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

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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 LRTIs, 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 CENTRAL (2014, Issue 3), MEDLINE (1966 to July week 4, 2014), EMBASE (1980 to July, 2014), and both WHO ICTRP and ClinicalTrials.gov (13 August 2014).

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 and resolved disagreements by consensus.

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 respiratory infections caused by the bacteria *Mycoplasma pneumoniae* in children

Review question

This review sought to answer the question of whether antibiotics are effective in the treatment of LRTIs caused by the bacteria *Mycoplasma pneumoniae* (*M. pneumoniae*) in children.

Background

M. pneumoniae is a bacterial infection, often responsible for lower respiratory tract infections (LRTIs) 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.

Search date

We searched for trials published and pending as at July 2014.

Study characteristics

Randomised controlled trials (RCTs) comparing either two types of antibiotic therapy or an antibiotic versus a placebo in children with pneumonia.

Key results

We identified seven studies (1912 children). Within each study, there were some children who had *M. pneumoniae* but we could not extract relevant data relating to efficacy or adverse events relating only to children with *M. pneumoniae.*

Quality of evidence

Overall the quality of the evidence for each of the main outcomes is very low as there are insufficient data for any outcome. Hence, currently, there is 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-Barré 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 LRTIs 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 mentions that there is little evidence of beneficial effect from antibiotic therapy (Phelan 1994). 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. We measured failure to improve 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).

We determined the proportions of participants who failed to improve on treatment and the mean clinical improvement using the following hierarchy of assessment measures. (We reported all outcomes, but where two or more assessment measures were reported in the same study and we obtained conflicting results, 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

For this 2014 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 3) (accessed 8 July 2014) limited to year published 2011 to 2014, which contains the Acute Respiratory Infection Group's Specialised Register, MEDLINE (1 January 2012 to June week 4, 2014) and EMBASE (1 January 2012 to July 2014).

Previously we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 2) (accessed 13 March 2012), which contains the Acute Respiratory Infection Group's Specialised Register, MEDLINE (1966 to February Week 5, 2012) and EMBASE (1980 to March 2012). Details of earlier searches are described in Appendix 1.

We used the search terms in Appendix 2 to search MEDLINE and CENTRAL. We combined the MEDLINE search 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-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search terms for EMBASE (Appendix 3).

We imposed no language or publication restrictions.

Searching other resources

We searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and the US National Institute of Health ClinicalTrials.gov platform (Appendix 4) for all registered trials, both published and pending, as at 13 August 2014. We further manually checked all references for reports of trials.

Data collection and analysis

Selection of studies

In the first publication of this review, three review authors (JG, AC, SM) independently reviewed the literature searches from the title, abstract or descriptions, to identify potentially relevant trials for full review. We conducted searches of bibliographies and texts to identify additional studies. Three review authors (JG, AC, SM) independently selected trials for inclusion from the full text using specific criteria. In the 2012 update two review authors (MG, AC) reviewed the literature searches. For this 2014 update two review authors (SG, AC) independently assessed the literature searches for inclusion and exclusion.

Data extraction and management

In the first publication of this review, three 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 antimicrobials, 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, two review authors (JG, AC) utilised the Jadad quality assessment scores (Gavranich 2005). In the 2012 update three review authors (JG, AC, SM) independently assessed the quality of studies included in the review using the 'Risk of bias' table available in Review Manager 5 (RevMan 2014), in accordance with the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). 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, we had planned to use a funnel plot to look for publication bias. However, data were unavailable and we were unable to include any studies 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 (RR) and 95% confidence interval (CI) (fixed-effect model) using the inverse of the variance of each study result for weighting. We planned to calculate the number needed to treat to benefit using the summary odds ratio (OR) 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 (MD) in outcomes could be estimated. In studies that reported outcomes using different measurement scales, we would have estimated the standardised MD. 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

Results of the search

We identified 91 potentially relevant titles in the initial search. After reviewing the abstracts, we obtained 17 papers in full text for consideration for inclusion in 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 (Ruhrmann 1982) and Spanish (Gomez Campdera 1996; Saez-Llorens 1998).

In the updated search in 2009 we identified 20 new records, of which we considered 11 for inclusion, but only included one (Esposito 2005). We excluded two as they did not meet the inclusion criteria (Bradley 2007; Lee 2008), two had no focus on the 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 2005), and one paper was unavailable for evaluation (Simon 2006). In the 2012 search we identified 77 studies, though none fulfilled the inclusion criteria.

In this 2014 search we identified a total of 22 studies and none fulfilled the specified inclusion criteria.

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; Ruhrmann 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; Ruhrmann 1982; Saez-Llorens 1998). In one study there were 12 children with *M. pneumoniae* infections and six were in the subgroup randomised to either azithromycin or amoxycillin-clavulanate, but the number assigned to each therapy was not available (Wubbel 1999). 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 amoxycillin-clavulanate (21 in the azithromycin group and nine in the amoxycillin-clavulanate group) and there were eight children in the study by Kogan 2003 (five in the azithromycin group and three in the amoxycillin-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 the entire study population was randomised to either a macrolide or non-macrolide antibiotic (Ruhrmann 1982; Soderstrom 1991). Ruhrmann 1982 included children with pneumonia who received either erythromycin 70 to 80 mg/kg/day or amoxycillin 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 randomised a subgroup of children under five years of age to azithromycin or amoxycillin-clavulanate (Gomez Campdera 1996; Harris 1998; Saez-Llorens 1998; Wubbel 1999). The dose of amoxycillin-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 amoxycillin 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; Ruhrmann 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 in four studies (Gomez Campdera 1996; Harris 1998; Saez-Llorens 1998; Wubbel 1999), but 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 we did not receive a reply at the time this review was completed.

Excluded studies

We have excluded 19 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; Bradley 2007; Chien 1993; Jensen 1967; Lee 2008; Lee 2012; Manfredi 1992; Nogeova 1997; Ronchetti 1994; Schonwald 1990; Sempertegui 2014; Wu 2014; 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 for included studies (see Characteristics of included studies) (Higgins 2011). 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 where a random number list was used (Esposito 2005; Ruhrmann 1982; Saez-Llorens 1998). The method of randomisation was unclear in one study where the method used was described as a list of randomised therapy assignments (Wubbel 1999). In the trial Soderstrom 1991, the method used was sequential patient numbers and we thought this to be inadequate. Three studies did not describe the method of randomisation (Gomez Campdera 1996; Harris 1998; Kogan 2003). Concealment of allocation was unclear in all except three studies; two assigned therapy by pharmacy (Saez-Llorens 1998; Wubbel 1999), and one allocated the duties of enrolment and randomisation to separate investigators (Esposito 2005).

Blinding

There was no blinding in four studies (Gomez Campdera 1996; Ruhrmann 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 Ruhrmann 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 were funded by Pfizer Incorporated, a large pharmaceutical company responsible for producing Zithromax, a popular azithromycin (Esposito 2005; Harris 1998; Wubbel 1999). 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

Ideally the primary and secondary outcomes should be reported here but the lack of data relevant for *M. pneumoniae* within each study precludes this and hence the data described below relate to the studies themselves where the subgroup was reported.

We identified seven trials with 1912 children. The number of children from one study was unavailable (Soderstrom 1991).

Data interpretation was significantly limited by the inability to extract data that specifically referred to children with lower respiratory tract infection (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 amoxycillin-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 amoxycillin-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 amoxycillin-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%) in children randomised to azithromycin or amoxycillin-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 amoxycillin-clavulanate group. Adverse events in those children under five years of age were 12.1% in the azithromycin group and 42.3% in the amoxycillin-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 amoxycillin group. Saez-Llorens 1998 reported a similar clinical response (99% versus 98%) in children under five years who were randomised to azithromycin or amoxycillin-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 amoxycillin-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 amoxycillin-clavulanate and 25% on erythromycin. Eleven patients did not complete the prescribed therapy. Esposito 2005, which grouped *Chlamydia pneumoniae* (*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) that 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 amoxycillin-clavulanate. This subgroup identified only 38 children with *M. pneumoniae* infection and there were insufficient data to analyse 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 (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.

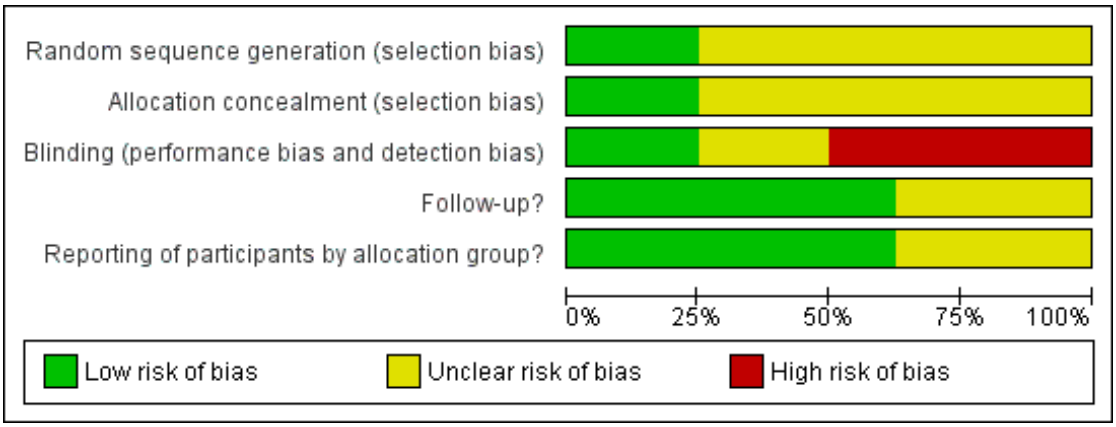
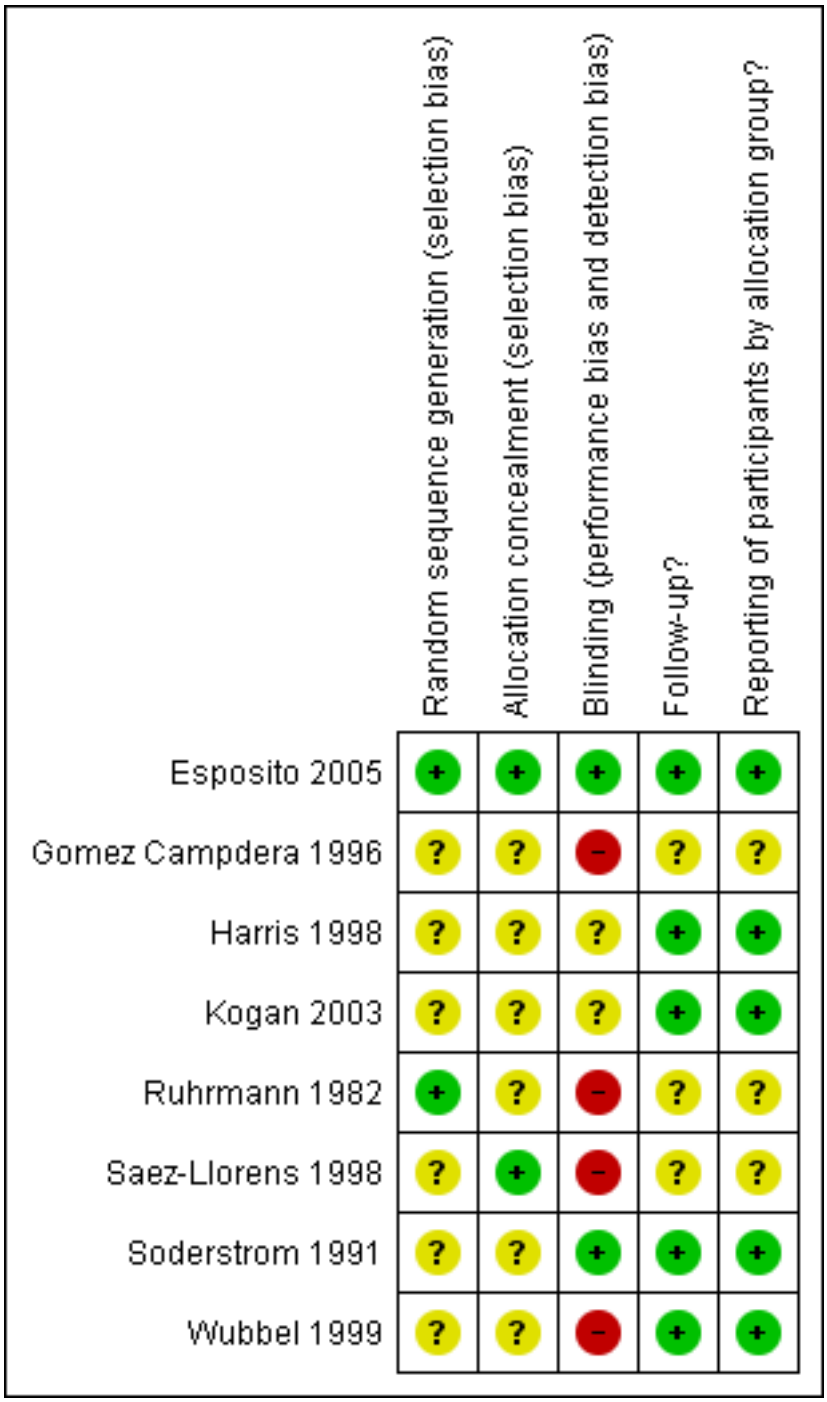


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Potential biases in the review process

We did not identify any potential biases in the review process.

Agreements and disagreements with other studies or reviews

Despite the commonality of *M. pneumoniae* LRTI in children (attributed in up to 40% of community-acquired pneumonia as 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. Such disparity in knowledge is exemplified by the conflicting advice given in paediatric textbooks (Phelan 1994; Rudolph 2003). This systematic review, as well as that conducted by Biondi 2014 showing concordant findings, reaffirms the need for such trials to be carried out.

AUTHORS' CONCLUSIONS

Implications for practice

Based on a single randomised controlled trial (RCT), it is likely that macrolides are efficacious in (at least) a small group of children with lower respiratory tract infection (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 manifestations range from being asymptomatic to death from its complications. 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 polymerase chain reaction (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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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Esposito 2005

Methods	• 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 was identified as having a history of recurrent respiratory tract infections (≥ 8 episodes/year in < 3-year olds or ≥ 6 episodes/year in ≥ 3-year olds) and an acute lower or upper respiratory tract infection, as diagnosed by a paediatrician and recorded on a medical chart • Exclusion criteria for the study group included acute streptococcal pharyngitis/acute otitis media/CAP 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 administration of benzathine penicillin G in the month preceding study enrolment • 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 • Acute *Mycoplasma pneumoniae* (*M. pneumoniae*) infection, *Chlamydia pneumoniae* (*C. pneumoniae*) 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
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 *M. pneumoniae* infection), and 208 were in the control group (mean age = 3.9, 57.2% male, 5 with acute *M. pneumoniae* 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	1. Clinical presentations 2. Bacteriological findings
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "All the patients were randomised in a blinded manner with a computerized list, by the only investigator responsible for randomisation"

Esposito 2005 (*Continued*)

		Comment: randomisation was appropriate
Allocation concealment (selection bias)	Low risk	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 (performance bias and detection bias) All outcomes	Low risk	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	Low risk	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	Low risk	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 amoxycillin-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 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 *M. pneumoniae* infection in each group not stated
Interventions	• Group A (n = 82): azithromycin 10 mg/kg/day OD for 3 days • Group B (n = 73): amoxycillin-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	1. Clinical presentations 2. Radiological findings 3. Adverse events
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not provided
Allocation concealment (selection bias)	Unclear risk	No description of allocation
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of outcome assessor
Follow-up? All outcomes	Unclear risk	There was no description of withdrawals or drop-outs
Reporting of participants by allocation group? All outcomes	Unclear risk	No mention of withdrawals or drop-outs

Harris 1998

Methods	• Participants were recruited from 23 centres with a diagnosis of CAP 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 1 of the following: fever or history of fever within 24 hours, cough, white cell count >= 12,000/mm^3, 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 amoxycillin-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 *M. pneumoniae* was determined by enzyme-linked immunosorbent assay and defined as either single positive serum IgM (>= 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 nor 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
Participants	• 456 children aged 6 months to 15 years with CAP were enrolled; males = 236 • 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

Harris 1998 (*Continued*)

	• 6 children discontinued treatment because of adverse events • The number of children with *M. pneumoniae* in the group randomised to macrolide versus non-macrolide (i.e. children < 5 years) was 30, with 21 in azithromycin group and 9 in amoxycillin-clavulanate group
Interventions	• Children under 5 years only • Group A (n = 125): azithromycin 10 mg/kg OD day 1, 1.5 mg/kg OD day 2 to 5, and placebo day 1 to 10 • Group B (n = 63): amoxycillin-clavulanate 40 mg/kg TID day 1 to 10 and placebo day 1 to 5
Outcomes	1. Clinical presentations 2. Radiological findings 3. Bacteriological findings 4. Adverse events
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not specified
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment were not identified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	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	Low risk	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	Low risk	The progress of all randomised children in each group was described, with numbers lost to exclusion and follow-up noted

Kogan 2003

Methods	• Participants with a diagnosis of CAP were recruited from 1 January 1996 to 1 January 1999 • Inclusion criteria were children with a clinical diagnosis of radiologically confirmed of presumed bacterial CAP, 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 amoxycillin or azithromycin, whereas participants in the atypical pneumonia group 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 for each child on study days 7 and 14. Evidence of infection was determined by indirect immunofluorescence and enzyme-linked immunosorbent assay to test sera for IgM antibodies to *M. pneumoniae*. An antibody titre > 1:16 on a single first serum specimen was considered positive for indirect immunofluorescence. Clinical response in the classic pneumonia group was defined as the proportion of children without fever on day 3 and/or improvement of more than 75% of radiographic baseline findings on study day 7
Participants	• 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 *M. pneumoniae* in the classic group was 8, with 5 in the azithromycin group and 3 in the amoxycillin-clavulanate group
Interventions	Patients with classic pneumonia: • Group A (n = 23): azithromycin 10 mg/kg OD for 3 days • Group B (n = 24): amoxycillin 75 mg/kg/day in 3 divided doses for 7 days
Outcomes	1. Clinical presentations 2. Radiological findings
Notes	-

Kogan 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomisation was not specified
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment were not identified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	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	Low risk	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	Low risk	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 chest X-ray. The study compared erythromycin therapy with amoxycillin 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, chest X-ray 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 *M. pneumoniae* infection in each group not stated

Ruhrmann 1982 (*Continued*)

Interventions	• Group A: erythromycin 70 to 80 mg/kg/day. Duration of therapy not stated • Group B: amoxycillin 60 to 70 mg/kg/day. Duration of therapy not stated
Outcomes	Clinical presentations
Notes	-

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A list of randomised numbers was used to allocate participants into treatment groups
Allocation concealment (selection bias)	Unclear risk	No mention of allocation concealment
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants or outcome assessors
Follow-up? All outcomes	Unclear risk	No description of losses to follow-up was included in the paper
Reporting of participants by allocation group? All outcomes	Unclear risk	Unclear mention of withdrawals or drop-outs

Saez-Llorens 1998

Methods	• Participants were recruited from emergency departments in Dallas and Panama with a diagnosis of CAP for the period February 1996 to December 1997 • Inclusion criteria were tachypnoea, fever, cough, crackles and chest X-ray 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 amoxycillin-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 days 2 to 3 and 10 to 25 • Baseline measurements were recorded using blood cultures, nasopharyngeal aspirate cultures and PCR for *M. pneumoniae* and *C. pneumoniae*. Antibody titres against the 2 micro-organisms were evaluated using serology. Additionally, full blood examination, 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
Participants	• 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) • 39 children dropped out. The number of children with *M. pneumoniae* infection in each group was not stated
Interventions	• Group A: azithromycin 10 mg/kg on day 1 and 5 mg/kg OD for days 2 to 5 • Group B: amoxycillin-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	1. Clinical presentations 2. Bacteriological findings 3. Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	List of randomised numbers assigned to therapy. Unclear how randomised numbers were generated but medication given by pharmacy
Allocation concealment (selection bias)	Low risk	Medications provided by pharmacy

Saez-Llorens 1998 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of outcome assessor
Follow-up? All outcomes	Unclear risk	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 risk	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) leukocytosis (> 10 x 109 leukocytes/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 *M. pneumoniae* 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. 2 patients dropped out. There were only 7 with bronchitis (lower respiratory tract infection) and *M. pneumoniae* 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	

Soderstrom 1991 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	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 (selection bias)	Unclear risk	Methods of allocation concealment were not specified
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The physician at the first visit and the nurse who met the patient at the follow-up visit did not know which prescription the patient had had" Comment: the outcome assessor was blinded. The participants and caregivers were presumably not blinded, as they were given prescriptions for their antibiotics
Follow-up? All outcomes	Low risk	Quote: "136/138 patients returned for follow-up within 10-12 days ... The 2 remaining patients interrupted the treatment within 2 days" Comment: 98.6% of participants were clinically assessed at the follow-up visit
Reporting of participants by allocation group? All outcomes	Low risk	The results table clearly compared the erythromycin and phenoxymethylpenicillin groups

Wubbel 1999

Methods	• Participants were recruited from an emergency clinic at the Children's Medical Centre Dallas, Texas with a diagnosis of CAP 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 amoxycillin-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, amoxycillin-clavulanate or erythromycin • There was no mention of blinding of participants, clinicians or outcome assessors, except the radiologists who reviewed all radiographs who 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 the 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 *M. pneumoniae* 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 (>= 1:10) or 4-fold increase in IgG titre
Participants	• 174 children aged 6 months to 16 years with CAP were enrolled • 6 patients were excluded because of normal chest X-rays. 21 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 *M. pneumoniae* was 12. However, it was not possible to determine how many children with *M. pneumoniae* were in the group < 5 years who were randomised to either azithromycin or amoxycillin-clavulanate because of the lack of individual patient data
Interventions	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): amoxycillin-clavulanate 40 mg/kg TID day 1 to 10

Wubbel 1999 (*Continued*)

Outcomes	1. Clinical presentations 2. Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Using a randomised list of therapy assignments..." Comment: the method of randomisation was not adequately specified
Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment were not identified
Blinding (performance bias and detection bias) All outcomes	High risk	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	Low risk	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	Low risk	The progress of all randomised children in each group was described

CAP: community-acquired pneumonia
IgG: immunoglobulin G
IgM: immunoglobulin M
n: number
OD: once daily
PCR: polymerase chain reaction
TID: three times a day

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

Study	Reason for exclusion
Atkinson 2007	Review of studies: cited most recent evidence for treating *M. pneumoniae* as "inconclusive"
Block 1995	Does not fulfil the inclusion criteria. Inappropriate comparator intervention as comparison between 2 drugs from the macrolide group - clarithromycin versus erythromycin ethylsuccinate
Bradley 2007	Does not fulfil the inclusion criteria and no specified aetiology. Inappropriate comparator intervention as comparison between fluoroquinolone and macrolides - levofloxacin versus clarithromycin/ceftriaxone with clarithromycin/erythromycin lactobionate. *M. pneumoniae* affecting the LRT and its treatments were not specifically identified
Chien 1993	Does not fulfil the inclusion criteria. Inappropriate comparator intervention as comparison between 2 drugs from the macrolide group - clarithromycin versus erythromycin
Esposito 2006	No focus on LRTIs. URTIs were the focus of this study
Fonseca-Aten 2006	No specified aetiology. *M. pneumoniae* affecting the LRT and its treatments were not specifically identified
Jensen 1967	Does not fulfil the inclusion criteria 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	Does not meet the inclusion criteria and too few participants. Inappropriate comparator intervention as comparison between 2 drugs from macrolide groups - clarithromycin versus erythromycin. Only 26 participants
Lee 2012	Does not fulfil the inclusion criteria. A small-scale (36 participants completed), adult-focused RCT with inappropriate comparator intervention as comparison between fluoroquinolone and combination macrolide and cephalosporin
Manfredi 1992	Does not fulfil the inclusion criteria. Inappropriate comparator intervention as comparison between 2 drugs from the macrolide group - azithromycin versus erythromycin
Nogeova 1997	Does not fulfil the inclusion criteria. Inappropriate comparator intervention as comparison between 2 drugs from the cephalosporin group - ceftibuten versus cefuroxime-axetil
Ronchetti 1994	Does not fulfil the inclusion criteria. Inappropriate comparator intervention as comparison between 2 drugs from the macrolide group - azithromycin versus josamycin
Sakata 2001	Study participants were not randomised
Schonwald 1990	Does not fulfil the inclusion criteria. Inappropriate comparator intervention as comparison between 2 drugs from the macrolide group - azithromycin versus erythromycin
Sempertegui 2014	Does not fulfil the inclusion criteria. Inappropriate comparator intervention as comparison between standard antimicrobial +/- zinc as an adjunct therapy

(*Continued*)

Simon 2006	Article unavailable for evaluation
Vasilos 1995	Study participants were not randomised
Wu 2014	Does not fulfil the inclusion criteria. Inappropriate comparator intervention as comparison between azithromycin +/- glucocorticoids as adjunct therapy
Yin 2002	Does not fulfil the inclusion criteria. Inappropriate comparator intervention as comparison between 2 drugs from the macrolide group - oral azithromycin versus intravenous erythromycin

LRT: lower respiratory tract
LRTI: lower respiratory tract infection
RCT: randomised controlled trial
URTI: upper respiratory tract infection

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Previous searches

2012 search details
MEDLINE (Ovid)
1 Pneumonia, Mycoplasma/
2 (mycoplasma adj3 pneumonia*).tw.
3 primary atypical pneumonia.tw.
4 or/1-3
5 Mycoplasma pneumoniae/
6 (mycoplasma pneumoniae or "M. pneumoniae").tw.
7 Mycoplasma Infections/
8 mycoplasma.tw.
9 or/5-8
10 exp Pneumonia/
11 (pneumon* or bronchopneumon* or pleuropneumon*).tw.
12 exp Bronchitis/
13 (bronchit* or tracheobronchit*).tw.
14 Respiratory Sounds/
15 wheez*.tw.
16 exp Respiratory Tract Infections/
17 (respiratory tract infection* or acute respiratory infection* or lower respiratory infection* or lower respiratory tract infection* or lrti).tw.
18 or/10-17
19 9 and 18
20 4 or 19
21 exp Anti-Bacterial Agents/
22 exp Macrolides/
23 exp Quinolones/
24 exp Tetracyclines/
25 antibiotic*.tw,nm.
26 (macrolide* or erythromycin* or roxithromycin* or clarithromycin* or azithromycin*).tw,nm.
27 or/21-26
28 20 and 27
EMBASE
#36 #27 AND #35
#35 #30 NOT #34
#34 #31 NOT #33
#33 #31 AND #32
#32 'human'/de AND [embase]/lim
#31 'animal'/de OR 'nonhuman'/exp OR 'animal experiment'/de AND [embase]/lim
#30 #28 OR #29
#29 random*:ab,ti OR placebo*:ab,ti OR allocat*:ab,ti OR trial:ti OR crossover*:ab,ti OR 'cross over':ab,ti OR (doubl* NEXT/1 blind*):ab,ti AND [embase]/lim

#28 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim
#27 #21 AND #26
#26 #22 OR #23 OR #24 OR #25
#25 erythromycin*:ab,ti OR roxithromycin*:ab,ti OR clarithromycin*:ab,ti OR azithromycin*:ab,ti OR macrolide*:ab,ti AND [embase]/lim
#24 antibiotic*:ab,ti AND [embase]/lim
#23 'macrolide'/exp OR 'quinolone derivative'/exp OR 'tetracycline derivative'/exp AND [embase]/lim
#22 'antibiotic agent'/exp AND [embase]/lim
#21 #4 OR #20
#20 #9 AND #19
#19 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#18 lrti:ab,ti AND [embase]/lim
#17 (infection* NEAR/1 ('respiratory tract' OR 'acute respiratory' OR 'lower respiratory' OR 'lower respiratory tract')):ab,ti AND [embase]/lim
#16 'respiratory tract infection'/de OR 'lower respiratory tract infection'/de AND [embase]/lim
#15 wheez*:ab,ti AND [embase]/lim
#14 'wheezing'/de AND [embase]/lim
#13 bronchit*:ab,ti OR tracheobronchit*:ab,ti AND [embase]/lim
#12 'bronchitis'/exp AND [embase]/lim
#11 pneumon*:ab,ti OR bronchopneumon*:ab,ti OR pleuropneumon*:ab,ti AND [embase]/lim
#10 'pneumonia'/exp AND [embase]/lim
#9 #5 OR #6 OR #7 OR #8
#8 mycoplasma:ab,ti AND [embase]/lim
#7 'mycoplasmosis'/de AND [embase]/lim
#6 'mycoplasma pneumoniae':ab,ti OR 'm. pneumoniae':ab,ti AND [embase]/lim
#5 'mycoplasma pneumoniae'/de AND [embase]/lim
#4 #1 OR #2 OR #3
#3 'primary atypical pneumonia':ab,ti AND [embase]/lim
#2 (mycoplasma NEAR/3 pneumonia):ab,ti AND [embase]/lim
#1 'mycoplasma pneumonia'/de AND [embase]/lim

2010 search details

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).

We used the following search terms for MEDLINE and CENTRAL and adapted them for EMBASE. We combined the search terms used in MEDLINE 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).

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

EMBASE

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
We imposed no language or publication restrictions.

2005 search details

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).
We used the following search terms for MEDLINE and CENTRAL and adapted them for EMBASE. We combined the search terms used in MEDLINE with the highly sensitive strategy devised by 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
We imposed no language or publication restrictions.

Appendix 2. MEDLINE, CENTRAL, WHO ICTRP and ClinicalTrials.gov search strategy

MEDLINE (Ovid)

1 Pneumonia, Mycoplasma/
2 (mycoplasma adj3 pneumon*).tw.
3 primary atypical pneumonia.tw.
4 or/1-3
5 Mycoplasma pneumoniae/
6 (mycoplasma pneumoniae or "M. pneumoniae").tw.
7 Mycoplasma Infections/
8 mycoplasma.tw.
9 or/5-8
10 exp Pneumonia/
11 (pneumon* or bronchopneumon* or pleuropneumon*).tw.
12 exp Bronchitis/
13 (bronchit* or tracheobronchit*).tw.
14 Respiratory Sounds/
15 wheez*.tw.
16 exp Respiratory Tract Infections/
17 (respiratory tract infection* or acute respiratory infection* or lower respiratory infection* or lower respiratory tract infection* or lrti).tw.
18 or/10-17
19 9 and 18
20 4 or 19
21 exp Anti-Bacterial Agents/
22 exp Macrolides/
23 exp Quinolones/
24 exp Tetracyclines/
25 antibiotic*.tw,nm.
26 (macrolide* or erythromycin* or roxithromycin* or clarithromycin* or azithromycin*).tw,nm.
27 or/21-26
28 20 and 27

Appendix 3. EMBASE search strategy

#36 #27 AND #35
#35 #30 NOT #34
#34 #31 NOT #33
#33 #31 AND #32
#32 'human'/de AND [embase]/lim
#31 'animal'/de OR 'nonhuman'/exp OR 'animal experiment'/de AND [embase]/lim
#30 #28 OR #29
#29 random*:ab,ti OR placebo*:ab,ti OR allocat*:ab,ti OR trial:ti OR crossover*:ab,ti OR 'cross over':ab,ti OR (doubl* NEXT/1 blind*):ab,ti AND [embase]/lim
#28 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim
#27 #21 AND #26
#26 #22 OR #23 OR #24 OR #25
#25 erythromycin*:ab,ti OR roxithromycin*:ab,ti OR clarithromycin*:ab,ti OR azithromycin*:ab,ti OR macrolide*:ab,ti AND [embase]/lim
#24 antibiotic*:ab,ti AND [embase]/lim
#23 'macrolide'/exp OR 'quinolone derivative'/exp OR 'tetracycline derivative'/exp AND [embase]/lim
#22 'antibiotic agent'/exp AND [embase]/lim

#21 #4 OR #20
#20 #9 AND #19
#19 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#18 lrti:ab,ti AND [embase]/lim
#17 (infection* NEAR/1 ('respiratory tract' OR 'acute respiratory' OR 'lower respiratory' OR 'lower respiratory tract')):ab,ti AND [embase]/lim
#16 'respiratory tract infection'/de OR 'lower respiratory tract infection'/de AND [embase]/lim
#15 wheez*:ab,ti AND [embase]/lim
#14 'wheezing'/de AND [embase]/lim
#13 bronchit*:ab,ti OR tracheobronchit*:ab,ti AND [embase]/lim
#12 'bronchitis'/exp AND [embase]/lim
#11 pneumon*:ab,ti OR bronchopneumon*:ab,ti OR pleuropneumon*:ab,ti AND [embase]/lim
#10 'pneumonia'/exp AND [embase]/lim
#9 #5 OR #6 OR #7 OR #8
#8 mycoplasma:ab,ti AND [embase]/lim
#7 'mycoplasmosis'/de AND [embase]/lim
#6 'mycoplasma pneumoniae':ab,ti OR 'm. pneumoniae':ab,ti AND [embase]/lim
#5 'mycoplasma pneumoniae'/de AND [embase]/lim
#4 #1 OR #2 OR #3
#3 'primary atypical pneumonia':ab,ti AND [embase]/lim
#2 (mycoplasma NEAR/3 pneumonia):ab,ti AND [embase]/lim
#1 'mycoplasma pneumonia'/de AND [embase]/lim

Appendix 4. WHO ICTRP and ClinicalTrials.gov searches

1 mycoplasma AND pneumonia AND antibiotics
2 (condition - mycoplasma pneumonia) + (intervention - antibiotics) + (type - interventional study)

WHAT'S NEW

Last assessed as up-to-date: 8 July 2014.

Date	Event	Description
8 July 2014	New search has been performed	A new author joined the review team.
8 July 2014	New citation required but conclusions have not changed	Searches updated. We did not include any new trials and we excluded three new trials (Lee 2012; Sempertegui 2014; Wu 2014).

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 3, 2005

Date	Event	Description
15 March 2012	New citation required but conclusions have not changed	A new author joined the review team.
13 March 2012	New search has been performed	Searches conducted.
22 February 2010	New search has been performed	Searches conducted. One new included trial (Esposito 2005) and six new excluded trials (Atkinson 2007; Bradley 2007; Esposito 2006; Fonseca-Aten 2006; Lee 2008; Simon 2006) have been added to the update.
22 February 2010	New citation required and conclusions have changed	A new author joined the review team. The conclusion has changed to reflect the new included trial
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, extracted data and wrote the review. Anne Chang (AC) edited and co-wrote the protocol, independently selected papers for inclusion, assessed quality, extracted data, and edited and co-wrote the review.

For the 2010 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.

For the 2012 update, Malcolm Gillies (MG) and AC reviewed the literature searches.

In this 2014 review update Samantha Gardiner (SG) and AC independently assessed the literature searches. SG updated the text body and table of excluded studies, which was checked by AC and the revised version reviewed by all authors.

DECLARATIONS OF INTEREST

Samantha J Gardiner: none known.

John B Gavranich: none known.

Anne B Chang is a recipient of a GlaxoSmithKline grant towards the study of microbia in bronchoalveolar lavage (BAL), a topic unrelated to this review. AC has received funding from Johnson and Johnson (J&J) to present at the World Paediatric series, though the talk does not endorse nor make reference to J&J. AC is also the principal investigator on a study examining azithromycin for bronchiolitis in Indigenous children.

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Internal sources

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

External sources

- NHMRC, Australia.

Practitioner Fellowship salary support for AC (grant 545216)

INDEX TERMS

Medical Subject Headings (MeSH)

*Mycoplasma pneumoniae; Amoxicillin-Potassium Clavulanate Combination [therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Azithromycin [therapeutic use]; Bronchitis [*drug therapy; microbiology]; Community-Acquired Infections [drug therapy; microbiology]; Erythromycin [therapeutic use]; Pneumonia, Mycoplasma [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans