to show conclusively that antibiotics are effective in children with LRTI caused by *M. pneumoniae*.

## BACKGROUND

### Description of the condition

*Mycoplasma pneumoniae* (*M. pneumoniae*) is widely recognised as an important cause of community-acquired lower respiratory tract infection (LRTI) in children, accounting for 14% to 34% of cases (Kogan 2003; Michelow 2004; Nelson 2002; Principi 2002). The highest attack rates are reported to occur in five to 20 year-olds and the infection is usually self-limiting, with symptoms lasting several weeks (Nelson 2002; Rudolph 2003). More recently *M. pneumoniae* has been identified as an important cause of LRTI in children under five years of age (Principi 2001). Pulmonary manifestations are typically tracheobronchitis or pneumonia but can be complicated by pleural effusion, lung abscess, pneumothorax, bronchiectasis and respiratory distress syndrome (Principi 2002). *M. pneumoniae* is also implicated in wheezing episodes in both asthmatic and non-asthmatic individuals (Phelan 1994; Principi 2001). Uncommon extrapulmonary manifestations may include erythema multiforme, myocarditis, encephalitis, Guillain-Barre syndrome,

transverse myelitis and haemolytic anaemia (Nelson 2002; Waites 2003). Radiographic findings are quite variable and non-diagnostic (Principi 2001). In some cases there can be significant radiological changes in the absence of clinical signs on auscultation of the chest (so-called 'walking pneumonia') (Rudolph 2003).

### Description of the intervention

Antibiotics are frequently used to treat LRTI and empiric antibiotic therapy is often chosen to cover both bacteria and atypical organisms (Kogan 2003). A review of several major textbooks offers conflicting advice for management of *M. pneumoniae* LRTI. The chapter on *M. pneumoniae* in a paediatric respiratory textbook (Phelan 1994) mentions that there is little evidence of beneficial effect from antibiotic therapy. This is in contrast to the recommendations in a major general paediatric textbook (Rudolph 2003) and paediatric infectious disease textbook (Katz 1998) which state that erythromycin is the treatment of choice.

## How the intervention might work

The use of antibiotics in treating LRTI in children would be expected to reduce the severity or duration (or both) of the infection and its associated symptoms.

## Why it is important to do this review

The conclusion that antibiotics are effective in *M. pneumoniae* chest infections seems to have been drawn from trials of antibiotic therapy for community-acquired or atypical pneumonia, where *M. pneumoniae* was identified as a causative organism in a subgroup of cases. In these studies, macrolide antibiotics, to which *M. pneumoniae* is susceptible, have been compared to non-macrolide antibiotics. However, it is not always possible to draw meaningful conclusions from the results, as the numbers of individuals with *M. pneumoniae* are small in most trials (Block 1995; Kogan 2003; Wubbel 1999).

Identification of *M. pneumoniae* infection as the causative infectious agent may, however, pose difficulties. Serological tests are the most common method used to diagnose *M. pneumoniae* infections, but can lead to difficulties with interpretation (Principi 2001). Measurement of immunoglobulin M (IgM) is used to diagnose acute infection, but the accuracy of the test depends on the method used. Not all methods are specific for IgM and an elevated IgM may persist for months after the acute infection (Murray 2003). Immuno-fluorescent antibody (IFA) assay is more sensitive and specific than the complement fixation (CF) test (Murray 2003; Principi 2001). Identification of *M. pneumoniae* in nasopharyngeal secretions by culture or polymerase chain reaction (PCR) may also cause difficulties with interpretation as this organism can persist for variable periods following the acute infection (Murray 2003). The 'gold standard' for diagnosis of *M. pneumoniae* infection is a four-fold increase in total antibody titre as measured in paired sera (Katz 1998; Murray 2003).

## OBJECTIVES

To determine whether antibiotics are effective in the treatment of childhood LRTI secondary to *M. pneumoniae* infections acquired in the community.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs) comparing antibiotics from the macrolide, tetracycline or quinolone class (i.e. antibiotics that are efficacious for mycoplasma) versus placebo, or antibiotics from any other class (i.e. medications that are not efficacious for mycoplasma).

#### Types of participants

Trials that included children under 18 years of age with community-acquired LRTI secondary to *M. pneumoniae*. Diagnosis of *M. pneumoniae* infection was via either a four-fold rise in total antibody titre from paired sera or total antibody titre  $\geq 1:512$  on a single specimen. We included other methods of diagnosis, such as culture or PCR of *M. pneumoniae* in nasopharyngeal secretions or demonstration of elevated IgM on a single specimen (IgM titre  $\geq 1:10$ ), and analysed these separately as a subgroup.

#### Exclusion criteria

1. Children with underlying chronic cardiorespiratory illnesses, such as cystic fibrosis, bronchiectasis, immunodeficiency, chronic neonatal lung disease and symptomatic congenital heart disease.
2. Children with non-community acquired LRTI.

#### Types of interventions

We evaluated two separate treatment regimes.

1. Any antibiotic versus placebo.
  2. Antibiotics from the macrolide, tetracycline or quinolone class versus placebo or antibiotics from any other class.
- We included trials that allowed the use of other medications or interventions in addition to antibiotic therapy if all participants had equal access to such medications or interventions.

#### Types of outcome measures

We made attempts to obtain data on at least the following outcome measures.

#### Primary outcomes

1. Proportions of participants who were not improved at follow up. Failure to improve was measured according to the hierarchy listed below.

#### Secondary outcomes

1. Mean difference in symptoms and signs (mean improvement in clinical state).
2. Proportions requiring hospitalisation.
3. Proportions experiencing pulmonary complications (empyema, pleural effusion, air leak).

4. Proportions experiencing non-pulmonary complications.
5. Proportions experiencing adverse effects (for example, nausea, diarrhoea, abdominal pain, rash).
6. Proportions experiencing complications (for example, requirement for medication change).

The proportions of participants who failed to improve on treatment and the mean clinical improvement were determined using the following hierarchy of assessment measures. All outcomes were reported but where two or more assessment measures were reported in the same study and conflicting results were obtained, we used the outcome measure that was listed first in the hierarchy.

1. Objective measurements of cough indices (cough frequency).
2. Symptomatic (cough, wheeze, dyspnoea, malaise, general well-being, headache) - assessed by the child (Likert scale, visual analogue scale, level of interference of symptoms, diary, quality of life).
3. Symptomatic (cough, wheeze, dyspnoea, malaise, general well-being, headache) - assessed by the parents/carers (Likert scale, visual analogue scale, level of interference of symptoms, diary, quality of life).
4. Symptomatic (cough, wheeze, dyspnoea, malaise, general well-being, headache) - assessed by the clinician (Likert scale, visual analogue scale, level of interference of symptoms, diary, quality of life).
5. Fever.
6. Non-clinical outcomes (chest radiology, white cell count, C-reactive protein, erythrocyte sedimentation rate, lung function).
7. Eradication of *M. pneumoniae* by PCR evaluation.

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 1), which contains the Acute Respiratory Infection Group's Specialised Register, MEDLINE (1966 to February Week 2, 2010) and EMBASE (1980 to February 2010).

The following search terms were used for MEDLINE and CENTRAL and adapted for EMBASE (see [Appendix 1](#)). The search terms used in MEDLINE were combined with a sensitive search strategy for identifying child studies ([Boluyt 2008](#)) and the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format ([Lefebvre 2008](#)). The previous search strategy is described in [Appendix 2](#).

### MEDLINE (Ovid)

1 exp MYCOPLASMA/

2 exp Mycoplasma pneumoniae/  
 3 mycoplasma.tw.  
 4 "m. pneumoniae".tw.  
 5 or/1-4  
 6 exp BRONCHITIS/  
 7 exp PNEUMONIA/  
 8 exp Respiratory Tract Infections/  
 9 bronchit\*.tw.  
 10 pneumon\*.tw.  
 11 wheez\*.tw.  
 12 tracheobronchit\*.tw.  
 13 respiratory tract infection\*.tw.  
 14 acute respiratory infection\*.tw.  
 15 or/6-14  
 16 exp Anti-Bacterial Agents/  
 17 exp MACROLIDES/  
 18 exp QUINOLONES/  
 19 exp TETRACYCLINES/  
 20 antibiotic\*.tw,nm.  
 21 (macrolide\* or erythromycin or roxithromycin or clarithromycin or azithromycin).tw,nm.  
 22 or/16-21  
 23 5 and 15 and 22  
 24 exp Infant/  
 25 (infant\* or infancy or newborn\* or baby\* or babies or neonat\* or preterm\* or prematur\*).tw.  
 26 exp Child/  
 27 (child\* or schoolchild\* or school age\* or preschool\* or kid or kids or toddler\*).tw.  
 28 Adolescent/  
 29 (adoles\* or teen\* or boy\* or girl\*).tw.  
 30 Minors/  
 31 Puberty/  
 32 (minor\* or pubert\* or pubescen\*).tw.  
 33 exp Pediatrics/  
 34 (pediatric\* or paediatric\*).tw.  
 35 exp Schools/  
 36 (nursery school\* or kindergar\* or primary school\* or secondary school\* or elementary school\* or high school\* or highschool\*).tw.  
 37 or/24-36  
 38 37 and 23  
 There were no language or publication restrictions.

### Searching other resources

We checked all references for reports of trials.

## Data collection and analysis

### Selection of studies

The review authors (JG, AC, SM) independently reviewed literature searches from the title, abstract or descriptions, to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. The review authors (JG, AC, SM) independently selected trials for inclusion from the full text using specific criteria.

### Data extraction and management

The review authors (JG, AC, SM) independently extracted data and resolved disagreement by consensus. We reviewed trials that satisfied the inclusion criteria and recorded the following information: study setting; year of study; source of funding; patient recruitment details (including number of eligible children); inclusion and exclusion criteria; randomisation and allocation concealment method; numbers of participants randomised; blinding (masking) of participants, care providers and outcome assessors; intervention (type of anti-microbials, dose, duration); control (type, dose, duration); co-interventions; numbers of patients not followed up; reasons for withdrawals from study protocol (clinical, side effects, refusal and other); details on side effects of therapy; and whether intention-to-treat (ITT) analyses were possible. We extracted data on the outcomes described previously. The review authors requested further information from the study authors where required.

### Assessment of risk of bias in included studies

In the original review (Gavranich 2005a) the review authors (JG, AC) utilised the Jadad and quality assessment scores. With this update, the review authors (JG, AC, SM) independently assessed the quality of studies included in the review using the 'Risk of bias' table available in RevMan 5 (RevMan 2008), in accordance with the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). We assessed five components of quality.

1. Adequate sequence generation. This assesses the quality of the method of randomisation.
2. Allocation concealment. This assesses whether or not enrolling staff were aware of the group to which participants would be allocated.
3. Blinding. This assesses the extent of blinding, with participant/caregiver and outcome assessor blinding taken into account.
4. Follow up. This assesses whether the proportion of participants lost to follow up is admissible, and whether adequate reasons for the losses were made available.
5. Reporting of participants by allocation group. This assesses whether the results were reported relative to the treatment groups.

### Measures of treatment effect

In the protocol we planned to calculate relative and absolute risk reductions using an ITT analysis for the dichotomous outcome variables of each individual study. However, data were unavailable.

### Dealing with missing data

The review authors wrote to the trial authors to enquire about availability of data but we did not receive any replies.

### Assessment of heterogeneity

In the protocol we planned to describe any heterogeneity between the study results and, depending upon the number of trials included in the review, a funnel plot was planned to look for publication bias. However, data were unavailable and no studies were included in a meta-analysis.

### Data synthesis

In the protocol we planned to include the results from studies that met the inclusion criteria and report any of the outcomes of interest in the subsequent meta-analysis. We planned to calculate the summary weighted risk ratio and 95% confidence interval (CI) (fixed-effect model) using the inverse of the variance of each study result for weighting (Cochrane statistical package, Review Manager 4.2). We planned to calculate the number needed to treat using the summary odds ratio and the average control event rate described in the relevant studies. We stated in the protocol that the cough indices were assumed to be normally distributed continuous variables so the mean difference in outcomes could be estimated (weighted mean difference). In studies that reported outcomes using different measurement scales, the standardized mean difference would be estimated. However, data were unavailable.

### Subgroup analysis and investigation of heterogeneity

In the protocol we intended to perform an a priori subgroup analysis for the following.

1. Children aged seven years and older.
2. Intervention type (class of antibiotics).
3. Diagnostic criteria used for identification of *M. pneumoniae*.

However, data were unavailable.

### Sensitivity analysis

In the protocol we planned a sensitivity analysis to assess the impact of the potentially important factors on overall outcomes.

1. Study quality.
2. Study size.
3. Variation in the inclusion criteria.
4. Differences in the medications used and duration of treatment in the intervention and comparison groups.
5. Differences in outcome measures.

6. Analysis by 'treatment received' rather than ITT. However, data were unavailable.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

### Results of the search

The initial search identified 91 potentially relevant titles. After reviewing the abstracts, we obtained 17 papers in full text for consideration for inclusion into the review. We included seven studies and details are provided in the [Characteristics of included studies](#) table. Three of the included studies were non-English: German (Ruhmann 1982) and Spanish (Gomez Campdera 1996; Saez-Llorens 1998).

The updated search in 2009 identified 20 new records, of which nine were considered for inclusion. One was included (Esposito 2005). We excluded two because of inappropriate interventions (Bradley 2007; Lee 2008), two had no focus on aetiology of the LRTI (Bradley 2007; Fonseca-Aten 2006) and three were review papers including the most recent review (Atkinson 2007). One only focused on upper respiratory tract infections (URTIs) (Esposito 2006), one result was the previous version of this review (Gavranich 2005a) and one paper was unavailable for evaluation (Simon 2006).

### Included studies

#### Participants

The studies involved children diagnosed with LRTI ranging in age from one month to 16 years. In all except three studies (Esposito 2005; Gomez Campdera 1996; Soderstrom 1991) children had pneumonia supported with abnormal chest X-ray and apart from two studies (Esposito 2005; Ruhmann 1982) the children were described as having community-acquired pneumonia. The study by Gomez Campdera 1996 did not define pneumonia and the study by Soderstrom 1991 included participants with acute bronchitis. The number of children with *M. pneumoniae* causing LRTI was not stated in four studies (Esposito 2005; Gomez Campdera 1996; Ruhmann 1982; Saez-Llorens 1998). In one study (Wubbel 1999) there were 12 children with *M. pneumoniae* infections and six were in the subgroup randomised to either azithromycin or amoxicillin-clavulanate, but the number assigned to each therapy was not available. In two other studies the number of children

with *M. pneumoniae* infections in each intervention group was provided. In the study by Harris 1998 there were 30 children who had *M. pneumoniae* infections randomised to either azithromycin or amoxicillin-clavulanate (21 in azithromycin group and nine in amoxicillin-clavulanate group) and there were eight children in the study by Kogan 2003 (five in the azithromycin group and three in the amoxicillin-clavulanate group). In the study by Soderstrom 1991 there were only seven patients with LRTI (bronchitis) and one case of *M. pneumoniae*, but the age of the participants with *M. pneumoniae* was not provided. The study by Esposito 2005 did not distinguish between upper and lower respiratory tract infections in their analysis of results, although the number of *M. pneumoniae* infections (which included both URTIs and LRTIs) was made available.

#### Interventions

Studies included in this review involved patients with LRTI randomised to either a macrolide antibiotic or another antibiotic, usually a different macrolide or non-macrolide antibiotic. In two studies (Ruhmann 1982; Soderstrom 1991) the entire study population was randomised to either a macrolide or non-macrolide antibiotic. Ruhmann 1982 included children with pneumonia who received either erythromycin 70 to 80 mg/kg/day or amoxicillin 60 to 70 mg/kg/day. The duration of therapy was not stated. The study by Soderstrom 1991 had a subgroup of participants (number of children not stated) with acute bronchitis who received either erythromycin 500 mg twice daily for seven days or phenoxymethylpenicillin 800 mg twice daily for seven days. Four studies (Gomez Campdera 1996; Harris 1998; Saez-Llorens 1998; Wubbel 1999) randomised a subgroup of children under five years of age to azithromycin or amoxicillin-clavulanate. The dose of amoxicillin-clavulanate was 40 mg/kg/day in three divided doses for 10 days in all studies. The dose of azithromycin was 10 mg/kg once daily for three days in one study (Gomez Campdera 1996) and 10 mg/kg on day one followed by 5 mg/kg once daily for day two to five in three studies (Harris 1998; Saez-Llorens 1998; Wubbel 1999). In the study by Kogan 2003 the intervention for the subgroup with classic pneumonia was either azithromycin 10 mg/kg once daily for three days or amoxicillin 75 mg/kg/day in three divided doses for seven days. The Esposito 2005 study compared azithromycin with symptom-specific agents to symptom-specific agents alone; the azithromycin that was given was 10 mg/kg/day, three days per week for three weeks and acetaminophen (at 10 mg/kg/dose) was the symptom-specific agent.

#### Outcome measures

#### Clinical

Clinical response was the main outcome but was not defined in three studies (Gomez Campdera 1996; Ruhmann 1982;

Soderstrom 1991). In three studies clinical cure was defined as complete resolution of symptoms and signs by day 15 to 19 (Harris 1998), day 10 to 25 (Saez-Llorens 1998) and day 10 to 37 (Wubbel 1999). In the study by Kogan 2003 the clinical response was defined as the proportion of children without fever on day three. The Esposito 2005 study evaluated clinical responses at both one month (defined as the complete resolution of the acute symptoms, with no relapse) and six months (defined as the presence of no more than two respiratory relapses).

### Radiological

Radiological outcome was recorded in three studies (Gomez Campdera 1996; Harris 1998; Kogan 2003) but was not defined in the study by Gomez Campdera 1996. Bacteriological outcome was recorded in three studies (Esposito 2005; Harris 1998; Saez-Llorens 1998) but was not defined in the study by Saez-Llorens 1998. Adverse events were recorded by four studies (Gomez Campdera 1996; Harris 1998; Saez-Llorens 1998; Wubbel 1999) and were only defined in the study by Harris 1998. We made attempts to obtain individual patient data from four studies (Esposito 2005; Harris 1998; Kogan 2003; Wubbel 1999) where the number of children with LRTI due to *M. pneumoniae* was not identified, but no reply was received at the time this review was completed.

### Excluded studies

We excluded 10 papers and details are provided in the [Characteristics of excluded studies](#) table. The main reasons for exclusion were the non-randomised nature of the study (Jensen 1967; Sakata 2001; Vasilos 1995) or use of inadequate placebo or comparator (Block 1995; Chien 1993; Jensen 1967; Manfredi 1992; Nogeova 1997; Ronchetti 1994; Schonwald 1990; Yin 2002). Three of the excluded studies were non-English: Japanese (Sakata 2001), Russian (Vasilos 1995) and Chinese (Yin 2002).

### Risk of bias in included studies

We assessed risk of bias using the 'Risk of bias' tables (Higgins 2009). We generated a graph and summary for the information, and the combined results for the different categories of risk are highlighted. Approximately 50% of included studies were not blinded, but good results were seen for both follow up and reporting of participants by allocation group overall (i.e. in more than half the included studies these were not found to be a source of bias).

### Allocation

All studies were described as randomised and the method of randomisation was clearly described and appropriate in three studies (Esposito 2005; Ruhmann 1982; Saez-Llorens 1998) where a random number list was used. The method of randomisation was

unclear in one study (Wubbel 1999) where the method used was described as a list of randomised therapy assignments. In the trial Soderstrom 1991 the method used was sequential patient numbers and this was thought to be inadequate. Three studies (Gomez Campdera 1996; Harris 1998; Kogan 2003) did not describe the method of randomisation. Concealment of allocation was unclear in all except three studies; two (Saez-Llorens 1998; Wubbel 1999) assigned therapy by pharmacy, and one (Esposito 2005) allocated the duties of enrolment and randomisation to separate investigators.

### Blinding

There was no blinding in four studies (Gomez Campdera 1996; Ruhmann 1982; Saez-Llorens 1998; Wubbel 1999). In three studies the blinding involved only the participant (Harris 1998), clinician (Kogan 2003) or radiologist (Soderstrom 1991). The Esposito 2005 study blinded the participant, caregiver, clinical outcome assessors and data/statistical analysts.

### Incomplete outcome data

Five of the included studies adequately followed up their participants. Three of the eight included studies had unclear levels of follow up. Gomez Campdera 1996 and Ruhmann 1982 made no mention of losses to follow up. While Saez-Llorens 1998 mentioned that 30 were lost to follow up, there was no mention of why or from which groups these losses occurred.

### Selective reporting

Although selective reporting was not readily identified, possible issues are highlighted in 'Other potential sources of bias'.

### Other potential sources of bias

Three of the eight included studies (Esposito 2005; Harris 1998; Wubbel 1999) were funded by Pfizer Incorporated, a large pharmaceutical company responsible for producing Zithromax, a popular azithromycin. This association may have influenced the subjective outcome measures of these studies (i.e. 'clinical success'). All three studies were concerned with the efficacy of azithromycin in treating LRTIs, and none found it to be a less effective drug than alternative antimicrobial therapy. Wubbel 1999 found no difference and Esposito 2005 and Harris 1998 found it to be a superior treatment.

### Effects of interventions

There were 1912 children enrolled from seven studies. The number of children from one study (Soderstrom 1991) was unavailable.

Data interpretation was significantly limited by the inability to extract data that specifically referred to children with LRTI caused by *M. pneumoniae*. There was only one study of children randomised to any antibiotic versus placebo (Esposito 2005). Most of the included studies comprised a subgroup of children who were randomised to a macrolide versus non-macrolide antibiotic. The total number of children in this subgroup was not known as the numbers were only available in four studies (Harris 1998; Kogan 2003; Ruhrmann 1982; Wubbel 1999). The number of children with LRTI secondary to *M. pneumoniae* in this subgroup was only available in two studies (Harris 1998; Kogan 2003) and the lack of individual patient data did not allow for inclusion of results in a meta-analysis. There was a total of 26 in the azithromycin group and 12 in the amoxicillin-clavulanate group.

In the study by Gomez Campdera 1996 the rate of clinical cure was 95.12% in the azithromycin group and 90.41% in the amoxicillin-clavulanate group. Radiological improvement was noted in 90.6% of the azithromycin group. Adverse events were recorded in 11.25% of the azithromycin group and 17.14% in the amoxicillin-clavulanate group. Harris 1998 reported no difference in the rate of clinical cure at day 15 to 19 (67.2% versus 66.7%) and four to six weeks (85.1% versus 85.4%) of children randomised to azithromycin or amoxicillin-clavulanate. *M. pneumoniae* was identified in 16% (30 of 188 children under five years of age). Eradication of *M. pneumoniae* occurred in 3/3 in the azithromycin group and in 0/1 in the amoxicillin-clavulanate group. Adverse events in those children under five years of age were 12.1% in the azithromycin group and 42.3% in the amoxicillin-clavulanate group.

One participant in each group discontinued treatment because of adverse events. In the study by Kogan 2003 which compared azithromycin to amoxicillin in children with classical pneumonia (eight children of 47 had *M. pneumoniae*), X-ray resolution was significantly better in those treated with azithromycin (81% versus 60.9% at day seven) but there was no difference in clinical symptoms or signs between groups. In those with atypical pneumonia (23 children of 59 had *M. pneumoniae*) there was no significant difference between children treated with azithromycin or erythromycin (Kogan 2003). Ruhrmann 1982 reported clinical cure after 3.79 days in the erythromycin group and 3.96 days in the amoxicillin group. Saez-Llorens 1998 reported a similar clinical response (99% versus 98%) in children under five years who were randomised to azithromycin or amoxicillin-clavulanate. Eradication of *M. pneumoniae* occurred in 23 out of 24 in the azithromycin group. Adverse events were reported in 11% on azithromycin, 30% on amoxicillin-clavulanate and 27% on erythromycin. Soderstrom 1991 did not report the clinical response in the subgroup of patients with bronchitis. In the study by Wubbel 1999, where 7% (12 of 168 children) had *M. pneumoniae*, no difference was found in children randomised to azithromycin or amoxicillin-clavulanate. Adverse events were reported in 14% on azithromycin, 67% on amoxicillin-clavulanate and 25% on erythromycin.

Eleven patients did not complete the prescribed therapy. Esposito 2005, which grouped *C. pneumoniae* and *M. pneumoniae* together (and did not distinguish between upper and lower respiratory tract infections) when reporting clinical success rates (with a total of 200/560 infected children), found a 100% success rate in the short term with azithromycin and symptomatic therapy, and a 73.2% success rate at the six-month follow up. Symptomatic treatment alone showed a success rate of 77.2% at one month and 56.0% at six months. Adverse events were not reported in this study.

## DISCUSSION

### Summary of main results

This review failed to find any randomised controlled trials (RCTs) which specifically looked at the effectiveness of antibiotics for lower respiratory tract infection (LRTI) secondary to *M. pneumoniae*. There was only one study of antibiotics versus placebo (Esposito 2005), but this study defined success rates relative to LRTI secondary to *M. pneumoniae* and *Chlamydia* defined by polymerase chain reaction (PCR) or paired sera. In this study significantly more children in the azithromycin group had 'clinical success' on follow up than the placebo group. From the other studies, in the subgroup of children with LRTI secondary to *M. pneumoniae* the intervention was a macrolide antibiotic versus a non-macrolide antibiotic, usually amoxicillin-clavulanate. This subgroup identified only 38 children with *M. pneumoniae* infection and there were insufficient data to analyze the efficacy of macrolide antibiotics in this group. Adverse events were common, reported in 11% to 67% of children. The majority of adverse events related to the gastrointestinal tract (diarrhoea, vomiting, abdominal pain, nausea, anorexia) and where reported were more common in younger children (under five years of age).

### Overall completeness and applicability of evidence

There were significant difficulties in interpreting the data from the included studies. Firstly, although all studies (except Soderstrom 1991) enrolled children with LRTI, only a proportion had *M. pneumoniae* infection. It was not possible to obtain information on the subgroup with *M. pneumoniae*. Secondly, the dose and type of antibiotics differed among studies. Thirdly, application of diagnostic criteria (serology versus PCR) varied and these are not necessarily interchangeable. Fourthly, the inclusion criteria differed (various types of LRTI manifestation) between studies. Furthermore the outcomes measured were variable and in some papers clinical cure was undefined.

### Quality of the evidence

In addition to the above, the quality of the studies varied (see [Figure 1](#); [Figure 2](#)) with non-blinded outcomes in the majority of the included studies.

**Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.**

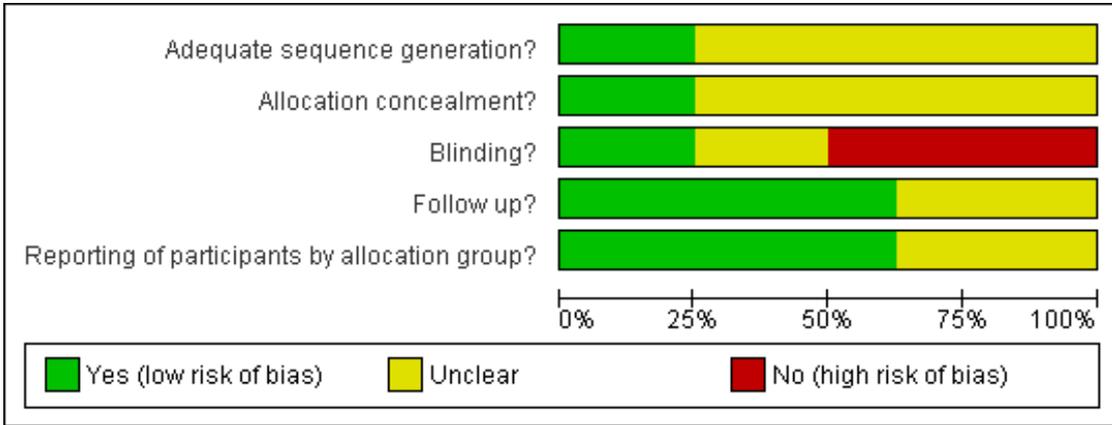


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Follow up?	Reporting of participants by allocation group?
Esposito 2005	+	+	+	+	+
Gomez Campdera 1996	?	?	-	?	?
Harris 1998	?	?	?	+	+
Kogan 2003	?	?	?	+	+
Ruhrmann 1982	+	?	-	?	?
Saez-Llorens 1998	?	+	-	?	?
Soderstrom 1991	?	?	+	+	+
Wubbel 1999	?	?	-	+	+

## Potential biases in the review process

No potential biases in the review process were identified.

## Agreements and disagreements with other studies or reviews

Despite the commonality of *M. pneumoniae* LRTI in children (up to 40% of community-acquired pneumonia reported by Waites 2003), there is surprisingly no RCT that has specifically evaluated the efficacy of antibiotics for the treatment of childhood LRTI secondary to *M. pneumoniae* infections acquired in the community. This is reflected in conflicting advice given in paediatric textbooks (Phelan 1994; Rudolph 2003) and this systematic review has highlighted the need for such studies.

## AUTHORS' CONCLUSIONS

### Implications for practice

Based on a single RCT, it is likely that macrolides are efficacious in (at least) a small group of children with LRTI secondary to *M. pneumoniae*. However, there is insufficient evidence to draw any specific conclusions about the efficacy of antibiotics for this condition in children. The use of antibiotics for *M. pneumoniae* LRTI has to be individualised and balanced with possible adverse events associated with antibiotic use.

### Implications for research

*M. pneumoniae* infection is relatively common and its clinical man-

ifestations range from being asymptomatic to death from complications of *M. pneumoniae* infection. As respiratory symptoms are the most common symptoms, there is a need for high quality, double-blinded RCTs to assess the efficacy and safety of antibiotics for LRTI secondary to *M. pneumoniae* in children. Studies should consider the various clinical and microbiological diagnostic criteria of *M. pneumoniae* infection and utilise clear outcome criteria. Community studies using PCR for rapid early diagnosis would be useful in evaluating the efficacy of antibiotics for *M. pneumoniae* for respiratory and non-respiratory manifestations as well as for prevention of complications and microbiological clearance of *M. pneumoniae*.

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## REFERENCES

### References to studies included in this review

#### Esposito 2005 {published data only}

Esposito S, Bosis S, Faelli N, Begliatti E, Droghetti R, Tremolati E, et al. Role of atypical bacteria and azithromycin therapy for children with recurrent respiratory tract infections. *Pediatric Infectious Disease Journal* 2005;24(5): 438–44.

#### Gomez Campdera 1996 {published data only}

Gomez Campdera JA, Navarro Gomez ML, Hernandez-Sampelayo T, Merello Godino C, Sanchez Sanchez C. Azithromycin in the treatment of ambulatory pneumonia in children. *Acta Pediatrica Espanola* 1996;54(8):554–62.

#### Harris 1998 {published data only}

Harris J-AS, Kolokathis A, Campbell M, Cassell GH, Hammerschlag MR. Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in

children. *Pediatric Infectious Disease Journal* 1998;17(10): 865–71.

#### 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;35(2):91–8.

#### Ruhrmann 1982 {published data only}

Ruhrmann H, Blenk H. Erythromycin versus amoxicillin for the treatment of pneumonia in children. *Infection* 1982; 10(Suppl):86–91.

#### Saez-Llorens 1998 {published data only}

Saez-Llorens X, Castano E, Wubbel L, Castrejon MM, de Morales I, Vallarino D, et al. Importance of Mycoplasma pneumoniae and Chlamydia pneumoniae in children

with community-acquired pneumonia. *Revista Medica de Panama* 1998;**23**(2):27–33.

**Soderstrom 1991** {published data only}

Soderstrom M, Blomberg J, Christensen P, Hovelius B. Erythromycin and phenoxymethylpenicillin (Penicillin V) in the treatment of respiratory tract infections as related to microbiological findings and serum C-reactive protein. *Scandinavian Journal of Infectious Disease* 1991;**23**:347–54.

**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;**18**(2):98–104.

## References to studies excluded from this review

**Atkinson 2007** {published data only}

Atkinson M, Yanney M, Stephenson T, Smyth A. Effective treatment strategies for paediatric community-acquired pneumonia. *Expert Opinion Pharmacotherapy* 2007;**8**(8): 1091–101.

**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;**14** (6):471–7.

**Bradley 2007** {published data only}

Bradley JS, Arguedas A, Blumer JL, Saez-Llorens X, Melkote R, Noel GJ. Comparative study of levofloxacin in the treatment of children with community-acquired pneumonia. *Paediatric Infectious Disease Journal* 2007;**26** (10):868–78.

**Chien 1993** {published data only}

Chien SM, Pichotta P, Siepmann N, Chan CK. Treatment of community-acquired pneumonia. A multicenter, double-blind, randomized study comparing clarithromycin with erythromycin. *Chest* 1993;**103**(3):697–701.

**Esposito 2006** {published data only}

Esposito S, Bosis S, Begliatti E, Droghetti R, Tremolati E, Tagliabue C, et al. Acute tonsillopharyngitis associated with atypical bacterial infection in children: natural history and impact of macrolide therapy. *Clinical Infectious Diseases* 2006;**43**:206–9.

**Fonseca-Aten 2006** {published data only}

Fonseca-Aten M, Okada PJ, Bowlware KL, Chavez-Bueno S, Meijias A, Rios AM, et al. Effect of clarithromycin on cytokines and chemokines in children with an acute exacerbation of recurrent wheezing: a double-blind, randomized, placebo-controlled trial. *Annals of Allergy, Asthma and Immunology* 2006;**97**:457–63.

**Jensen 1967** {published data only}

Jensen KJ, Senterfit LB, Scully WE, Conway TJ, West RF, Drummy WM. *Mycoplasma pneumoniae* infections in children. An epidemiological appraisal in families treated

with oxytetracycline. *American Journal of Epidemiology* 1967;**86**(2):419–32.

**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;**41**:54–61.

**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;**4**(6):364–70.

**Nogeova 1997** {published data only}

Nogeova A, Galova K, Krizan L, Sufiarska S, Cizmarova E, Raskova J, et al. Cefibuten vs cefuroxime-axetil in initial therapy for community-acquired bronchopneumonia: randomized multicentric study in 140 children. *Infectious Diseases in Clinical Practice* 1997;**6**(2):133–4.

**Ronchetti 1994** {published data only}

Ronchetti R, Blasi F, Grossi E, Pecori A, Bergonzi F, Ugazio A, et al. The role of azithromycin in treating children with community-acquired pneumonia. *Current Therapeutic Research and Clinical Experimentation* 1994;**55**(4):965–70.

**Sakata 2001** {published data only}

Sakata H. Clinical study on azithromycin in lower respiratory infections in children. *Japanese Journal of Chemotherapy* 2001;**49**(6):363–8.

**Schonwald 1990** {published data only}

Schonwald S, Gunjaca M, Kolacny-Babic L, Car V, Gosev M. Comparison of azithromycin and erythromycin in the treatment of atypical pneumonia. *Journal of Antimicrobial Chemotherapy* 1990;**25**:123–6.

**Simon 2006** {published data only}

Simon A, Schildgen O. Antimicrobial therapy in childhood asthma and wheezing. *Treatments in Respiratory Medicine* 2006;**5**(4):255–69.

**Vasilos 1995** {published data only}

Vasilos LV, Rumel NB, Shchuka SS. Chemotherapeutic effectiveness of erythromycin, rifampicin and tetracyclines in chlamydiosis and mycoplasmosis in children. *Antibiotiki i Khimioterapiia* 1995;**40**(6):40–2.

**Yin 2002** {published data only}

Yin T, Jiang Y-F. Comparison of azithromycin and erythromycin in the treatment of pediatric mycoplasma pneumoniae pneumonia. *Chinese Journal of Antibiotics* 2002;**27**(4): 240–2.

## Additional references

**Boluyt 2008**

Boluyt N, Tjosvold L, Lefebvre C, Klassen T. Usefulness of systematic review search strategies in finding child health systematic reviews in Medline. *Archives of Pediatrics and Adolescent Medicine* 2008;**162**(2):111–6.

**Dickersin 1994**

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286–91.

**Gavranich 2005a**

Gavranich JB, Chang AB. Antibiotics for community acquired lower respiratory tract infections (LRTI) secondary to *Mycoplasma pneumoniae* in children. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD004875.pub2]

**Higgins 2009**

Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.0.2 [updated September 2009]. The Cochrane Collaboration. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org) 2009.

**Katz 1998**

Katz SL, Gershon AA, Hoetz PJ. *Krugman's Infectious Disease of Children*. 10th Edition. USA: Mosby, 1998.

**Lefebvre 2008**

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK: Wiley-Blackwell, 2008.

**Michelow 2004**

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;**113**(4):701–7.

**Murray 2003**

Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Tenover FC, Tenover BC. *Manual of Clinical Microbiology*. 8th Edition. Vol. 1. Washington DC: ASM Press, 2003.

**Nelson 2002**

Nelson CT. *Mycoplasma* and *Chlamydia pneumoniae* in pediatrics. *Seminars in Respiratory Infections* 2002;**17**(1): 10–4.

**Phelan 1994**

Phelan PD, Olinsky A, Robertson CF. *Respiratory Illness in Children*. 4th Edition. Oxford, UK: Blackwell Scientific Publications, 1994.

**Principi 2001**

Principi N, Esposito S. Emerging role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in paediatric respiratory-tract infections. *Lancet Infectious Diseases* 2001;**1**:334–44.

**Principi 2002**

Principi N, Esposito S. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* cause lower respiratory tract disease in paediatric patients. *Current Opinion in Infectious Diseases* 2002;**15**(3):295–300.

**RevMan 2008**

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

**Rudolph 2003**

Rudolph CD, Rudolph AM, Hostetter MK, Lister G, Siegel NJ. *Rudolph's Pediatrics*. 21st Edition. USA: McGraw-Hill Medical Publishing Division, 2003.

**Waites 2003**

Waites KB. New concepts of *Mycoplasma pneumoniae* infections in children. *Pediatric Pulmonology* 2003;**36**: 267–78.

**References to other published versions of this review****Gavranich 2005b**

Gavranich JB, Chang AB. Antibiotics for community acquired lower respiratory tract infections (LRTI) secondary to *Mycoplasma pneumoniae* in children. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD004875.pub2]

\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Esposito 2005

Methods	<p>Participants were recruited from the outpatient clinic of the Institute of Pediatrics, University of Milan, Italy, between November 2000 and March 2002. The study group were identified as having a history of recurrent respiratory tract infections (RRTIs) (<math>\geq 8</math> episodes/year in <math>&lt; 3</math>-year olds or <math>\geq 6</math> episodes/year in <math>\geq 3</math>-year olds) and an acute LRTI or upper respiratory tract infection (URTI), as diagnosed by a paediatrician and recorded on a medical chart. Exclusion criteria for the study group included acute streptococcal pharyngitis/acute otitis media/community-acquired pneumonia at enrolment, severe concomitant disease, nosocomially-acquired infection, topical/systemic steroid therapy in the 48 hours preceding study enrolment, systemic antibiotic treatment in the 48 hours preceding study enrolment, administration of azithromycin therapy in the week preceding study enrolment, and intramuscular (IM) administration of benzathine penicillin G in the month preceding study enrolment</p> <p>The control group were chosen from otherwise healthy participants undergoing minor surgical treatment during the study period. They were to be of a similar age and gender to the study group, without a history of respiratory tract infection or antibiotic treatment in the 3 months before enrolment</p> <p>Acute <i>M. pneumoniae</i> infection, <i>C. pneumoniae</i> infection, or both was diagnosed if the child had a significant antibody response in paired sera or if the DNA of the bacteria was detected in nasopharyngeal aspirates, or both</p>
Participants	560 children, aged 1 to 14 years. 352 had acute respiratory infections and a history of recurrent respiratory tract infections (mean age = 3.6, 57.1% male, 136 with acute <i>M. pneumoniae</i> infection), and 208 were in the control group (mean age = 3.9, 57.2% male, 5 with acute <i>M. pneumoniae</i> infection)
Interventions	Patients were randomised to receive azithromycin (n = 177, 10 mg/kg/day, 3 days/week for 3 weeks) with symptom-specific agents (acetaminophen, 10 mg/kg per dose) or symptom-specific agents alone (n = 175)
Outcomes	<ol style="list-style-type: none"> <li>1. Clinical presentations</li> <li>2. Bacteriological findings</li> </ol>
Notes	-

#### Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "All the patients were randomised in a blinded manner with a computerized list, by the only investigator responsible for randomisation." Comment: Randomisation was appropriate

Esposito 2005 (Continued)

Allocation concealment?	Yes	The enrolment officer was different to the investigator assigned to randomisation. Consequently, the enroller was unaware of which treatment group the participants would be allocated to
Blinding? All outcomes	Yes	Clinical outcome assessor blinded. Although patients and caregivers were not blinded, caregivers were “instructed not to inform the evaluator, who was blinded with respect to randomisation, whether the child had received azithromycin.” Quote: “Data entry and statistical analyses were carried out in a blinded manner, with SAS software.” Comment: Raw data analyses were also blinded
Follow up? All outcomes	Yes	Quote: “All of the enrolled patients completed the 1-month follow-up evaluation.” Quote: “A total of 339 patients (96.3%) completed the 6-month follow-up evaluation.” Comment: A high proportion of participants were followed up
Reporting of participants by allocation group? All outcomes	Yes	The progress of all the children in both groups was described, although at 6 months 13 children were noted to be lost to follow up. The tables of results (both 1-month and 6-month follow ups) account for all available children

## Gomez Campdera 1996

Methods	Participants were recruited from emergency department with a diagnosis of pneumonia for the periods 1 May 1994 to 30 April 1995 and 1 December 1995 to 30 June 1996. Inclusion and exclusion criteria were not stated. Study participants were randomised to azithromycin or either amoxicillin-clavulanate if under 5 years and erythromycin if over 5 years. The method of randomisation was not described. The study was not blinded. There was no description of withdrawals or drop-outs. There was no assessment of compliance. Clinical outcomes were evaluated on day 3, 10 and 30, and chest X-ray (CXR) was repeated on day 30. Outcome measures included clinical response, hospitalisation, radiological improvement and adverse events. Clinical response was classified as unchanged, improved, cured or worse. These categories were not defined. Radiological improvement at day 30 was not defined
Participants	155 children aged 6 months to 16 years with pneumonia. Males = 84. Number of children with <i>M. pneumoniae</i> infection in each group not stated
Interventions	Group A (n = 82): azithromycin 10 mg/kg/day OD for 3 days Group B (n = 73): amoxicillin-clavulanate 40 mg/kg/day TID for 10 days if under 5 years and erythromycin 40 mg/kg/day TID for 10 days if over 5 years
Outcomes	<ol style="list-style-type: none"> <li>1. Clinical presentations</li> <li>2. Radiological findings</li> <li>3. Adverse events</li> </ol>
Notes	-

### *Risk of bias*

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation was not provided
Allocation concealment?	Unclear	No description of allocation
Blinding? All outcomes	No	No blinding of outcome assessor
Follow up? All outcomes	Unclear	There was no description of withdrawals or drop-outs
Reporting of participants by allocation group? All outcomes	Unclear	No mention of withdrawals or drop-outs

Methods	<p>Participants were recruited from 23 centres with a diagnosis of community-acquired pneumonia from 31 January 1994 to 31 May 1995. Inclusion criteria were children with clinically suspected pneumonia based on a radiological finding and the presence of tachypnoea. In addition patients had at least one of the following: fever or history of fever within 24 hours, cough, WCC <math>\geq</math> 12000/mm, or chest findings suggestive of pneumonia. Exclusion criteria were hypersensitivity to macrolides, penicillin or beta-lactam antibiotics, pregnancy or lactation, parenteral therapy required because of severe or multilobar pneumonia, treatment with any other systemic antibiotics within enrolment, evidence of underlying haematological, renal, hepatic or cardiovascular disease, chronic steroid use or concomitant treatment with theophylline, carbamazepine, ergotamine, digitalis glycosides, terfenadine, loratadine or astemizole. Study was a multi-centre, parallel group in which participants were randomised 2:1 to azithromycin or either amoxicillin-clavulanate if under 5 years and erythromycin if over 5 years. The method of randomisation was not described. Participants were blinded to therapy but there was no mention of blinding of clinicians or outcome assessors. There was a description of withdrawals or drop-outs. There was an assessment of compliance by comparing medication bottle weights at beginning and end of study. Participants were evaluated at 4 clinic visits: baseline; study days 2 to 5; study days 15 to 19; and 4 to 6 weeks post-therapy. Laboratory tests were obtained at baseline and on study days 15 to 19. Chest X-rays were obtained at baseline and 4 to 6 weeks post-therapy. Evidence of infection with <i>M. pneumoniae</i> was determined by enzyme-linked immunosorbent assay and defined as either single positive serum IgM (<math>\geq</math> 1:10) or 4-fold increase in IgG titre. Clinical response at study days 15 to 19 was classified as: cure, complete resolution of signs and symptoms of pneumonia; improvement, incomplete resolution of signs and symptoms of pneumonia; failure, persistence (or progression) of signs and symptoms of pneumonia after 3 days of therapy or development of new clinical findings consistent with active infection or persistence (or progression) of radiological findings obtained when clinically indicated. Clinical response 4 to 6 weeks post-therapy was classified as follows: cure; complete resolution of signs and symptoms of pneumonia and improvement or resolution of radiographic findings; failure; persistence (or progression) of signs and symptoms of pneumonia after 3 days of therapy or development of new clinical findings consistent with active infection or persistence (or progression) of radiological findings. Bacteriological response was classified as follows: eradication (presumed or proven), elimination of the original organism from the same site during or after completion of therapy and includes cases where repeat specimens were not obtained and patients considered a clinical cure or improved; persistence, failure to eradicate the organism and includes cases where specimens were not obtainable at the time alternative therapy was instituted and the patient was considered a clinical failure. Adverse events were monitored throughout the study by reported symptoms, physical examinations and laboratory tests. Events were rated by severity (mild, moderate or severe at the discretion of the investigator), organ system and relation to study drug</p>
Participants	<p>456 children aged 6 months to 15 years with community-acquired pneumonia (CAP) were enrolled. 36 patients (25 in azithromycin group and 11 in comparator group) were excluded for methodologic reasons leaving 420 patients (285 in azithromycin and 135 in comparator group) available for analysis. Six children discontinued treatment because of adverse events. Males = 236. The number of children with <i>M. pneumoniae</i> in the group randomised to macrolide versus non-macrolide (i.e. children &lt; 5 years) was 30 with 21 in azithromycin group and 9 in amoxicillin-clavulanate group</p>

**Harris 1998** (Continued)

Interventions	Children under 5 years only Group A (n = 125): azithromycin 10 mg/kg OD day 1.5 mg/kg OD day 2 to 5, and placebo day 1 to 10 Group B (n = 63): amoxicillin-clavulanate 40 mg/kg TDS day 1 to 10 and placebo day 1 to 5	
Outcomes	<ol style="list-style-type: none"> <li>1. Clinical presentations</li> <li>2. Radiological findings</li> <li>3. Bacteriological findings</li> <li>4. Adverse events</li> </ol>	
Notes	-	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Unclear	The method of randomisation was not specified
Allocation concealment?	Unclear	Methods of allocation concealment were not identified
Blinding? All outcomes	Unclear	Although the study design noted it was a "double blinded trial", most methods of blinding used were not specified. Participants and their caregivers were probably blinded because "the placebo and study drug formulations were similar in texture, color and taste."
Follow up? All outcomes	Yes	Clinical and laboratory outcomes were measured in 92.1% Quote: "A total of 36 patients [of 456] . . . were excluded from efficacy analysis for methodologic reasons such as no follow-up evaluation or concomitant antibiotic use."
Reporting of participants by allocation group? All outcomes	Yes	The progress of all randomised children in each group was described, with numbers lost to exclusion and follow up noted

Methods	<p>Participants with a diagnosis of community-acquired pneumonia were recruited from 1 January 1996 to 1 January 1999. Inclusion criteria were children with a clinical diagnosis radiologically confirmed of presumed bacterial community-acquired pneumonia, eligible for treatment with oral antibiotics and without signs of respiratory insufficiency. Exclusion criteria were history or evidence of chronic pathology of any organ system, chronic pulmonary disease, history of prematurity, treatment with any antibiotics within 5 days prior to enrolment, or known hypersensitivity to beta-lactam antibiotics or macrolides. The study population was divided into 2 groups according to clinical and radiological patterns. One group included those children who presented with signs of classic bacterial pneumonia, with high fever and chest findings of crackles or signs of consolidation, and chest X-rays with segmental, alveolar, or lobar consolidation. The second group included patients with atypical pneumonia, with prominent and frequently paroxysmal cough, variable fever, few clinical signs of consolidation, crackles and wheezing, and chest X-rays with a mixed alveolar-interstitial pattern. Participants with classic pneumonia were randomised to either amoxicillin or azithromycin, whereas participants in the atypical pneumonia were randomly assigned to either azithromycin or erythromycin. The method of randomisation was not described. There was no mention of blinding except for blinding of the radiologist who viewed follow up chest X-rays done on study days 7 and 14. There was a description of withdrawals or drop-outs. There was no assessment of compliance. Outcomes were evaluated at 3 clinic visits, on study days 3, 7 and 14. A chest X-ray was done in each child on study days 7 and 14. Evidence of infection was determined by indirect immunofluorescence (IFI) and enzyme-linked immunosorbent assay to test sera for IgM antibodies to <i>M. pneumoniae</i>. An antibody titre &gt; 1:16 on a single first serum specimen was considered positive for IFI. Clinical response in the classic pneumonia group was defined as proportion of children without fever on day 3 and/or improvement of more than 75% of radiographic baseline findings on study day 7</p>	
Participants	<p>110 children aged 1 month to 14 years were enrolled. 4 children developed serious pneumonia in the first 12 hours of enrolment and were excluded from the study (3 from the atypical group and 1 from the classic group). The remaining 106 completed the study. The mean age was 4.9 years and 53 were male. 47 met the criteria for classic pneumonia. The number of children with <i>M. pneumoniae</i> in the classic group was 8, with 5 in azithromycin group and 3 in amoxicillin-clavulanate group</p>	
Interventions	<p>Patients with classic pneumonia:  Group A (n = 23): azithromycin 10 mg/kg OD for 3 days  Group B (n = 24): amoxicillin 75 mg/kg/day in 3 divided doses for 7 days</p>	
Outcomes	<ol style="list-style-type: none"> <li>1. Clinical presentations</li> <li>2. Radiological findings</li> </ol>	
Notes	-	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>

**Kogan 2003** (Continued)

Adequate sequence generation?	Unclear	The method of randomisation was not specified
Allocation concealment?	Unclear	Methods of allocation concealment were not identified
Blinding? All outcomes	Unclear	Almost no methods of blinding were specified. Participants and caregivers may have been aware of their treatment group, as the frequency and duration of drug administrations were different between the groups Quote: "All chest X-rays done ... were seen by the same radiologist, who was not familiar with the patients' clinical history and treatment group." Comment: Radiology assessment was blinded
Follow up? All outcomes	Yes	Quote: "Of the 110 enrolled patients, 4 children developed severe pneumonia in the first 12 hr of enrolment and were excluded from the study... The remaining 106 children completed the study." Comment: No participants were lost to follow up
Reporting of participants by allocation group? All outcomes	Yes	The progress of all randomised children in each group was described. Results tables compared outcomes between groups

**Ruhrmann 1982**

Methods	Participants were selected at the children's hospital in Hamburg, Germany. Patients were diagnosed with pneumonia based on CXR. The study compared erythromycin therapy with amoxicillin therapy. The duration of the study was not specified, nor were the inclusion and exclusion criteria. Although the treatment allocation was randomised, there was no blinding of the outcome assessor or the participant. Baseline measurements were recorded using temperature, full blood examination (FBE), CXR and cough presence. Outcome measures were noted over 10 days and were not well-described, with 'clinical improvement' being documented without any clear definition
Participants	120 children aged 6 months to 14 years with pneumonia. Gender ratio not stated. Number of children with <i>M. pneumoniae</i> infection in each group not stated
Interventions	Group A: erythromycin 70 to 80 mg/kg/day. Duration of therapy not stated Group B: amoxicillin 60 to 70 mg/kg/day. Duration of therapy not stated
Outcomes	Clinical presentations

Ruhrmann 1982 (Continued)

Notes	-	
<b>Risk of bias</b>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A list of randomised numbers was used to allocate participants into treatment groups
Allocation concealment?	Unclear	No mention of allocation concealment
Blinding? All outcomes	No	No blinding of participants or outcome assessors
Follow up? All outcomes	Unclear	No description of losses to follow up was included in the paper
Reporting of participants by allocation group? All outcomes	Unclear	Unclear mention of withdrawals or drop-outs

Saez-Llorens 1998

Methods	<p>Participants were recruited from emergency departments in Dallas and Panama with a diagnosis of community-acquired pneumonia for the period February 1996 to December 1997. Inclusion criteria were tachypnoea, fever, cough, crackles and CXR with changes compatible with pneumonia. Exclusion criteria were hypersensitivity to macrolides or beta-lactam antibiotics, pregnancy, nosocomial pneumonia, use of systemic antibiotics 72 hours prior to recruitment, chronic illness such as HIV, malignancy, cystic fibrosis, haematologic, renal, cardiovascular, hepatic or pulmonary diseases, as well as patients on teofilin, antihistamines, steroids or any medications with potential interaction with macrolides. Study participants were randomised to azithromycin or either amoxicillin-clavulanate if under 5 years and erythromycin if over 5 years. A random number list was used and therapy assigned by pharmacy. The study was not blinded. There were 39 drop-outs, although reasons were not specified. There was no assessment of compliance. Clinical outcomes were evaluated on day 2 to 3 and 10 to 25.</p> <p>Baseline measurements were recorded using blood cultures, nasopharyngeal aspirate cultures and PCR for <i>M. pneumoniae</i> and <i>C. pneumoniae</i>. Antibody titres against the 2 microorganisms were evaluated using serology. Additionally, FBE, urea and electrolytes, liver function tests and tuberculin tests were used to assess infection. Clinical response was evaluated as a cure or fail, and clinical cure was defined as complete resolution or evident improvement of all clinical signs and symptoms. Clinical failure was defined as persistent or progressive symptoms after 3 days of treatment</p>
Participants	<p>Total of 335 children aged 6 months to 15 years with CAP; 168 from Dallas with 106 under 5 years (males = 92) and 167 from Panama with 142 under 5 years (males = 98). Thirty-nine children dropped out. Number of children with <i>M. pneumoniae</i> infection in each group not stated</p>

Interventions	Group A: azithromycin 10 mg/kg on day 1 and 5mg/kg once daily (OD) for days 2 to 5 Group B: amoxicillin-clavulanate 40 mg/kg/day 3 times daily (TID) for 10 days if under 5 years and erythromycin 40 mg/kg/day TID for 10 days if over 5 years	
Outcomes	1. Clinical presentations 2. Bacteriological findings 3. Adverse events	
Notes	-	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Unclear	List of randomised numbers assigned to therapy. Unclear how randomised numbers were generated but medication given by pharmacy
Allocation concealment?	Yes	Medications provided by pharmacy
Blinding? All outcomes	No	No blinding of outcome assessor
Follow up? All outcomes	Unclear	30 drop-outs but no description of withdrawals or drop-outs were provided in accordance to groups
Reporting of participants by allocation group? All outcomes	Unclear	No mention of withdrawals or drop-outs relative to allocated groups

**Soderstrom 1991**

Methods	Participants aged > 10 years were recruited with any of the following diagnoses: sinusitis, tonsillitis, purulent nasopharyngitis or bronchitis. Inclusion criteria defined acute bronchitis by the presence of at least 4 of the following 5 criteria: (a) cough; (b) increased amounts of sputum; (c) rhonchus; (d) leucocytosis (> 10 x 10 <sup>9</sup> leucocytes/l); and (e) temperature > 38 degrees C. Exclusion criteria were allergies to erythromycin or penicillin, those treated with steroids, theophylline or antibiotics within 10 days preceding consultation. The patients in each diagnosis group were randomly assigned to treatment with erythromycin capsules or phenoxymethylpenicillin tablets. The patients were given sequential patient numbers, which indicated which of the 2 treatments should be given to each patient. The physician at the first visit and the nurse who met the patient at follow up visits were blinded to the intervention. There is no mention of whether the participant was blinded to intervention. There was a description of withdrawals or drop-outs. Compliance was assessed by analysing urine sample collected during treatment (days 3 to 7). The patients kept a daily record of symptoms and were reviewed by nurse 10 to 12 days after their initial visit. Evidence of <i>M. pneumoniae</i> infection was made on the basis of 4-fold rise in antibody titre. Outcome measures included clinical response and adverse reactions. Clinical response was classified as asymptomatic, minor symptoms, Streptococcal relapse/re-infection and treatment failure. These clinical outcomes were not defined
Participants	138 patients were recruited with age range 10 to 70 years (median 32.5). Males = 56. Two patients dropped out. There were only 7 with bronchitis (lower respiratory tract infection) and <i>M. pneumoniae</i> was identified in 1 case
Interventions	Group A: erythromycin 500 mg twice daily for 7 days Group B: penicillin V 800 mg twice daily for 7 days
Outcomes	Clinical presentations
Notes	-

**Risk of bias**

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	The paper states that patients were "randomly assigned", but simply states that "patients were given sequential patient numbers, which indicated which of the two treatments should be given to each patient." It is unclear how treatment groups were indicated by patient number, and so the randomisation cannot be assessed
Allocation concealment?	Unclear	Methods of allocation concealment were not specified
Blinding? All outcomes	Yes	Quote: "The physician at the first visit and the nurse who met the patient at the follow-

Soderstrom 1991 (Continued)

		<p>up visit did not know which prescription the patient had had.”</p> <p>Comment: The outcome assessor was blinded. The participants and caregivers were presumably not blinded, as they were given prescriptions for their antibiotics</p>
<p>Follow up? All outcomes</p>	<p>Yes</p>	<p>Quote: “136/138 patients returned for follow-up within 10-12 days ... The 2 remaining patients interrupted the treatment within 2 days.”</p> <p>Comment: 98.6% of participants were clinically assessed at the follow-up visit</p>
<p>Reporting of participants by allocation group? All outcomes</p>	<p>Yes</p>	<p>The results table clearly compared the erythromycin and phenoxymethylpenicillin groups</p>

Methods	<p>Participants were recruited from emergency clinic Children's Medical Centre Dallas, Texas with a diagnosis of community-acquired pneumonia from February 1996 to December 1997. Inclusion criteria were children with tachypnoea, fever, cough or rales and an abnormal chest X-ray consistent with pneumonia and considered to have community-acquired infection. Exclusion criteria were hypersensitivity to macrolides or beta-lactam antibiotics, pregnancy or lactation, nosocomial-acquired infections, hospitalisation, systemic antibiotic within 72 hours before enrolment, cefixime or ceftriaxone within the previous 7 days and chronic diseases. Participants were also excluded if they were receiving medications that had potential adverse interactions with erythromycin or azithromycin. Study participants were randomised to azithromycin or either amoxicillin-clavulanate if under 5 years and erythromycin if over 5 years. A list of randomised therapy assignments was used by research pharmacist to provide patients with either azithromycin, amoxicillin-clavulanate or erythromycin. There was no mention of blinding of participants, clinicians or outcome assessors except radiologists who reviewed all radiographs and were not familiar with the patient's clinical history or results of special studies. There was a description of withdrawals or drop-outs. There was an assessment of compliance by measuring the volume of drug in the bottle at 2 to 5-week visit. Clinical evaluation occurred at enrolment, 2 to 3 days and 10 to 37 days after start of therapy. At day 2 to 3 a telephone call was made to the caregiver to assess symptoms, interventions and adverse reactions. Patients were assessed at weeks 2 to 5 for symptoms, adverse reactions and outcome. At this assessment bacteriological samples were collected - nasopharyngeal and pharyngeal swabs for culture and PCR and serum for convalescent antibody titres. A chest X-ray was repeated only if a patient had signs of persistent or new infection. Clinical response was defined as: cure, resolution of all signs and symptoms; improvement, incomplete resolution of all signs and symptoms; and failure, persistence or progression after 3 days of therapy, new clinical findings suggesting active infection or death related to pneumonia. Bacteriological response was not defined. Adverse events were monitored throughout the study. Evidence of infection with <i>M. pneumoniae</i> was determined by serology (enzyme-linked immunosorbent assay), and culture or PCR from nasopharyngeal swabs. Positive serology was defined as either single positive serum IgM (<math>\geq 1:10</math>) or 4-fold increase in IgG titre</p>
Participants	<p>174 children aged 6 months to 16 years with CAP were enrolled. Six patients were excluded because of normal chest X-rays. Twenty-one children were excluded from clinical evaluation; 10 failed to return for follow-up examination and 11 did not complete treatment. Gender ratio was not mentioned. The total number of children with <i>M. pneumoniae</i> was 12. However, it was not possible to determine how many children with <i>M. pneumoniae</i> were in the group &lt; 5 years who were randomised to either azithromycin or amoxicillin-clavulanate because of lack of individual patient data</p>
Interventions	<p>Children under 5 years only  Group A (n = 39): azithromycin 10 mg/kg OD day 1, followed by 5 mg/kg OD day 2 to 5  Group B (n = 49): amoxicillin-clavulanate 40 mg/kg TDS day 1 to 10</p>
Outcomes	<ol style="list-style-type: none"> <li>1. Clinical presentations</li> <li>2. Adverse events</li> </ol>
Notes	-

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "Using a randomised list of therapy assignments..." Comment: The method of randomisation was not adequately specified
Allocation concealment?	Unclear	Methods of allocation concealment were not identified
Blinding? All outcomes	No	Quote: "This study was a prospective, randomised, unblinded trial..." Comment: While mostly unblinded, one outcome was partially blinded. Radiographs were secondarily assessed by "radiologists who were not familiar with the patients' clinical history or results of special studies."
Follow up? All outcomes	Yes	Quote: "Of the 168 patients who were assessed for etiology of pneumonia, 21 were excluded from clinical evaluation; 10 failed to return for follow-up examination and 11 did not complete treatment." Comment: 147/168 (87.5%) were continuously followed throughout the study
Reporting of participants by allocation group? All outcomes	Yes	The progress of all randomised children in each group was described

CAP: community-acquired pneumonia  
 CXR: chest X-ray  
 FBE: full blood examination  
 hr: hour  
 IFI: immunofluorescence  
 IM: intramuscular  
 LRTI: lower respiratory tract infection  
 n: number  
 OD: daily  
 PCR: polymerase chain reaction  
 RRTIs: recurrent respiratory tract infections  
 TID: three times a day  
 URTI: upper respiratory tract infection  
 WCC: white cell count

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

Study	Reason for exclusion
Atkinson 2007	Review of studies: cited most recent evidence for treating <i>M. pneumoniae</i> as 'inconclusive'
Block 1995	Inappropriate intervention. Comparison between 2 drugs from macrolide group - clarithromycin versus erythromycin ethylsuccinate
Bradley 2007	Inappropriate intervention and no specified aetiology. Comparison between fluoroquinolone and macrolides - levofloxacin versus clarithromycin/ceftriaxone with clarithromycin/erythromycin lactobionate. <i>M. pneumoniae</i> affecting LRT and its treatments were not specifically identified
Chien 1993	Inappropriate intervention. Comparison between 2 drugs from macrolide group - clarithromycin versus erythromycin
Esposito 2006	No focus on LRTIs. URTIs were the focus of this study
Fonseca-Aten 2006	No specified aetiology. <i>M. pneumoniae</i> affecting LRT and its treatments were not specifically identified
Jensen 1967	Inappropriate intervention and study not randomised. Study looked at treatment of all affected individuals with oxytetracycline and there was no placebo group. Household contacts were treated with either oxytetracycline or placebo to determine effectiveness of oxytetracycline in secondary prevention of mycoplasma infections. Allocation of treatment of household contacts was not randomised
Lee 2008	Inappropriate intervention and too few participants. Comparison between 2 drugs from macrolide groups - clarithromycin versus erythromycin. Only 26 participants
Manfredi 1992	Inappropriate intervention. Comparison between 2 drugs from macrolide group - azithromycin versus erythromycin
Nogeova 1997	Inappropriate intervention. Comparison between 2 drugs from cephalosporin group - ceftibuten versus cefuroxime-axetil
Ronchetti 1994	Inappropriate intervention. Comparison between 2 drugs from macrolide group - azithromycin versus josamycin
Sakata 2001	Study participants were not randomised
Schonwald 1990	Inappropriate intervention. Comparison between 2 drugs from macrolide group - azithromycin versus erythromycin
Simon 2006	Article unavailable for evaluation
Vasilos 1995	Study participants were not randomised

(Continued)

Yin 2002	Inappropriate intervention. Comparison between 2 drugs from macrolide group - oral azithromycin versus intravenous erythromycin
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LRT: lower respiratory tract

LRTI: lower respiratory tract infection

URTI: upper respiratory tract infection

## DATA AND ANALYSES

This review has no analyses.

## APPENDICES

### Appendix I. Embase.com search strategy

1. 'mycoplasma'/de OR 'mycoplasma pneumoniae'/de
2. 'm. pneumoniae':ab,ti OR mycoplasma:ab,ti
3. #1 OR #2
4. 'bronchitis'/exp OR 'pneumonia'/exp
5. bronchit\*:ab,ti OR pneumon\*:ab,ti OR wheez\*:ab,ti OR tracheobronchit\*:ab,ti
6. 'respiratory tract infection'/de OR 'lower respiratory tract infection'/de
7. 'respiratory tract infection':ab,ti OR 'respiratory tract infections':ab,ti OR 'acute respiratory infection':ab,ti OR 'acute respiratory infections':ab,ti
8. #4 OR #5 OR #6 OR #7
9. 'antibiotic agent'/exp
10. antibiotic\*:ab,ti
11. 'macrolide'/exp OR 'quinolone derivative'/exp OR 'tetracycline derivative'/exp
12. macrolide\*:ab,ti OR quinolone\*:ab,ti OR tetracycline\*:ab,ti OR erythromycin\*:ab,ti OR roxithromycin\*:ab,ti OR clarithromycin\*:ab,ti OR azithromycin\*:ab,ti
13. #9 OR #10 OR #11 OR #12
14. #3 AND #8 AND #13
15. 'child'/exp
16. child\*:ab,ti OR schoolchild\*:ab,ti OR 'school age':ab,ti OR 'school aged':ab,ti OR 'school ages':ab,ti OR preschool\*:ab,ti OR kid:ab,ti OR kids:ab,ti OR toddler\*:ab,ti
17. 'adolescent'/exp
18. adoles\*:ab,ti OR teen\*:ab,ti OR boy\*:ab,ti OR girl\*:ab,ti
19. 'puberty'/exp
20. minor\*:ab,ti OR juvenile\*:ab,ti OR pubert\*:ab,ti OR pubescen\*:ab,ti
21. 'pediatrics'/exp
22. pediatric\*:ab,ti OR paediatric\*:ab,ti
23. 'school'/exp
24. (school\* NEAR/2 (nursery OR primary OR secondary OR high OR elementary)):ab,ti OR kindergar\*:ab,ti OR highschool\*:ab,ti
25. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
26. #14 AND #25
27. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
28. random\*:ab,ti OR placebo\*:ab,ti OR factorial\*:ab,ti OR crossover\*:ab,ti OR 'cross over':ab,ti OR assign\*:ab,ti OR allocat\*:ab,ti OR volunteer\*:ab,ti OR ((singl\* OR doubl\*) NEAR/2 (blind\* OR mask\*)):ab,ti
29. #27 OR #28
30. #26 AND #29

## Appendix 2. Previous searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2005, issue 1), which contains the Acute Respiratory Infections Group's Specialised Register; MEDLINE (1966 to February 2005) and EMBASE (1980 to December 2004).

The following search terms were used for MEDLINE and CENTRAL and adapted for EMBASE. The search terms used in MEDLINE were combined with the highly sensitive strategy devised by Dickersin ([Dickersin 1994](#)).

### MEDLINE

1 exp MYCOPLASMA/  
2 exp Mycoplasma pneumoniae/  
3 mycoplasma  
4 or/1-3  
5 exp BRONCHITIS/  
6 exp PNEUMONIA/  
7 exp Respiratory Tract Infections/  
8 bronchitis  
9 pneumonia  
10 atypical pneumonia  
11 respiratory tract infection\$  
12 acute respiratory infection\$  
13 or/5-12  
14 exp Anti-Bacterial Agents/  
15 exp MACROLIDES/  
16 exp QUINOLONES/  
17 exp TETRACYCLINES/  
18 antibiotic\$  
19 (macrolide\$ or erythromycin or roxithromycin or clarithromycin or azithromycin)  
20 or/14-19  
21 exp CHILD/  
22 (child or children)  
23 (paediatric or pediatric)  
24 or/21-23  
25 4 and 13 and 20 and 24  
There were no language or publication restrictions.

### WHAT'S NEW

Last assessed as up-to-date: 21 February 2010.

Date	Event	Description
22 February 2010	New search has been performed	Searches conducted. One new included trial ( <a href="#">Esposito 2005</a> ) and six new excluded trials ( <a href="#">Atkinson 2007</a> ; <a href="#">Bradley 2007</a> ; <a href="#">Esposito 2006</a> ; <a href="#">Fonseca-Aten 2006</a> ; <a href="#">Lee 2008</a> ; <a href="#">Simon 2006</a> ) have been added to the update.

(Continued)

22 February 2010	New citation required and conclusions have changed	A new author joined to review team. The conclusion has changed to reflect the new included trial
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## HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 3, 2005

Date	Event	Description
22 July 2008	Amended	Converted to new review format.
23 May 2005	Amended	Review first published Issue 3, 2005

## CONTRIBUTIONS OF AUTHORS

In the first version, John Gavranich (JG) wrote the protocol, independently selected papers for inclusion, assessed quality and extracted data, and wrote review.

Anne Chang (AC) edited and co-wrote protocol, independently selected papers for inclusion, assessed quality and extracted data, and edited and co-wrote review. For the updated version, Selamawit Mulholland (SM) and AC selected papers for inclusion.

SM included the risk of bias tables and figures and updated the included/excluded studies and their characteristics and the text accordingly. These were adapted and checked by AC. The revised version was reviewed by all review authors.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- West Moreton Health Service District, Ipswich, Australia.
- Royal Children's Hospital, Brisbane, Australia.

## External sources

- No sources of support supplied

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Mycoplasma pneumoniae; Anti-Bacterial Agents [\*therapeutic use]; Bronchitis [\*drug therapy; microbiology]; Community-Acquired Infections [drug therapy; microbiology]; Pneumonia, Mycoplasma [\*drug therapy]

### MeSH check words

Child; Humans