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Antibiotics for bronchiolitis in children

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Antibiotics for bronchiolitis in children (Review)

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[Intervention Review]

Antibiotics for bronchiolitis in children

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ABSTRACT

Background

Bronchiolitis is a serious, potentially life-threatening respiratory illness commonly affecting babies. It is often caused by respiratory syncytial virus (RSV). Antibiotics are not recommended for bronchiolitis unless there is concern about complications such as secondary bacterial pneumonia or respiratory failure. Nevertheless, they are used at rates of 34% to 99% in uncomplicated cases.

Objectives

To evaluate the effectiveness of antibiotics for bronchiolitis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2010, issue 4), which includes the Cochrane Acute Respiratory Infection Group's Specialised Register, and the Database of Abstracts of Reviews of Effects, MEDLINE (January 1966 to November 2010), EMBASE (1990 to December 2010) and Current Contents (2001 to December 2010).

Selection criteria

Randomised controlled trials (RCTs) comparing antibiotics to placebo in children under two years diagnosed with bronchiolitis, using clinical criteria (including respiratory distress preceded by coryzal symptoms with or without fever). Primary clinical outcomes included time to resolution of signs or symptoms (pulmonary markers included respiratory distress, wheeze, crepitations, oxygen saturation and fever). Secondary outcomes included hospital admissions, length of hospital stay, re-admissions, complications or adverse events and radiological findings.

Data collection and analysis

Two review authors independently analysed the search results.

Main results

Five studies (543 participants) met our inclusion criteria. One study randomised 52 children to either ampicillin or placebo and found no significant difference between the two groups for length of illness. A small study (21 children) with higher risk of potential bias randomised children with proven RSV infection to clarithromycin or placebo and found clarithromycin may reduce hospital re-admission (8% antibiotics versus 44% placebo; Fishers exact; P = 0.081). The two studies (267 children) providing adequate data for

length of hospital stay showed no difference between antibiotics and control (pooled mean difference 0.34; 95% CI -0.71 to 1.38). Two studies randomised children to intravenous ampicillin, oral erythromycin and control and found no difference for most symptom measures. None of the trials reported deaths.

Authors' conclusions

This review found minimal evidence to support the use of antibiotics for bronchiolitis. Research to identify a possible small subgroup of patients who have complications from bronchiolitis such as respiratory failure and who may benefit from antibiotics is justified.

PLAIN LANGUAGE SUMMARY

Antibiotics for bronchiolitis in babies

Bronchiolitis is a serious respiratory illness that often affects young babies. It is most commonly caused by respiratory syncytial virus (RSV) and is the most common reason for hospitalisation in babies under the age of six months. Babies usually present with runny nose, cough, shortness of breath and signs of respiratory distress which can become life-threatening. Despite its viral cause, antibiotics are prescribed in 34% to 99% of cases. Prescribers may be expecting benefits from anti-inflammatory effects attributed to some antibiotics or be concerned about secondary bacterial infection, particularly in children who are very unwell and require intensive care admission.

This systematic review found five trials (543 participants) comparing antibiotics with placebo or no antibiotics. Two of these also compared intravenous and oral antibiotics. Two trials showed that antibiotics are no better than placebo at reducing the length of illness of bronchiolitis and hospitalisation. Two more recent studies comparing antibiotics with no antibiotics found no improvement in the length of illness or hospitalisation. One smaller, poorer quality trial found benefit for antibiotics over placebo for some outcomes. Only one of the five included trials had a low risk of bias. Antibiotics may be justified in children who are very unwell and requiring intensive care admission. Antibiotics need to be used cautiously owing to the potential for side effects, cost to the patient and the community and increasing bacterial resistance to antibiotics.

BACKGROUND

Description of the condition

Bronchiolitis is a serious, potentially life-threatening respiratory illness that often affects young babies. It occurs most frequently in the first year of life and is the commonest cause of hospital admissions in infants under six months of age (Wohl 1978). The most commonly identified pathogen is respiratory syncytial virus (RSV). Other viruses such as human meta-pneumovirus (HMPV), influenza, parainfluenza, adenovirus and rhinovirus have also been implicated (Williams 2004). Other less common pathogens include *Mycoplasma pneumoniae (M. pneumoniae)* which can occur in sporadic outbreaks (Glezen 1971; Rose 1987). The diagnosis is most often made on clinical grounds, which usually includes tachypnoea and wheezing in children under two years of age (Bordley 2004). Immunofluorescence and culture of the nasopharyngeal aspirate may be used to determine the causative organism and may reduce antibiotic use (Christakis 2005). A chest X-ray may show hyperinflation and patchy atelectasis (Smyth 2006). There are few effective therapies, including antiviral therapies (Smyth 2006).

Description of the intervention

Antibiotics are not recommended unless there is concern about complications such as secondary bacterial pneumonia (Fitzgerald 2004; Lozano 2002). This is based on evidence suggesting a low risk of bacteraemia (0.2%) in children with bronchiolitis and fever - a lower risk than for children with a fever without a recognisable illness, where the rate ranges from 2% to 7% (Greenes 1999). Antibiotic use comes with significant harms including common adverse reactions (rash, abdominal pain, diarrhoea and vomiting), cost and community bacterial resistance (Brook 1998).
Infants with severe bronchiolitis requiring mechanical ventilation have been shown to have high rates of bacterial co-infection. Bacterial co-infection rates vary from 21% (Thorburn 2006) to 26% (Kneyber 2005) measured in both from endotracheal aspirates. Consistent with these results, Kneyber 2005 reported antibiotic

use at 95% in infants with bronchiolitis in intensive care.
Antibiotics are commonly used in hospitalised infants even in children who are not ventilated, at rates of 34% (Vogel 2003), 45% (Christakis 2005; Thorburn 2006) and 99% (Kabir 2003). In one outpatient study antibiotics were used in 53% of children with bronchiolitis. (Halna 2005)

How the intervention might work

Antibiotics may be useful in cases of illness where superinfection with bacteria occurs, although it is unlikely that antibiotics will be effective for a condition that only has a viral cause. However, some antibiotics may have anti-inflammatory effects which may improve symptoms.

Why it is important to do this review

The use of antibiotics for uncomplicated bronchiolitis is common yet is not justified by our understanding of bronchiolitis as a viral illness. The discord between clinical practice and the pathophysiological understanding of bronchiolitis as a viral illness will benefit from the empirical evidence offered by this systematic review.

OBJECTIVES

The objective of this review is to evaluate clinical outcomes resulting from the use of antibiotics for bronchiolitis in children compared to placebo or other interventions.

METHODS

Criteria for considering studies for this review

Types of studies

Single or double-blind randomised controlled trials (RCTs) comparing antibiotics to placebo or control to treat bronchiolitis.

Types of participants

Children under the age of two years diagnosed with bronchiolitis using clinical criteria, such as respiratory distress preceded by coryzal symptoms, with or without fever.

Types of interventions

Oral, intravenous, intramuscular or inhaled antibiotics versus placebo.

Types of outcome measures

Primary outcomes

Time for the resolution of symptoms/signs:

1. pulmonary markers;
2. respiratory distress;
3. wheeze;
4. crepitations;
5. oxygen saturation; and
6. fever.

Secondary outcomes

1. Hospital admissions.
2. Time to discharge from hospital.
3. Re-admissions.
4. Complications/adverse events developed.
5. Radiological findings.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases: *The Cochrane Library*, Cochrane Central Register of Controlled Trials (CENTRAL 2010, issue 4), which includes the Cochrane Acute Respiratory Infection Group's Specialised Register, and the Database of Abstracts of Reviews of Effects (DARE 2010, Issue 4), MEDLINE (January 1966 to November Week 3, 2010), EMBASE (1990 to December 2010) and Current Contents (2001 to December 2010).
We used multiple strategies to identify as many trials as possible that met the inclusion criteria, regardless of language or publication status. We used the following search terms to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision): Ovid format (Lefebvre 2011). We modified these terms to search EMBASE (see Appendix 1) and Current Contents (see Appendix 2).

MEDLINE (OVID)

1 exp Bronchiolitis/
2 bronchiolit$.mp.
3 exp Respiratory Syncytial Viruses/

4 exp Respiratory Syncytial Virus Infections/
5 (respiratory syncytial virus$ or RSV$).mp.
6 1 or 2 or 3 or 4 or 5
7 exp Anti-Bacterial Agents/
8 antibiotic$.mp.
9 exp Macrolides/
10 (macrolide$ or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin).mp.
11 exp Cephalosporins/
12 (cephalosporin$ or cephalexin or cephaclor or cefaclor or cefepime or cefotaxime or cephamycin$ or cefotetan or cefoxitin or cefmetazole or cefpirome or cefpodoxime or ceftazidime or ceftriaxone or cephamandole or cephazolin).mp.
13 exp Penicillins/
14 (penicillin$ or amoxicillin or amoxycillin or ampicillin or benzylpenicillin or cloxacillin or dicloxacillin or flucloxacillin or piperacillin or ticarcillin or sulbactam).mp.
15 exp Fluoroquinolones/
16 (fluoroquinolone$ or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or pefloxacin or fleroxacin or levofloxacin or moxifloxacin).mp.
17 exp Tetracycline/
18 (tetracycline$ or doxycycline or methacycline or minocycline).mp.
19 (amikacin or gentamicin or neomycin or netilmicin).mp.
20 (clindamycin or lincomycin).mp.
21 (chloramphenicol or amantadine or cotrimoxazole or trimethoprim).mp.
22 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23 exp Child/
24 (children or infant$ or pediatric or pediatric).mp.
25 23 or 24
26 6 and 22 and 25

Searching other resources

We considered all languages. We handsearched the references of all identified studies. One review author (GS) and an expert librarian (LE) carried out the search. We contacted experts in the field looking for unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (GS, CDM) independently scanned abstracts from the initial search results to identify trials that loosely met the inclusion criteria. Two review authors (CDM, JD) independently reviewed the full-text articles and applied the inclusion criteria.

Data extraction and management

Two review authors (CDM, JD) independently extracted data from included studies using data extraction forms which included type of intervention, adverse events, continuous and dichotomous outcomes. We also noted the setting (hospital or primary care), study population and any additional interventions or tests.

Assessment of risk of bias in included studies

We rated the quality of each eligible RCT according to the 'Risk of bias' tool available in RevMan 5.1 (RevMan 5.1) and criteria set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed methodological quality under the headings of allocation, blinding, incomplete outcome data, selective reporting and other potential sources of bias. Two review authors (JD, CDM) independently assessed the methodological quality of the new included trials for this review update. We resolved any disagreement between the review authors by discussion.

Measures of treatment effect

We analysed data using RevMan 5.1 (RevMan 5.1). We expressed continuous data comparisons using mean differences (MD) where there was one study or standardised mean difference (SMD) where more than one study used different measurement scales. We expressed dichotomous data using odds ratios (OR). We pooled data into clinical outcomes where multiple trial results for the same clinical presentation existed and heterogeneity did not preclude pooling of results

Unit of analysis issues

The unit of analysis for each outcome was the individual research participant.

Dealing with missing data

Intention-to-treat (ITT) analyses were conducted in Kneyber 2008 (no drop outs) and Kabir 2009 (10% drop outs, 32/327). In the other three included studies it is not clear if ITT analyses were carried out. In Mazumder 2009, 17.5% of participants dropped out (22/126), while Field 1966 and Tahan 2007 had small numbers of drop outs.

Assessment of heterogeneity

We were only able to combine data for deaths and length of hospital stay. Given there were no deaths we cannot assess heterogeneity for that outcome. The two studies providing sufficient data to compare length of hospital stay gave heterogenous results.

Assessment of reporting biases

There was no evidence of publication bias nor reporting bias.

Data synthesis

We undertook meta-analysis for outcomes where there were sufficient comparable data. Only two outcomes fitted this bill: deaths and length of hospital stay. We were not able to combine symptom measures owing to a lack of comparability of outcome measures or the timing of measure was irreconcilably different. We undertook narrative synthesis of the majority of results.

Subgroup analysis and investigation of heterogeneity

Not applicable.

Sensitivity analysis

Not applicable.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Initial database searching revealed the following results: 173 articles in MEDLINE, 102 articles in EMBASE, 23 articles in CENTRAL and two articles in DARE. Of these 300 articles, we rejected 297 on the basis of title and abstract alone leaving three studies. In this 2011 update, an additional 259 studies were identified, with 35 duplicates and 220 rejected on title and abstract alone with four studies remaining. Of the seven studies identified from initial and updated searches, two were excluded: one because it did not involve clinical criteria for inclusion (Friis 1984) and one because it did not involve an antibiotic (Boogaard 2007). Five studies did meet inclusion criteria (Field 1966; Kabir 2009; Kneyber 2008; Mazumder 2009; Tahan 2007).

Included studies

Field 1966, Tahan 2007, Kneyber 2008, Mazumder 2009 and Kabir 2009 met the inclusion criteria randomising children to antibiotics or control group. All study participants were children under two years of age except for Tahan 2007 which only included children under seven months of age. Two studies were conducted in low-income countries (Kabir 2009; Mazumder 2009), both in Bangladesh. These two studies compared oral erythromycin with intravenous ampicillin and control. One study was conducted in an upper-middle income country (Tahan 2007) (Turkey) and this study compared clarithromycin with placebo. Kneyber 2008, conducted in a high-income country, compared azithromycin with placebo. Field 1966, also conducted in a high-income country, compared oral ampicillin with placebo. All studies included participants who were hospitalised and only one study recruited from an outpatients department (Mazumder 2009).

Excluded studies

Boogaard 2007 did not study antibiotics for bronchiolitis. One study was excluded (Friis 1984) because it dealt with both pneumonia and bronchiolitis using crepitations and radiography as criteria for patient selection. The study did perform a subgroup analysis of the two groups (antibiotics and placebo) based on virological diagnosis and these results are discussed.

Risk of bias in included studies

Risk of bias is summarised in Figure 1 and Figure 2.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

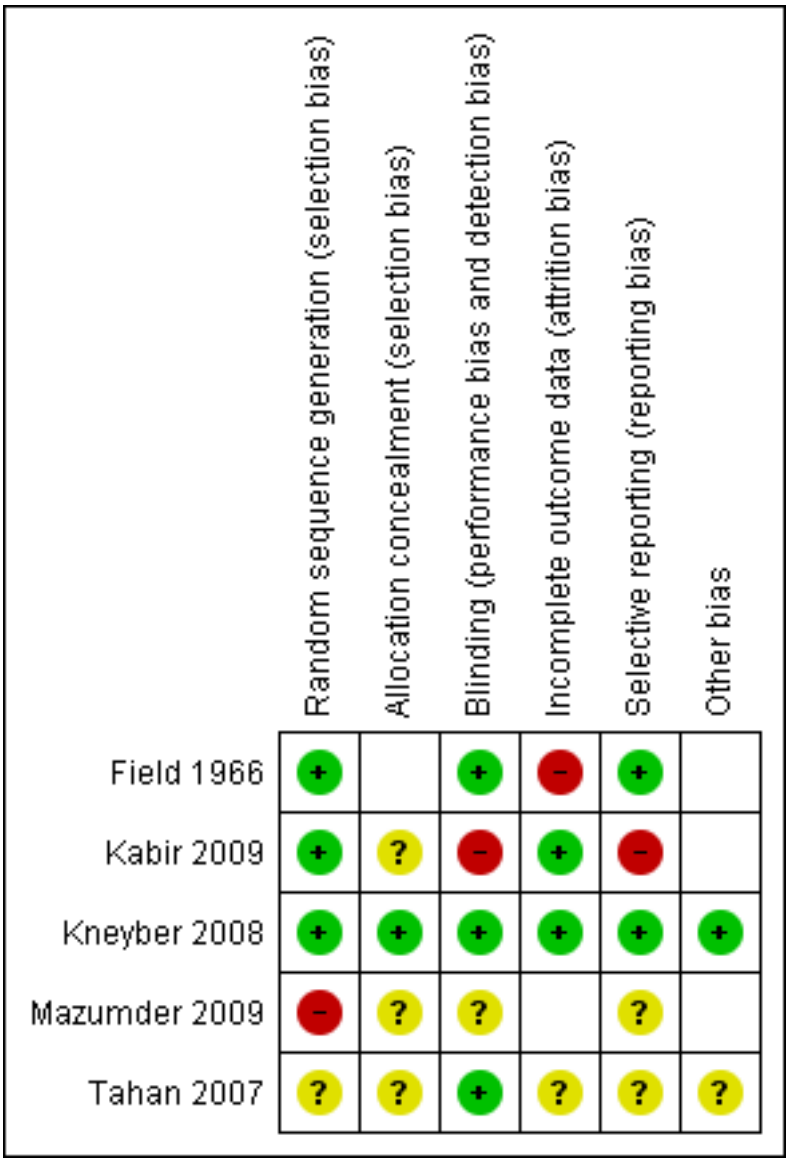
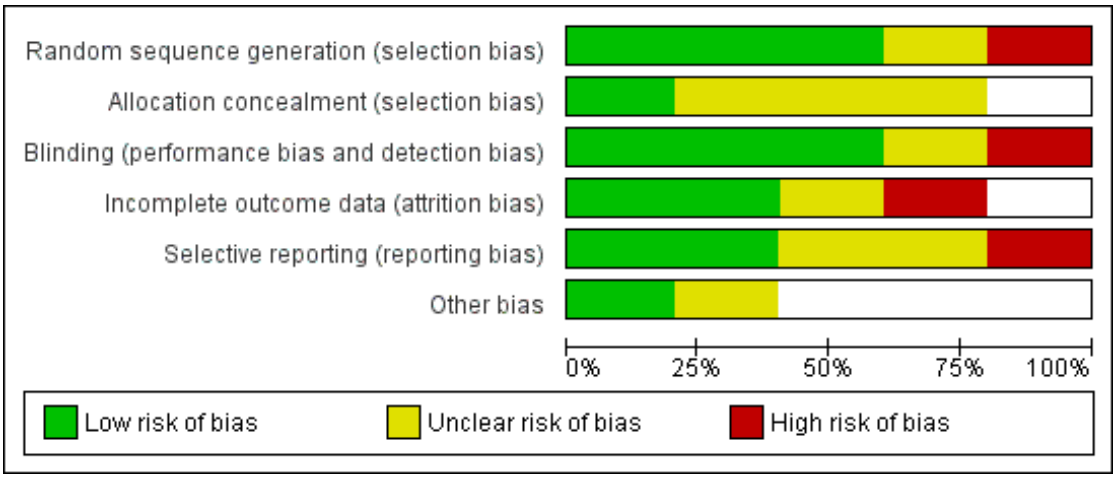


Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Sequence generation was adequately described by Kneyber 2008 and Kabir 2009. Field 1966 probably also used an adequate randomisation procedure. The randomisation process for Tahan 2007 is not adequately described and it was not adequately described in Mazumder 2009. Only one of the five included studies adequately described allocation concealment (Kneyber 2008).

Blinding

Three studies described adequate blinding of participants (all infants), their parents and the investigators. Two did not discuss blinding (Kabir 2009; Mazumder 2009). None of the studies described blinding of the outcome assessor.

Incomplete outcome data

In the Mazumder 2009 trial, 22 participants (out of 124) were excluded because they did not attend regular follow up (18) or were persistently unwell. In the Kabir 2009 trial, 17 children were referred to tertiary care where there was access to paediatric intensive care and for 15 children their parents withdrew or they left their respective hospitals. In Tahan 2007, nine participants were excluded because they took corticosteroids. There were only 15 participants in each group and six were excluded from the placebo group for taking corticosteroids and three from the clarithromycin group. In Field 1966, eight patients were excluded from the study owing to symptom severity (three from the ampicillin group and five from the placebo group) with an extra two participants (one from each group) lost to follow up at the end of the trial. There were no drop outs from the Kneyber 2008 trial.

Selective reporting

There are no concerns about selective reporting.

Other potential sources of bias

No other concerns were identified.

Effects of interventions

Oral ampicillin versus placebo

Field 1966 randomised infants with the clinical presentation of bronchiolitis to either placebo (24 patients) or ampicillin (28 patients). The main outcome measure was length of illness. This was found to be 9.54 days in the group receiving ampicillin and 9.7 days in the group receiving placebo. This was not a significant difference as calculated by the study authors. There were insufficient data provided for us to independently confirm this. There were no deaths in either group.

One excluded study (Friis 1984) analysed separately a subgroup of children in their trial who tested positive for RSV. This trial randomised 150 children who had either fine crepitating rales or pulmonary consolidation on chest radiograph to either antibiotics (ampicillin) or no antibiotics. While this trial did not start by selecting children with a clinical presentation of bronchiolitis, the results of the subgroup analysis are relevant. In children who were RSV-positive, there was no significant difference found between the antibiotic and no antibiotic groups for the outcomes of fever, pulmonary symptoms, duration of hospital stay, otitis media or chest radiograph findings.

Oral macrolide antibiotic versus placebo

Tahan 2007 randomised infants younger than seven months admitted to a department of paediatrics in Turkey to clarithromycin for three weeks (15) or placebo (15) if they were found to be positive for an RSV immunofluorescent test. Nine participants were excluded owing to corticosteroid use leaving 12 in the clarithromycin group and nine in the placebo group. Median hospital stay on clarithromycin was 2.13 days (interquartile range: 2 to 2.83) compared to 3.67 days (3 to 4.17). One participant was readmitted in the clarithromycin group (8.3%) and four in the placebo group (44%). Duration of beta-agonist use in the clarithromycin group was five days (interquartile range: 5 to 7), for placebo seven days (5 to 7). Duration of oxygen use in the clarithromycin group was 31 hours (interquartile range: 28 to 42), for placebo 72 hours (52 to 80). Duration of intravenous fluids for the clarithromycin group was 26 hours (interquartile range: 22 to 36) and for placebo 56 hours (46 to 66).

Kneyber 2008 randomised infants younger than 24 months with clinically-suspected viral bronchiolitis who were admitted to hospital in the Netherlands to azithromycin (32 children) and placebo (39 children). The primary outcome was length of hospital admission, which was 5.5 days (standard deviation (SD) 2.55) in the azithromycin group and 5.82 days (SD 2.0), resulting in a mean difference of -0.32 (95% confidence interval (CI) -1.40 to 0.76). Beta-agonists were used by 17 participants (mean duration: 2.8 days +/- 0.6 standard error (SE)) in the azithromycin group and 23 participants (three days +/- 0.4 SE) in the placebo group. Oxygen was used by 20 participants in the azithromycin group (mean duration: 3.8 days +/- 0.4 SE) and 31 participants in the placebo group (mean duration 3.4 days +/- 0.3). Other outcomes are tabled (Table 1).

Oral macrolide antibiotic (erythromycin) versus parenteral ampicillin versus control

Mazumder 2009 randomised infants younger than 24 months (and older than one month) with clinically suspected bronchiolitis to intravenous ampicillin (29 children), oral erythromycin (32 children) and no antibiotics (43 children). Symptoms (wheeze, shortness of breath, oxygen saturation less than 96%, lack of social smile and feeding difficulties) were measured on days one, three and five. There were significantly fewer children with wheeze in the oral erythromycin group on day three but significantly fewer children with wheeze in the control group on day five. None of the other symptom measures differed significantly between the three groups. Full results as reported by this study for the three groups are tabled with Chi^2 test results and significance levels (Table 2). The two antibiotic arms of this trial were also combined and compared with control. For most comparisons there was no significant difference between antibiotics and control. For the outcome of wheeze on day 3, significantly fewer children had wheeze in the antibiotics arm (OR 0.27; 95% CI 0.12 to 0.62) (Analysis 7.1). However, on day five significantly more children in the antibiotics arm had wheeze compared with control (OR 5.55; 95% CI 1.18 to 26.05) (Analysis 7.1).

Kabir 2009 randomised infants younger than 24 months with clinical signs of bronchiolitis (hospitalised with runny nose, cough, breathing difficulty, chest indrawing and rhonchi on auscultation). Symptom resolution was measured as rapid (less than four days) or gradual (more than four days). None of the symptom measures differed significantly between parenteral ampicillin, oral erythromycin and control (Table 3). Length of hospital stay did not differ significantly between parenteral ampicillin and oral erythromycin and control (Analysis 3.1).

Meta-analysis

There were no deaths in any arms of any of the five included trials. For the outcome of length of hospital stay, the oral erythromycin arm has been used from Kabir 2009 to provide a comparison with the azithromycin arm of Kneyber 2008. There was no significant difference (MD 0.34; 95% CI -0.71 to 1.38). The two study results are heterogenous. Unfortunately incomplete data from Tahan 2007 precludes comparison with this study.

While Kabir 2009 and Mazumder 2009 have the same intervention arms they either measured symptoms at markedly different times (for example, fever, wheeze, cough, shortness of breath) or used an incomparable measure (for example, oxygen saturation < 96% (Mazumder 2009) versus oxygen saturation < 90% (Kabir 2009)).

DISCUSSION

Summary of main results

Four included studies did not find any difference between antibiotics and placebo for their primary outcomes of length of illness (Field 1966) or length of hospital stay (Kabir 2009; Kneyber 2008; Mazumder 2009). One small study of uncertain quality found

that three weeks of clarithromycin significantly reduced hospital admission compared to placebo (Tahan 2007). Another study of uncertain quality found mixed results for the effects of antibiotics on wheeze but no difference for other symptom measures (Mazumder 2009).

Overall completeness and applicability of evidence

Clinicians may be concerned that if they do not use antibiotics in a child presenting with a fever and clinical symptoms and signs of bronchiolitis, they may be putting the child at risk of serious complications such as pneumonia, septicaemia and death. It has already been noted that children with this presentation are very unlikely to have an occult bacteraemia (Greenes 1999). In one study, paediatricians were less likely to evaluate febrile infants presenting with clinical signs of bronchiolitis for sepsis. In this series of 219 febrile infants with clinical signs of bronchiolitis, none had a serious bacterial infection and it was concluded that selective evaluation for sepsis in this population of febrile infants is appropriate (Luginbuhl 2008).

This 2011 updated review includes four new randomised controlled trials (RCTs), all of which investigated the use of macrolide antibiotics for bronchiolitis. Macrolides are thought to have anti-inflammatory activities as well as antibiotic activity (Culic 2001) and so were thought to have potential in treating bronchiolitis, a viral condition. Additionally clarithromycin, a macrolide antibiotic, has been shown to have immune modulatory effects (Ichiyama 2001). One included study (Tahan 2007) hypothesised that clarithromycin would be beneficial for bronchiolitis and found clinical benefit from clarithromycin. However, firm conclusions about the benefits of clarithromycin for bronchiolitis cannot be drawn from this study of 21 participants because of the small numbers and the high risk of potential bias.

Another study examining a macrolide antibiotic, azithromycin (Kneyber 2008), hypothesised that macrolide antibiotics would make no difference for bronchiolitis and this was what this study found. Kneyber 2008 was a larger study and had fewer quality appraisal concerns. Mazumder 2009 and Kabir 2009 compared intravenous ampicillin and oral erythromycin for bronchiolitis and found no significant difference between the two. There was also no significant difference with control. For Mazumder 2009, the mixed results of antibiotics on the outcome of wheeze and high risk of potential bias means this study cannot support the use of antibiotics in bronchiolitis. No firm conclusions can be drawn from the empirical evidence contained in this review regarding the benefits of macrolide antibiotics for bronchiolitis.

Methods to reduce antibiotic use for bronchiolitis have been investigated. Wilson 2002 found that a clinical pathway reduced inpatient antibiotic use for bronchiolitis from 27% to 9%.

Children with a serious illness requiring admission to intensive care and especially those requiring ventilation may have higher rates of bacterial co-infection possibly justifying the increased use of antibiotics in this setting (Kneyber 2005; Thorburn 2006). There have been no RCTs assessing the usefulness of antibiotics for bronchiolitis in an intensive care setting. Bloomfield 2004 found that aside from intensive care admission (2.9% with bacteraemia), children with a respiratory syncytial virus (RSV) infection are more likely to be bacteraemic if they have a nosocomial RSV infection (6.5% bacteraemia) or cyanotic congenital heart disease (6.6% bacteraemia). The baseline rate of bacteraemia in children with RSV bronchiolitis in this study was 0.6%. However, a small study conducted in a paediatric intensive care unit in the United States found that otherwise low-risk infants (23 infants) with RSV bronchiolitis and respiratory failure had rates of concomitant bacterial pneumonia at 20% or higher (Levin 2010). Further evaluation of the risk of secondary bacterial infection following bronchiolitis would help inform the role of antibiotics in this viral infection, especially in the context of respiratory failure.

Quality of the evidence

Three small RCTs have examined antibiotics versus placebo with only 72 participants in antibiotic arms and 72 participants in placebo arms. The two studies (Field 1966; Kneyber 2008) describing adequate randomisation conducted in high-income countries did not find any difference between antibiotic and placebo arms. The study which found clarithromycin more likely to reduce hospital admission than placebo did not adequately describe randomisation nor allocation concealment and 30% of those randomised were excluded owing to co-administration of corticosteroids (Tahan 2007). The inconsistency of results seems most likely to be owing to the differences in methodological quality. The study by Tahan 2007 was the only one to use clarithromycin and the only study to use antibiotics for three weeks. Three studies have been conducted in low-income countries (Kabir 2009; Mazumder 2009; Tahan 2007). Both Mazumder 2009 and Kabir 2009 were studies which were at high risk of potential bias. The included study of highest quality in this review (Kneyber 2008) is underpowered to make strong conclusions about the worth of antibiotics for bronchiolitis.

Potential biases in the review process

This 2011 updated review is stronger owing to the inclusion of four new RCTs and makes a substantial contribution, especially with regards to the role of macrolides in bronchiolitis. No new unpublished data have been included. However, the review authors have no reason to suspect that the search strategy has biased the review results. Raw data could not be obtained from one study conducted 40 years ago (Field 1966), nor from Tahan 2007, Mazumder 2009 or Kabir 2009, which is a weakness of this review.

Some RCT authors did provide raw data for this review (Kneyber 2008).

Agreements and disagreements with other studies or reviews

Excluded studies comparing antibiotics to placebo in participants with bronchiolitis did not find any significant difference (Friis 1984).

AUTHORS' CONCLUSIONS

Implications for practice

Overall, this review found conflicting results. However, the two higher quality but small studies do not support the use of antibiotics for bronchiolitis. One small study with a higher risk of potential bias supported the use of macrolide antibiotics, while two larger studies with higher risk of potential bias did not support the use of antibiotics, including macrolide antibiotics, for bronchiolitis. Antibiotics may be justified in children with bronchiolitis who have respiratory failure.

Implications for research

Research to identify a possible small subgroup of patients presenting with bronchiolitis-like symptoms who may benefit from antibiotics is justified. These might include those with respiratory failure, in intensive care, with nosocomially acquired RSV, and with cyanotic congenital heart disease. Otherwise, research may be better focused on determining the reasons for clinicians to use antibiotics so readily for bronchiolitis and therefore their use of antibiotics for bronchiolitis, as well as ways to reduce anxiety.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Field 1966

Methods	Randomised controlled trial
Participants	Babies
Interventions	Ampicillin Placebo
Outcomes	Length of hospital stay Symptoms (not specified) Switch to treatment arm Death
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients were blinded but not doctors nor outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	No intention-to-treat analysis but withdrawal rates were acceptable
Selective reporting (reporting bias)	Low risk	

Kabir 2009

Methods	Randomised controlled trial
Participants	Children under 2 years of age with clinical suspected bronchiolitis
Interventions	IV ampicillin (parenteral ampicillin 50 mg/kg/6-hourly + supportive care), oral erythromycin (oral erythromycin 10 mg/kg 6-hourly + supportive care), control
Outcomes	Respiratory rate, oxygen saturation, wheeze, fever, length of hospital stay, shortness of breath
Notes	

Kabir 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Seems unlikely, not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 participants dropped out (10%), 17 were referred to paediatric intensive care and 15 withdrew from the study or left the recruiting hospitals
Selective reporting (reporting bias)	High risk	

Kneyber 2008

Methods	Double-blinded, placebo-controlled, randomised controlled trial
Participants	Hospitalised infants younger than 24 months with clinically-confirmed viral lower respiratory tract infection
Interventions	Azithromycin 10 mg/kg/day, once daily for 3 days
Outcomes	Respiratory rate, accessory muscle use, malaise severity, disease complications, use of alternative therapies, length of hospital stay, length of intensive care stay, deaths, need for NG feeding
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Adequate block randomisation
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and doctors

Kneyber 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow up
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Mazumder 2009

Methods	Randomised controlled trial
Participants	Children aged 1 month to 2 years presenting to an outpatients department in a teaching hospital
Interventions	Supportive management, supportive management plus IV ampicillin, supportive management plus oral erythromycin
Outcomes	Breathing difficulty, feeding difficulty, social smile, tachypnoea, hypoxia, wheeze, rhonchi, crepitation, WBC, Hb, ESR, CRP, X-ray, rate of recovery
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Odds and evens
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Unsure

Tahan 2007

Methods	Double-blind, randomised controlled trial
Participants	Infants less than or equal to 7 months with immunologically confirmed RSV infection admitted to 1 hospital
Interventions	Clarithromycin 15 mg/kg/day, once daily for 3 weeks

Tahan 2007 (*Continued*)

Outcomes	Respiratory rate, wheeze, use of supplemental oxygen, cyanosis, hospital admission, length of stay	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"... infants were randomized by a single study nurse..." "Simple randomisation was used"
Allocation concealment (selection bias)	Unclear risk	Allocation after enrolment by study nurse
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of patients and investigators
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	30 patients were randomised, however 9 were later excluded as they received corticosteroid therapy
Selective reporting (reporting bias)	Unclear risk	Unsure if trial was registered
Other bias	Unclear risk	Unsure if there were any conflicts of interest

CRP: C reactive protein
ESR: erythrocyte sedimentation rate
Hb: haemoglobin
IV: intravenous
NG: nasogastric
RSV: respiratory syncytial virus
WBC: white blood count

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

Study	Reason for exclusion
Boogaard 2007	Did not study antibiotics
Friis 1984	The patient selection criteria were fine crepitations or consolidation on chest radiograph which was not consistent with our inclusion criteria of a purely clinical presentation of bronchiolitis

DATA AND ANALYSES

Comparison 1. Length of symptoms (not specified)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of symptoms	2	123	Mean Difference (IV, Fixed, 95% CI)	0.32 [-1.14, 1.78]
2 Duration of fever (days)	1	71	Mean Difference (IV, Fixed, 95% CI)	0.47 [-0.12, 1.06]

Comparison 2. Death

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths	5	543	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Length of hospital stay

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of hospital stay	3	288	Mean Difference (IV, Random, 95% CI)	0.34 [-0.71, 1.38]

Comparison 4. Use of alternative therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Use of alternative therapy	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Oxygen	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Bronchodilator use	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Corticosteroid use	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Naso-gastric feeding	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Duration of bronchodilator use	1	71	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-1.25, 0.91]
3 Days of supplementary oxygen	1	71	Mean Difference (IV, Fixed, 95% CI)	0.36 [-0.46, 1.18]
4 Days of tube feeding	1	71	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.98, 1.12]

Comparison 5. PICU admission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PICU admission	1	71	Odds Ratio (M-H, Fixed, 95% CI)	0.39 [0.02, 10.03]

Comparison 6. Re-admission

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Re-admission	1	21	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.29]

Comparison 7. Symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Wheeze	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Day 1	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Day 5	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Day 7	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Shortness of breath	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Day 1	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Day 5	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Day 7	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Oxygen saturation (< 96%)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Day 1	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Day 5	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Not smiling socially	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Day 1	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Day 5	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Feeding difficulties	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Day 1	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Day 5	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Fever	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Day 2	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Cough	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Day 7	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Length of symptoms (not specified), Outcome 1 Duration of symptoms.

Review: Antibiotics for bronchiolitis in children

Comparison: 1 Length of symptoms (not specified)

Outcome: 1 Duration of symptoms

Study or subgroup	Antibiotics N	Mean(SD)[days]	Placebo N	Mean(SD)[days]	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Field 1966	28	9.54 (0)	24	9.7 (0)		0.0 [0.0, 0.0]
Kneyber 2008	32	4.94 (3.78)	39	4.62 (2.05)		0.32 [-1.14, 1.78]
Total (95% CI)	**60**		**63**			**0.32 [-1.14, 1.78]**

Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Length of symptoms (not specified), Outcome 2 Duration of fever (days).

Review: Antibiotics for bronchiolitis in children

Comparison: 1 Length of symptoms (not specified)

Outcome: 2 Duration of fever (days)

Study or subgroup	Antibiotics N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kneyber 2008	32	1.47 (1.41)	39	1 (1.08)		100.0 %	0.47 [-0.12, 1.06]
Total (95% CI)	**32**		**39**			**100.0 %**	**0.47 [-0.12, 1.06]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.55 (P = 0.12)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Death, Outcome 1 Deaths.

Review: Antibiotics for bronchiolitis in children

Comparison: 2 Death

Outcome: 1 Deaths

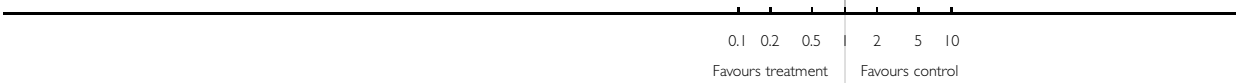
Study or subgroup	Antibiotics n/N	Placebo / Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Field 1966	0/28	0/24		0.0 [0.0, 0.0]
Kabir 2009	0/198	0/97		0.0 [0.0, 0.0]
Kneyber 2008	0/32	0/39		0.0 [0.0, 0.0]
Mazumder 2009	0/61	0/43		0.0 [0.0, 0.0]
Tahan 2007	0/12	0/9		0.0 [0.0, 0.0]
Total (95% CI)	**331**	**212**		**0.0 [0.0, 0.0]**

Total events: 0 (Antibiotics), 0 (Placebo / Control)

Heterogeneity: $Chi^2 = 0.0$, df = 0 ($P<0.00001$); $I^2 = 0.0\%$

Test for overall effect: Z = 0.0 ($P < 0.00001$)

Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3 Length of hospital stay, Outcome 1 Length of hospital stay.

Review: Antibiotics for bronchiolitis in children

Comparison: 3 Length of hospital stay

Outcome: 1 Length of hospital stay

Study or subgroup	Antibiotics (macrolides) N	Mean(SD)[days]	Control N	Mean(SD)[days]	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Kabir 2009	99	4.44 (1.93)	97	3.67 (1.45)		0.77 [0.29, 1.25]
Kneyber 2008	32	5.5 (2.55)	39	5.82 (2)		-0.32 [-1.40, 0.76]
Tahan 2007	12	2.13 (0)	9	3.67 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**143**		**145**			**0.34 [-0.71, 1.38]**

Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 3.25$, df = 1 (P = 0.07); $I^2 = 69\%$

Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Use of alternative therapy, Outcome 1 Use of alternative therapy.

Review: Antibiotics for bronchiolitis in children

Comparison: 4 Use of alternative therapy

Outcome: 1 Use of alternative therapy

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Oxygen				
Kneyber 2008	20/32	31/39		0.43 [0.15, 1.24]
2 Bronchodilator use				
Kneyber 2008	17/32	23/39		0.79 [0.31, 2.02]
3 Corticosteroid use				
Kneyber 2008	1/32	7/39		0.15 [0.02, 1.27]
4 Naso-gastric feeding				
Kneyber 2008	16/32	16/39		1.44 [0.56, 3.69]

Analysis 4.2. Comparison 4 Use of alternative therapy, Outcome 2 Duration of bronchodilator use.

Review: Antibiotics for bronchiolitis in children

Comparison: 4 Use of alternative therapy

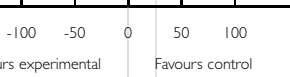
Outcome: 2 Duration of bronchodilator use

Study or subgroup	Antibiotics N	Mean(SD)[days]	Placebo N	Mean(SD)[days]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kneyber 2008	32	2.79 (2.49)	39	2.96 (2.06)		100.0 %	-0.17 [-1.25, 0.91]
Total (95% CI)	**32**		**39**			**100.0 %**	**-0.17 [-1.25, 0.91]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.31 (P = 0.76)

Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4 Use of alternative therapy, Outcome 3 Days of supplementary oxygen.

Review: Antibiotics for bronchiolitis in children

Comparison: 4 Use of alternative therapy

Outcome: 3 Days of supplementary oxygen

Study or subgroup	Antibiotics N	Mean(SD)[days]	Placebo N	Mean(SD)[days]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kneyber 2008	32	3.75 (1.74)	39	3.39 (1.78)		100.0 %	0.36 [-0.46, 1.18]
Total (95% CI)	**32**		**39**			**100.0 %**	**0.36 [-0.46, 1.18]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.86 (P = 0.39)

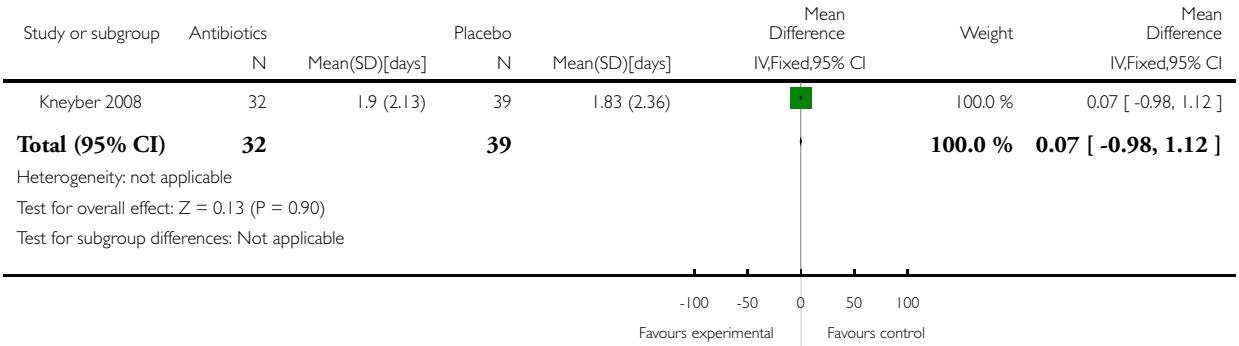
Test for subgroup differences: Not applicable

Analysis 4.4. Comparison 4 Use of alternative therapy, Outcome 4 Days of tube feeding.

Review: Antibiotics for bronchiolitis in children

Comparison: 4 Use of alternative therapy

Outcome: 4 Days of tube feeding

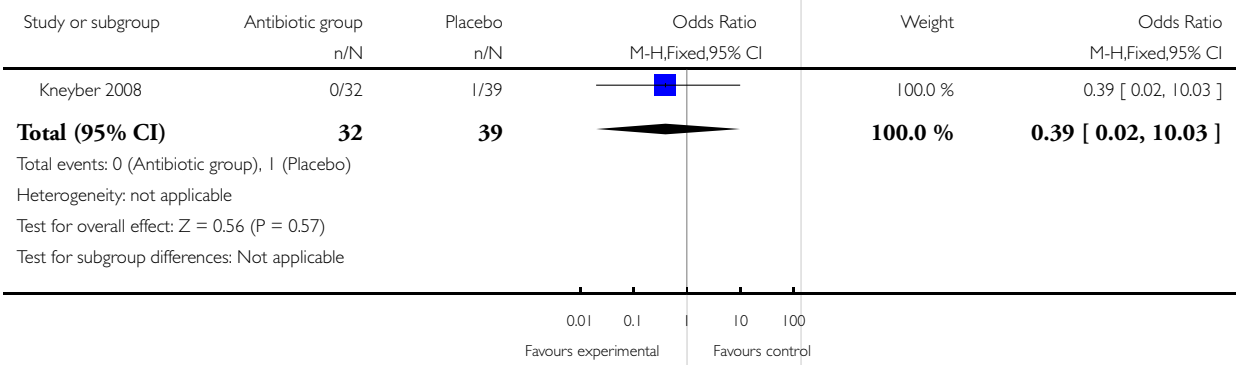


Analysis 5.1. Comparison 5 PICU admission, Outcome 1 PICU admission.

Review: Antibiotics for bronchiolitis in children

Comparison: 5 PICU admission

Outcome: 1 PICU admission

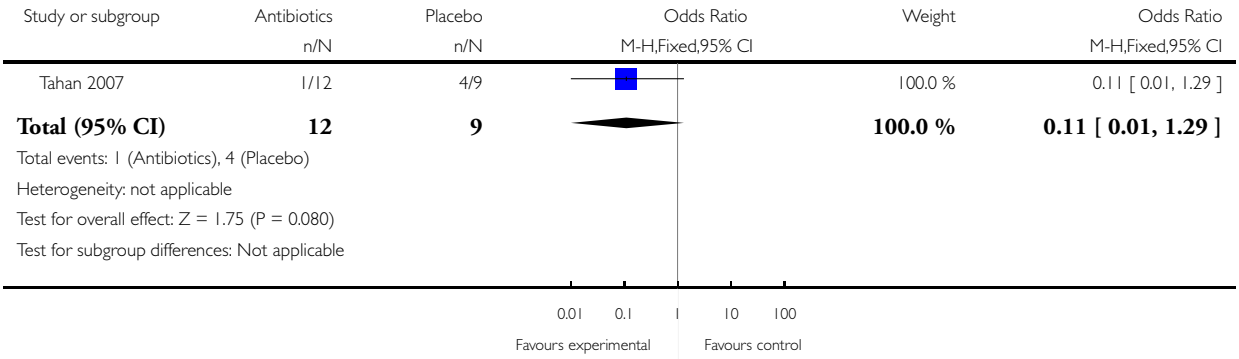


Analysis 6.1. Comparison 6 Re-admission, Outcome 1 Re-admission.

Review: Antibiotics for bronchiolitis in children

Comparison: 6 Re-admission

Outcome: 1 Re-admission

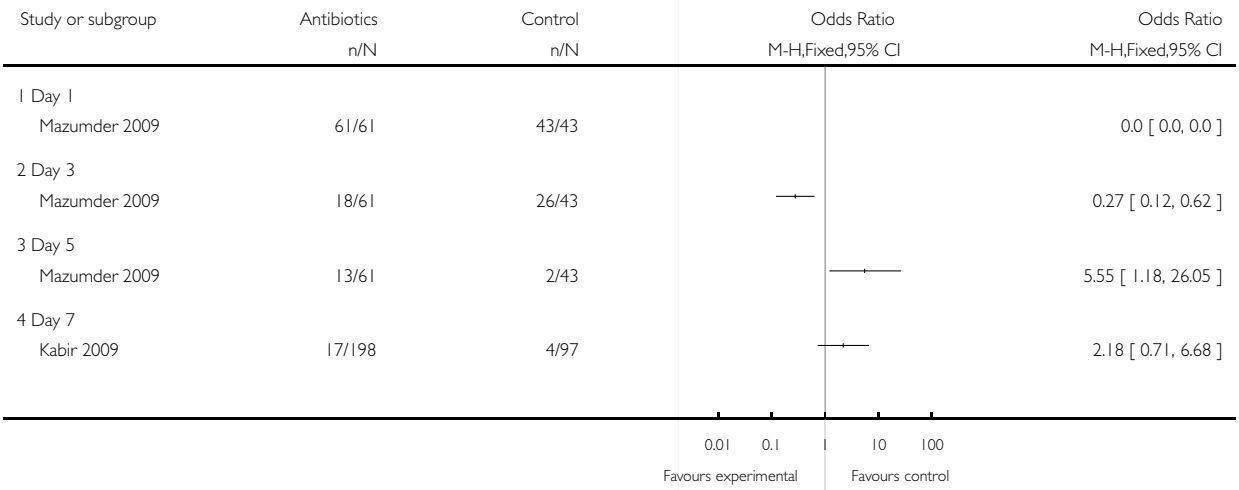


Analysis 7.1. Comparison 7 Symptoms, Outcome 1 Wheeze.

Review: Antibiotics for bronchiolitis in children

Comparison: 7 Symptoms

Outcome: 1 Wheeze



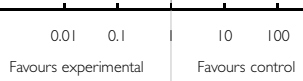
Analysis 7.2. Comparison 7 Symptoms, Outcome 2 Shortness of breath.

Review: Antibiotics for bronchiolitis in children

Comparison: 7 Symptoms

Outcome: 2 Shortness of breath

Study or subgroup	Antibiotics n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Day 1				
Mazumder 2009	61/61	43/43		0.0 [0.0, 0.0]
2 Day 3				
Mazumder 2009	34/61	27/43		0.75 [0.34, 1.66]
3 Day 5				
Mazumder 2009	16/61	15/43		0.66 [0.28, 1.55]
4 Day 7				
Kabir 2009	17/198	2/97		4.46 [1.01, 19.72]



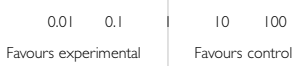
Analysis 7.3. Comparison 7 Symptoms, Outcome 3 Oxygen saturation (< 96%).

Review: Antibiotics for bronchiolitis in children

Comparison: 7 Symptoms

Outcome: 3 Oxygen saturation (< 96%)

Study or subgroup	Antibiotics n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Day 1				
Mazumder 2009	33/61	23/43		1.02 [0.47, 2.24]
2 Day 3				
Mazumder 2009	15/61	5/43		2.48 [0.83, 7.44]
3 Day 5				
Mazumder 2009	5/61	2/43		1.83 [0.34, 9.91]



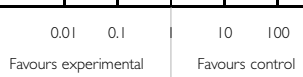
Analysis 7.4. Comparison 7 Symptoms, Outcome 4 Not smiling socially.

Review: Antibiotics for bronchiolitis in children

Comparison: 7 Symptoms

Outcome: 4 Not smiling socially

Study or subgroup	Antibiotics n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Day 1				
Mazumder 2009	40/61	30/43		0.83 [0.36, 1.91]
2 Day 3				
Mazumder 2009	6/61	5/43		0.83 [0.24, 2.91]
3 Day 5				
Mazumder 2009	0/61	0/43		0.0 [0.0, 0.0]



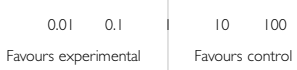
Analysis 7.5. Comparison 7 Symptoms, Outcome 5 Feeding difficulties.

Review: Antibiotics for bronchiolitis in children

Comparison: 7 Symptoms

Outcome: 5 Feeding difficulties

Study or subgroup	Antibiotics n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Day 1				
Mazumder 2009	25/61	25/43		0.50 [0.23, 1.10]
2 Day 3				
Mazumder 2009	6/61	5/43		0.83 [0.24, 2.91]
3 Day 5				
Mazumder 2009	0/61	0/43		0.0 [0.0, 0.0]



Analysis 7.6. Comparison 7 Symptoms, Outcome 6 Fever.

Review: Antibiotics for bronchiolitis in children

Comparison: 7 Symptoms

Outcome: 6 Fever

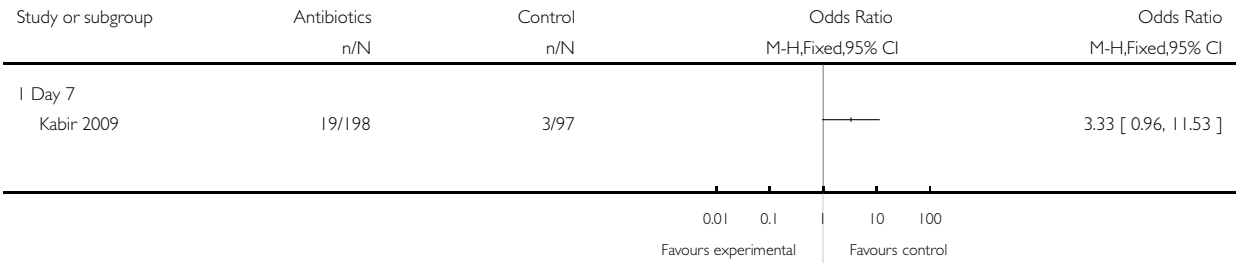
Study or subgroup	Antibiotics n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
1 Day 2				
Kabir 2009	11/198	4/97		1.37 [0.42, 4.41]

Analysis 7.7. Comparison 7 Symptoms, Outcome 7 Cough.

Review: Antibiotics for bronchiolitis in children

Comparison: 7 Symptoms

Outcome: 7 Cough



ADDITIONAL TABLES

Table 1. Kneyber: azithromycin versus placebo for bronchiolitis

Variable	Azithromycin (n = 32)	Placebo (n = 39)	Outcome	Significance level
Days of symptoms	4.94 (SD 3.78)	4.62 (SD 2.05)	Mean difference 0.32 (95% CI -1.14 to 1.78)	P = 0.65
Days in hospital	5.5 (SD 2.54)	5.82 (SD 1.98)	Mean difference -0.32 (95% CI -1.40 to 0.76)	P = 0.56
Duration of fever (days)	1.47 (SD 1.41)	1.00 (SD 1.08)	Mean difference 0.47 (95% CI -0.12 to 1.06)	P = 0.12
Duration of bronchodilator use	2.79 (SD 2.49)	2.96 (SD 2.06)	Mean difference -0.17 (95% CI -1.25 to 0.91)	P = 0.81
Bronchodilator use	17	23	Odds ratio 0.79 (95% CI 0. 31 to 2.02)	P = 0.62

Table 1. Kneyber: azithromycin versus placebo for bronchiolitis (*Continued*)

Supplementary oxygen	20 (62.5%)	31 (79.49%)	Odds ratio 0.43 (95% CI 0. 15 to 1.24)	P = 0.11
Days of extra oxygen	3.75 (SD 1.74)	3.39 (SD 1.78)	Mean difference 0.36 (95% CI -0.46 to 1.18)	P = 0.48
PICU admission	0 (0%)	1 (2.56%)	Odds ratio 0.39 (95% CI 0. 02 to 10.03)	P = 1.00
Tube feeding	16 (50.00%)	16 (41.03%)	Odds ratio 1.44 (95% CI 0. 56 to 3.69)	P = 0.45
Days of tube feeding	1.90 (SD 2.13)	1.83 (SD 2.36)	Mean difference 0.07 (95% CI -0.98 to 1.12)	P = 0.90

PICU: paediatric intensive care unit
SD: standard deviation
CI: confidence interval

Table 2. Mazumder: IV ampicillin versus oral erythromycin versus control

Variable	**Day 1**			**Outcome**	**Day 3**			**Outcome**	**Day 5**			**Outcome**
	IV ampicillin	Oral erythromycin	Control	Chi ^{2} test (P value)	IV ampicillin	Oral erythromycin	Control	Chi ^{2} test (P value)	IV ampicillin	Oral erythromycin	Control	Chi^2 test (P value)
Wheeze	29/29 (100%)	32/32 (100%)	43/43 (100%)	N/A	16/29 (55%)	2/32 (6%)	26/43 (60%)	24. 82 (P < 0.001)	6/29 (21%)	7/32 (22%)	2/43 (5%)	5. 69 (P = 0.058)
Shortness of breath	29/29 (100%)	32/32 (100%)	43/43 (100%)	N/A	18/29 (62%)	16/32 (50%)	27/43 (63%)	1.97 (P = 0.37)	8/29 (28%)	8/32 (25%)	15/43 (35%)	0.95 (P = 0.62)
Oxygen saturation (< 96%)	18/29 (62%)	15/32 (47%)	23/43 (53%)	1.42 (P = 0.49)	8/29 (28%)	7/32 (22%)	5/43 (12%)	3.05 (P = 0.22)	2/29 (7%)	3/32 (9%)	2/43 (5%)	0.65 (P = 0.72)
Not smiling socially	19/29 (66%)	21/32 (66%)	30/43 (70%)	0.20 (P = 0.90)	3/29 (10%)	3/32 (9%)	5/43 (12%)	0.10 (P = 0.95)	0/29 (0%)	0/32 (0%)	0/43 (0%)	N/A

Table 2. Mazumder: IV ampicillin versus oral erythromycin versus control (*Continued*)

Feeding difficulty	12/29 (41%)	13/32 (41%)	25/43 (58%)	2.98 (P = 0.23)	3/29 (10%)	3/32 (9%)	5/43 (12%)	0.10 (P = 0.95)	0/29 (0%)	0/32 (0%)	0/43 (0%)	N/A

IV: intravenous

Table 3. Kabir: IV ampicillin versus oral erythromycin versus control

Variable	**Intervention**			**Outcome**
	IV ampicillin	Oral erythromycin	Control	Chi^2 test (P value)
Day 2				
Oxygen sats (< 90%)	2/99 (2%)	6/99 (6%)	6/97 (6%)	2.45 (P = 0.29)
Fever	5/99 (5%)	6/99 (6%)	4/97 (4%)	0.38 (P = 0.83)
Day 7				
Wheeze	8/99 (8%)	9/99 (9%)	4/97 (4%)	2.04 (P = 0.36)
Shortness of breath	8/99 (8%)	9/99 (9%)	2/97 (2%)	4.68 (P = 0.10)
Cough	10/99 (10%)	9/99 (9%)	3/97 (3%)	4.06 (P = 0.13)

IV: intravenous
PICU: paediatric intensive care unit
SD: standard deviation
CI: confidence interval

APPENDICES

Appendix 1. Embase.com search strategy

#36 #24 AND #35
#35 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #33 OR #34
#34 #31 AND #32
#33 placebo*
#32 blind* OR mask*
#31 single* OR doubl* OR trebl* OR tripl*
#30 clinical AND trial*
#29 'double blind' OR 'single blind'
#28 'placebo'/exp
#27 'clinical trial'/exp
#26 random*
#25 'randomized controlled trial'/exp
#24 #23 AND [embase]/lim
#23 #19 AND #22
#22 #20 OR #21
#21 child* OR infant* OR pediatric* OR pediatric*
#20 'child'/exp
#19 #5 AND #18
#18 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
#17 tetracycline* OR doxycycline OR methacycline OR minocycline OR amikacin OR gentamicin OR neomycin OR netilmicin OR clindamycin OR lincomycin OR chloramphenicol OR amantadine OR cotrimoxazole OR trimethoprim
#16 'tetracycline derivative'/exp
#15 fluoroquinolone* OR ciprofloxacin OR enoxacin OR norfloxacin OR ofloxacin OR pefloxacin OR fleroxacin OR levofloxacin OR moxifloxacin
#14 'quinolone derivative'/exp
#13 penicillin* OR amoxicillin OR amoxycillin OR ampicillin OR benzylpenicillin OR cloxacillin OR dicloxacillin OR flucloxacillin OR piperacillin OR ticarcillin OR sulbactam
#12 'penicillin derivative'/exp
#11 cephalosporin* OR cephalexin OR cephaclor OR cefaclor OR cefepime OR cefotaxime OR cephamycin* OR cefotetan OR cefoxitin OR cefmetazole OR cefpirome OR cefpodoxime OR ceftazidime OR ceftriaxone OR cephamandole OR cephazolin
#10 'cephalosporin derivative'/exp
#9 macrolide* OR azithromycin OR clarithromycin OR erythromycin OR roxithromycin OR spiramycin
#8 'macrolide'/exp
#7 antibiotic*
#6 'antibiotic agent'/exp
#5 #1 OR #2 OR #3 OR #4
#4 'respiratory syncytial virus' OR 'respiratory syncytial viruses' OR 'respiratory syncytial virus infection' OR 'respiratory syncytial virus infections' OR rsv*
#3 'respiratory syncytial pneumovirus'/exp
#2 bronchiolit*
#1 'bronchiolitis'/exp

Appendix 2. Current Contents search strategy

11 #10 AND #9 AND #8 Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC
10 #7 OR #6 OR #5 OR #4 OR #3 Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC
9 #2 OR #1 Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC
8 Topic=(Child* or infant* or pediatric or paediatric) Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC
7 Topic=(tetracycline* or doxycycline or methacycline or minocycline or amikacin or gentamicin or neomycin or netilmicin or clindamycin or lincomycin or chloramphenicol or amantadine or cotrimoxazole or trimethoprim) Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC
6 Topic=(fluoroquinolone* or ciprofloxacin or enoxacin or norfloxacin or ofloxacin or pefloxacin or fleroxacin or levofloxacin or moxifloxacin) Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC
5 Topic=(penicillin* or amoxicillin or amoxycillin or ampicillin or benzylpenicillin or cloxacillin or dicloxacillin or flucloxacillin or piperacillin or ticarcillin or sulbactam)Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC
4 Topic=(cephalosporin* or cephalexin or cephaclor or cefaclor or cefepime or cefotaxime or cephamycin* or cefotetan or cefoxitin or cefmetazole or cefpirome or cefpodoxime or ceftazidime or ceftriaxone or cephamandole or cephazolin) Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC
3 Topic=(macrolide* or azithromycin or clarithromycin or erythromycin or roxithromycin or spiramycin) Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC
2 Topic=(Respiratory syncytial pneumovirus or Respiratory Syncytial Virus or Respiratory Syncytial Viruses or Respiratory Syncytial Virus Infection or Respiratory Syncytial Virus Infections or RSV*) Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC
1 Topic=(Bronchiolit*)Databases=ABES, SBS, CM, LS, PCES, ECT, AH, EC, BC

WHAT'S NEW

Last assessed as up-to-date: 9 December 2010.

Date	Event	Description
16 June 2011	Amended	Review First Published date amended.

HISTORY

Protocol first published: Issue 2, 2005

Review first published: Issue 1, 2007

Date	Event	Description
10 December 2010	New citation required and conclusions have changed	A new review author joined the team to update the review. The conclusions are stronger as they are based on more trials and address the question of macrolide antibiotics for bronchiolitis
10 December 2010	New search has been performed	We updated the searches and included four new trials (Kabir 2009; Kneyber 2008; Mazumder 2009; Tahan 2007).

(*Continued*)

1 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

GS co-wrote the protocol; reviewed the search result; performed quality appraisal; extracted data and drafted the final version.

JD gave advice on performing the systematic review; critically appraised primary data, extracted data and helped write the final version.

CDM gave advice on performing the systematic review; performed quality appraisal; extracted data and helped write the final version.

LE conducted the literature search and approved the final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Queensland, Australia.

In kind

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Ampicillin [therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Bronchiolitis [*drug therapy]; Clarithromycin [therapeutic use]; Erythromycin [therapeutic use]; Length of Stay; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant