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Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age (Review)

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
Figure 1.	7
Figure 2.	8
Figure 3.	9
RESULTS	11
DISCUSSION	13
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	15
REFERENCES	16
CHARACTERISTICS OF STUDIES	21
DATA AND ANALYSES	26
Analysis 1.1. Comparison 1 Antibiotic compared to control in the treatment of ARI in children, Outcome 1 Otitis.	26
Analysis 1.2. Comparison 1 Antibiotic compared to control in the treatment of ARI in children, Outcome 2 Otitis - high-income countries.	27
Analysis 1.3. Comparison 1 Antibiotic compared to control in the treatment of ARI in children, Outcome 3 Pneumonia.	27
APPENDICES	27
WHAT'S NEW	30
CONTRIBUTIONS OF AUTHORS	30
DECLARATIONS OF INTEREST	30
SOURCES OF SUPPORT	30
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	30
INDEX TERMS	30

[Intervention Review]

Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age

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ABSTRACT

Background

Undifferentiated acute respiratory infections (ARIs) are a large and heterogeneous group of infections not clearly restricted to one specific part of the upper respiratory tract, which last for up to seven days. They are more common in pre-school children in low-income countries and are responsible for 75% of the total amount of prescribed antibiotics in high-income countries. One possible rationale for prescribing antibiotics is the wish to prevent bacterial complications.

Objectives

To assess the effectiveness and safety of antibiotics in preventing bacterial complications in children aged two months to 59 months with undifferentiated ARIs.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 7), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to August week 1, 2015) and EMBASE (1974 to August 2015).

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs comparing antibiotic prescriptions with placebo or no treatment in children aged two months to 59 months with an undifferentiated ARI for up to seven days.

Data collection and analysis

Two review authors independently assessed trial quality and extracted and analysed data using the standard Cochrane methodological procedures.

Main results

We identified four trials involving 1314 children. Three trials investigated the use of amoxicillin/clavulanic acid to prevent otitis and one investigated ampicillin to prevent pneumonia.

The use of amoxicillin/clavulanic acid compared to placebo to prevent otitis showed a risk ratio (RR) of 0.70 (95% confidence interval (CI) 0.45 to 1.11, three trials, 414 selected children, moderate-quality evidence). Methods of random sequence generation and allocation concealment were not clearly stated in two trials. Performance, detection and reporting bias could not be ruled out in three trials.

Ampicillin compared to supportive care (continuation of breastfeeding, clearing of the nose and paracetamol for fever control) to prevent pneumonia showed a RR of 1.05 (95% CI 0.74 to 1.49, one trial, 889 selected children, moderate-quality evidence). The trial was non-blinded. Random sequence generation and allocation concealment methods were not clearly stated, so the possibility of reporting bias could not be ruled out.

Harm outcomes could not be analysed as they were expressed only in percentages.

We found no studies assessing mastoiditis, quinsy, abscess, meningitis, hospital admission or death.

Authors' conclusions

There is insufficient evidence for antibiotic use as a means of reducing the risk of otitis or pneumonia in children up to five years of age with undifferentiated ARIs. Further high-quality research is needed to provide more definitive evidence of the effectiveness of antibiotics in this population.

PLAIN LANGUAGE SUMMARY

Antibiotics for common respiratory infections with unclear causes and undifferentiated symptoms in children up to five years of age

Review question

Do antibiotics prevent more severe infections in children up to five years old with common upper acute respiratory infections (ARIs)?

Background

Common upper ARIs are a large and varied groups of infections. They occur in any part of the upper respiratory system, last for up to seven days and have a wide variety of causes. They may lead to complications such as ear, throat and sinus infections. More common in pre-school children, they are the most frequent reason for parents to seek medical assistance. Furthermore, they are responsible for 75% of the total prescribed antibiotics in high-income countries. One possible rationale for prescribing antibiotics is the wish to prevent bacterial complications.

Methods

This review focuses on the use of antibiotics to prevent clinical bacterial complications in children up to five years of age with common and undifferentiated ARIs. This is an update of a review previously published in 2014. The evidence is current to August 2015. In this update we retrieved 616 new studies, but none met our inclusion criteria.

Studies characteristics

We included four trials (1314 children) in this review. Three trials (414 children, during seven days) investigated the use of an antibiotic (amoxicillin/clavulanic acid) to prevent otitis media. One trial (889 children, during two weeks) investigated the use of another antibiotic (ampicillin) to prevent pneumonia. Only one trial addressed harms. However, we could not analyse the data as it was expressed in percentages rather than absolute terms. No studies assessed other severe complications (mastoiditis, quinsy, abscess, meningitis), hospital admission or death.

Key results

Current evidence does not provide support for the use of antibiotics to prevent otitis media and pneumonia in children up to five years of age with common upper ARIs.

Quality of the evidence

In the trials treating otitis media, the quality of the evidence was moderate as the methods for avoiding bias were not clearly stated. Furthermore, in one trial a pharmaceutical company prepared the placebo syrup used in the trial.

In the study treating pneumonia, we classified the quality of the evidence as moderate, because the families previously knew if their children were receiving antibiotics or not. Furthermore, the methods for avoiding bias were not clearly stated by the trial authors.

Further high-quality research is needed to provide more definitive evidence of the effectiveness of antibiotics in this population.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Amoxicillin/clavulanic acid compared with placebo for children with undifferentiated ARI to prevent complications (otitis)

Patients: children up to 5 years of age with previous episodes of AOM and undifferentiated ARI

Settings: 2 trials were conducted in private centres (1 multicentre study conducted in paediatric centres in France; 1 study in an otologic centre in Finland); 1 trial was conducted in the paediatric department of a hospital in Jordan

Intervention: amoxicillin/clavulanic acid

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Amoxicillin/clavulanic acid				
Otitis media	Medium risk population		RR 0.70 (0.45 to 1.11)	414 (3)	⊕⊕⊕⊕ moderate ¹	—
Follow-up: 7 to 12 days	18 per 100	13 per 100 (8 to 20)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AOM: acute otitis media; **ARI:** acute respiratory infection; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

*The basis for the **assumed risk** (e.g. median control group risk across studies) was calculated on the basis of the control event rate. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

¹Random sequence generation and allocation concealment are unclear in two of the included trials. The method of blinding is unclear in all three trials. Nevertheless, the three trials were described as randomised and double-blind. The studies were conducted on just two continents. Only one of the three studies was produced in the last 10 years.

Summary of findings 2.

Ampicillin compared with control for children with undifferentiated ARI to prevent complications (pneumonia)

Patient or population: children under 5 years of age with undifferentiated ARI

Settings: 1 trial conducted in a government health clinic in Indonesia

Intervention: ampicillin

Comparison: adjunctive therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Supportive care	Ampicillin				
Pneumonia - 12 to 58 months of age Follow-up: 2 weeks	Medium risk population		RR 1.10 (0.71 to 1.69)	563 (1)	⊕⊕⊕⊖ m oderate ¹	—
	12 per 100	13 per 100 (9 to 20)				
Pneumonia - 0 to 11 months of age Follow-up: 2 weeks	Medium risk population		RR 0.96 (0.52 to 1.76)	326 (1)	⊕⊕⊕⊖ m oderate ¹	—
	12 per 100	12 per 100 (6 to 21)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ARI: acute respiratory infection; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

*The basis for the **assumed risk** (e.g. median control group risk across studies) was calculated on the basis of the control event rate. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

¹Random sequence generation method and allocation concealment are unclear. There was no blinding. Data were extracted from only one included study, which was conducted more than 20 years ago.

BACKGROUND

Description of the condition

Undifferentiated acute respiratory infections (ARIs) are a large and heterogeneous group of infections. They affect any area between the nose and the epiglottis and last for up to seven days (Schuetz 2012). Undifferentiated ARIs and acute infection-related cough, with potentially suppurative infections, such as acute otitis media, acute sinusitis and acute pharyngitis, are the most common reasons that parents seek medical attention for their children (Akkerman 2005; Dowell 1998; WHO 2007). These infections are more common in pre-school children, particularly those living in low-income countries (Benguigui 2003; Emmelin 2007; Garenne 1992; Krishnan 2015; Rudan 2008). Even in high-income countries, ARIs are worrisome (Akkerman 2005; Nascimento-Carvalho 2006; Tan 2008; Zar 2014). According to Hay 2002, two out of three children younger than four in the UK visit their general practitioner (GP) at least once a year with an ARI. Up to three-quarters of these present with a cough. This accounts for at least two million annual face-to-face consultations related to new episodes of cough, with up to half a million re-consultations and many more episodes of respiratory illness not currently seen by GPs. Estimating the cost of GP time at GBP 7.30 per consultation and antibiotics at GBP 3 per prescription (assuming a 40% prescribing rate), the crude annual National Health Service (NHS) cost of treating cough in pre-school children was estimated to be at least GBP 20 million (Hay 2002).

In Hay 2002, a study was cited that found the most common respiratory diagnoses in pre-school children to be 'cold or sinusitis' (33%), 'bronchitis' (15%), 'tracheitis' (12%), 'pneumonia or bronchiolitis' (12%), 'pharyngitis' (10%), 'influenza' (9%), 'laryngitis or croup' (7%) and 'otitis media' (2%) (Hope-Simpson 1973). According to another study cited in this review, there is large variation amongst doctors diagnosing and treating adults who present to primary care facilities with a respiratory tract illness (Howie 1971). This variation may be more apparent in pre-school children because they present with fewer symptoms than older children and adults, they rarely expectorate sputum with their cough and it is not possible to establish the presence or absence of subjective symptoms, such as chest pain and sore throat (Margolis 1998). Precise diagnoses can often only be made retrospectively, therefore it has been recommended that research on acute problems in primary care settings be based on presenting symptoms or disease categories (Fahey 1998a; Fahey 1998b).

Description of the intervention

The immunological immaturity of young children translates into an enhanced susceptibility to many infections, with important health consequences as well as higher rates and longer duration of micro-organism shedding (Posfay-Barbe 2008). Early initiation of adequate antibiotic therapy is considered a cornerstone in the treatment of bacterial ARIs and is associated with improved clinical outcomes (Kumar 2009). However, overuse or prolonged use of antibiotics in patients with ARIs is associated with the increased resistance of common bacteria, high costs and adverse reactions (Chung 2007; Costelloe 2010; Little 2002).

Most childhood ARIs have a viral aetiology and are self limiting (Farha 2005; Jansen 2006; Kusel 2007), even though ARIs are responsible for 75% of prescribed antibiotics in high-income countries (Jansen 2006). There is growing evidence from systematic

reviews of acute tonsillitis/pharyngitis, otitis media, common cold and sinusitis that the benefits of antibiotics for symptom resolution are likely to be modest for most patients (Kenealy 2013; Spinks 2013; Venekamp 2015).

Concern about complications, diagnostic uncertainties and perceived parental expectations are some of the alleged reasons for this kind of prescribing, especially in young children (Del Mar 2012; Kumar 2003).

How the intervention might work

The decision to prescribe antibiotics is complex. Research, especially among adults, has suggested that low rates of antibiotic prescription in primary care settings might be associated with higher rates of infection (Little 2002). Therefore, reductions in prescription levels may lead to increases in mastoiditis (Sharland 2005), and increased hospital admissions for respiratory infections in the UK and the USA. In the USA, this increased level of hospital admissions was observed only among the elderly (Majeed 2004; Petersen 2007). These studies cannot determine whether adverse events occur less frequently in those people who receive antibiotics for minor infections than in those who do not. In addition, early initiation of adequate antibiotic therapy is considered the cornerstone in the treatment of bacterial ARIs and is associated with improved clinical outcomes (Kumar 2009).

Why it is important to do this review

Bacteria from different species commonly exchange genetic material, including 'resistance' genes. Antibiotics will affect pathogenic as well as nonpathogenic bacteria. Thus, it also creates the opportunity to transmit the genes related to bacterial resistance. The rate of antibiotic use is highest in children aged up to 59 months, most likely because they are considered prone to infections (McCaig 1995). The World Health Organization (WHO) has identified antibiotic resistance as one of the greatest threats to human health. In the European Union, about 25,000 patients die annually from multidrug-resistant bacterial infections, which equates to healthcare costs and lost productivity of at least EUR 1.5 billion annually (Lancet 2009). Antimicrobial resistance can be attributed to indiscriminate or poor use of antibiotics. Individuals prescribed antibiotics in primary care settings for a respiratory infection might develop bacterial resistance, which can persist for up to 12 months. This increases population carriage of resistant organisms to first-line antibiotics and the use of second-line antibiotics (Costelloe 2010).

Clinical guidelines are supposed to help doctors prescribe antibiotics judiciously (Brink 2015; Nascimento-Carvalho 2006; Tan 2008; van Balen 2004; WHO 2012), and might have a positive impact on antibiotic use. However, decisions to prescribe antibiotics may lead to inappropriate diagnoses in order to justify prescribing antibiotics (Thompson 2008). In the UK the National Institute for Health and Clinical Excellence (NICE) guidelines were developed to help GPs reduce unnecessary antibiotic prescriptions for ARIs (Tan 2008). Between 1996 and 2000, there was a marked decrease in antibiotic prescriptions in the UK. However, overall prescriptions are increasing again and associated with non-specific upper respiratory tract infection diagnoses (Thompson 2009). This suggests that GPs may be avoiding using some diagnostic labels if formal guidelines suggest that antibiotic prescriptions are unnecessary (Thompson 2009). Concern from GPs and families

regarding the danger of developing complications is probably an underlying cause of this diagnostic shift (Tan 2008). It must be emphasised that the success of these guidelines, which must always be supported by high-quality evidence (Gjelstad 2013), will rely on the continuing education of prescribers and patients. Updating is also necessary when new information becomes available, particularly from randomised controlled trials (RCTs) and surveillance studies of local aetiology and antibiotic susceptibility patterns (Brink 2015). Meanwhile, RCTs generally do not have statistical power to examine the effects of interventions on rare outcomes and the patients included may not be representative of those seen in routine clinical practice.

The use of tests and laboratory markers has also been suggested to help physicians in this decision-making process (Baron 2013; Doan 2014; Larsson 2005; Schuetz 2012). However, there is a lack of clear and definitive parameters to indicate using antibiotics. As a result, there is a pressing need to clarify whether prescribing antibiotics in children with undifferentiated ARIs and cough related to acute infections actually benefits the patients in everyday practice.

OBJECTIVES

To assess the effectiveness and safety of antibiotics in preventing bacterial complications in children aged two months to 59 months with undifferentiated ARIs.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT) or quasi-RCTs comparing antibiotic prescriptions with placebo or non-treatment in children from two to 59 months of age with undifferentiated ARIs and cough related to acute infections.

Types of participants

Children from two to 59 months of age with undifferentiated ARIs and cough related to ARIs for up to seven days. Whenever data were available, we analysed the children by age subgroups to observe possible changes in the effectiveness of the intervention. Subgroups included those up to 12 months of age and from 12 months to 59 months. Had data been available, we would have separately analysed children with underlying immunodeficiencies or anatomical defects

Types of interventions

Antibiotics prescribed for undifferentiated ARIs and cough related to acute infections regardless of dosage and delivery system. We intended to compare antibiotics administered either alone or as an adjunctive therapy (antipyretics, bronchodilators, mucolytic agents, fluid supplements, etc.) to a placebo or no treatment.

Types of outcome measures

Primary outcomes

Cases of:

1. otitis media;
2. mastoiditis;
3. quinsy;
4. pneumonia;
5. abscess;
6. meningitis;
7. rates of admission to hospital;
8. death.

Secondary outcomes

Cases of antibiotic side effects, for example:

1. diarrhoea;
2. vomiting;
3. gastro-intestinal symptoms;
4. rashes.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 7), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to August week 1, 2015) and EMBASE (1974 to August 2015).

We combined the search terms set out in Appendix 1 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 used the same terms to search CENTRAL and adapted them to search EMBASE (Appendix 2). There were no language or publication restrictions.

Searching other resources

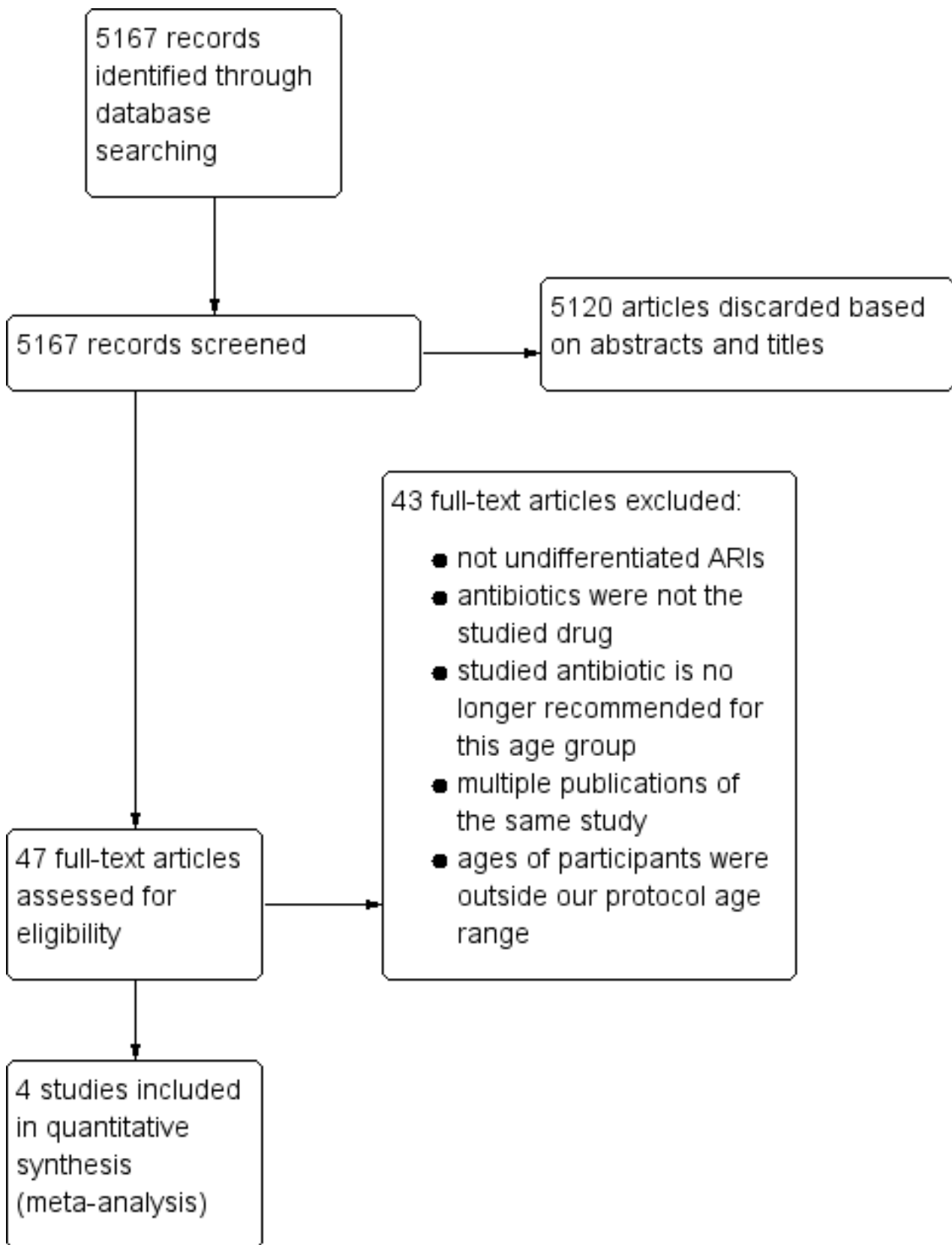
We searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for completed and ongoing trials (latest search August 2015). We screened bibliographies of the trials in order to identify additional trials.

Data collection and analysis

Selection of studies

Two review authors (MG, MS) independently selected trials for inclusion. They screened the titles and abstracts for relevance, study design, types of participants, intervention and outcome measures. We used an eligibility form based on the selection criteria. We resolved disagreements by discussion. The review authors reviewed the full texts of the potentially relevant articles and independently assessed their eligibility. We also searched for full reports of all studies deemed relevant based on the abstract. Two review authors (MG, MS) independently assessed the selected studies. We listed the excluded studies and the reasons for exclusion. When essential information was not available, we excluded the trials from the review (Figure 1). Subsequently, we entered all search results into Review Manager 5.3 (RevMan 2014).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors (MG, MS) independently extracted data from the full reports into an extraction form that was designed for this purpose. The review authors (MG, MS) cross-checked data and resolved discrepancies through discussion. MG entered data into RevMan 2014, while MS validated the data.

Assessment of risk of bias in included studies

Two review authors (MG, MS) independently screened the methodological quality of the trials to be reported in the Results section. We resolved disagreement arising from different interpretations through consensus. We used the following criteria to assess the risk of bias (Higgins 2011). The risk of bias is presented graphically in Figure 2 and summarised in Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

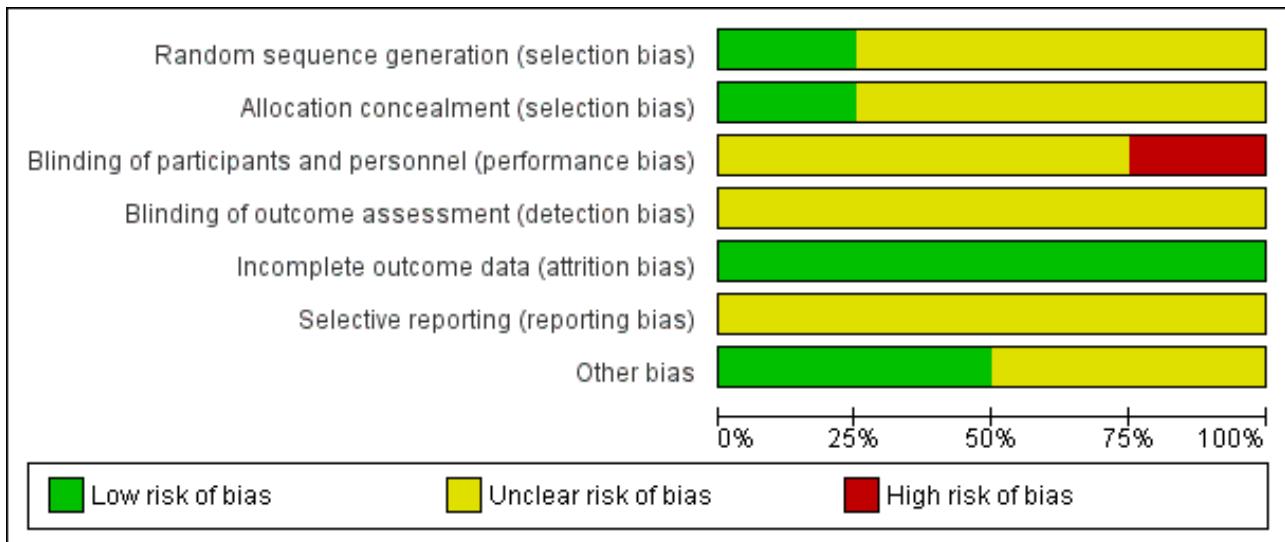


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Autret-Leca 2002	?	?	?	?	+	?	?
Heikkinen 1995	+	+	?	?	+	?	+
Rwalah 2011	?	?	?	?	+	?	+
Sutrisna 1991	?	?	-	?	+	?	?

Generation of the allocation sequence

Adequate (low risk of bias): if the allocation sequence was generated by a computer or random number table. We considered drawing of lots, tossing of a coin, shuffling of cards or throwing dice as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.

Unclear (uncertain risk of bias): if the trial was described as randomised, but information about the sequence generation process to permit judgement of adequacy or inadequacy was not sufficient.

Inadequate (high risk of bias): if the allocation involved judgement or some method of non-random categorisation of participants, such as: allocation by judgement of the clinician; allocation by preference of the participant; allocation based on the results of a

laboratory test or a series of tests; allocation by availability of the intervention.

Allocation concealment

Adequate (low risk of bias): if participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.

Unclear (uncertain risk of bias): if the trial was described as randomised, but the method used to conceal the allocation was not described.

Inadequate (high risk of bias): if the allocation sequence was known to the investigators who assigned participants.

Blinding (or masking)

Adequate (low risk of bias): if the trial was not blinded, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; if there was blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others was unlikely to introduce bias.

Unclear (uncertain risk of bias): if the trial was described as double-blind, but the method of blinding was not described.

Inadequate (high risk of bias): if there was no blinding or incomplete blinding, and the outcome or outcome measurement was likely to be influenced by lack of blinding; if blinding of key study participants and personnel was attempted, but it is likely that the blinding could have been broken; if either participants or some key study personnel were not blinded, and the non-blinding of others was likely to introduce bias.

Incomplete outcome data

Adequate (low risk of bias): if there were no missing outcome data; if reasons for missing outcome data are unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); if missing outcome data are balanced in numbers across intervention groups, with similar reasons for missing data across groups; if the proportion of missing outcomes compared with the observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; if missing data have been imputed using appropriate methods.

Unclear (uncertain risk of bias): if the report gave the impression that there had been no drop-outs or withdrawals, but this was not specifically stated.

Inadequate (high risk of bias): if the number or reasons for drop-outs and withdrawals were not described. If the reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; if the proportion of missing outcomes compared with the observed event risk induced clinically relevant bias in the intervention effect estimate; if 'as-treated' analysis was done with substantial departure of the intervention received from that assigned at randomisation.

Selective outcome reporting

Adequate (low risk of bias): if the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; if the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified.

Unclear (uncertain risk of bias): if the report gives insufficient information to permit judgement of adequacy or inadequacy. It is likely that the majority of studies will fall into this category.

Inadequate (high risk of bias): if not all of the study's pre-specified primary outcomes have been reported; if one or more primary outcomes are reported using measurements, analysis methods or subsets of the data (for example, subscales) that were not pre-specified; if one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); if one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; if the study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Other potential threats to validity

Adequate (low risk of bias): the study appears to be free of other sources of bias.

Unclear (uncertain risk of bias): if there may be a risk of bias, but there is insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.

Inadequate (high risk of bias): if there is at least one important risk of bias, such as: a potential source of bias related to the specific study design used; or it was stopped early due to some data-dependent process (including a formal-stopping rule); or had extreme baseline imbalance; or has been claimed to have been fraudulent; or had some other problem.

Measures of treatment effect

Two review authors (MG, MS) analysed data using [RevMan 2014](#). All the data were dichotomous. We used the risk ratio (RR) to measure treatment effectiveness.

Unit of analysis issues

All the included studies were parallel RCTs. The unit of analysis for each outcome was the individual research participant. We did not select any trial with a non-standard design, such as cross-over or cluster-RCTs.

Dealing with missing data

When the missing data seemed to be unrelated to the actual values, we analysed the study according to the intention-to-treat (ITT) principle.

When the reasons for the missing data were unclear but seemed to be unrelated to clinical motives, we also conducted the analyses according to the ITT principle. We also conducted a sensitivity analysis, imagining a scenario in which there was the best possible response to the use of antibiotic to prevent the studied outcome. We should emphasise that it is unlikely that this hypothetical scenario occurs in clinical practice. It should be interpreted only as an estimate of the theoretical maximum benefit that could be obtained through the use of antibiotics. We addressed the potential impacts of the missing data on the findings of the review in the [Discussion](#) section ([Higgins 2011](#)).

Assessment of heterogeneity

We assessed the heterogeneity of the trials by visually inspecting the forest plots and by performing the Chi² test (P value < 0.1 representing heterogeneity). We also used the I² statistic to quantify inconsistencies among the trials. If the I² had exceeded

50% and visual inspection of forest plots had supported these findings, we would have considered it to be indicative of substantial heterogeneity. Had this happened, we would have explored the underlying causes according to the limits permitted by the available data (Higgins 2011).

Assessment of reporting biases

It was not possible to examine the existence of publication bias graphically using a funnel plot (trial effect versus trial size) because we did not have more than five studies available for any one comparison.

Data synthesis

For similar types of studies we performed a meta-analysis to calculate a weighted intervention effect across the trials. We used the fixed-effect model for combination analysis. We expressed the results as RR with a 95% confidence interval (CI). Participants were analysed in their original randomised group using intention-to-treat (ITT) analysis. We also expressed the results as number needed to treat to benefit (NNTB) when appropriate. If considered appropriate, we pooled results of similar groups of trials. We used the fixed-effect model and a 95% CI.

GRADE and 'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: otitis media and pneumonia. None of the included trials addressed our other outcomes, such as mastoiditis, quinsy, abscess, meningitis, admission to hospital, gastro-intestinal symptoms or rashes. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence as it relates to the studies that contribute data to the meta-analyses for the pre-specified outcomes (Atkins 2004). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to downgrade or upgrade the quality of studies using footnotes, and we made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We investigated possible heterogeneity according to variations in the participants, interventions and outcomes. Whenever data were available, we analysed the children by age subgroups to observe possible changes in the effectiveness of the intervention. Subgroups included those up to 12 months of age and from 12 months to 59 months. We also intended to analyse separately those who attended day care and those who did not, as well as those with underlying immunodeficiencies or anatomical defects. However, no data were available for these comparisons.

We separately analysed subgroups that come from low-income countries due to the high frequency of bacterial aetiology infections in children with ARIs. Finally, we analysed subgroups of the different available outcomes: otitis and pneumonia.

Sensitivity analysis

We carried out a subgroup analysis for subsets of high and low-income countries due to the higher frequency of bacterial

complications expected in children from low-income regions (Analysis 1.2).

After reading the included articles we decided to conduct another analysis. However, we should emphasise that this was an exploratory analysis and was not previously included in the protocol. In one trial (Heikkinen 1995), 11 children failed to complete the study: seven in the intervention group and four in the control group. The reasons why the children did not complete the study are unclear. We simulated the best-case scenario for the antibiotic effect, conducting an analysis taking into account the best results that could have been found with antibiotic treatment if these 11 children had completed the study. As such, we considered what the results would have been if the seven children who did not complete the study that had received treatment had not developed otitis. On the other hand, we also considered that the four patients in the control group that did not finish the study did develop the infection.

RESULTS

Description of studies

Results of the search

This review was first published in 2014 (Alves Galvão 2014). At that time, we had retrieved 4551 records from the electronic searches. Out of these, 4507 studies were initially discarded based on their abstracts and titles. In this 2015 update, we retrieved 616 new studies and we initially discarded 613 studies based on their abstracts and titles. Overall, we retrieved a total of 5167 studies and discarded 5120 trials based on their abstracts and titles.

We assessed the remaining 47 trials in detail. Four trials were included and 43 did not meet the selection criteria (Figure 1). The four included trials are published trials and are described in the [Characteristics of included studies](#) table.

Included studies

The four included trials (Autret-Leca 2002; Heikkinen 1995; Rwalah 2011; Sutrisna 1991), involving 1314 children, studied the use of antibiotics in the prevention of two complications of undifferentiated acute respiratory infections. Three of them dealt with the use of amoxicillin/clavulanic acid to prevent otitis in children with a previous history of this infection (Autret-Leca 2002; Heikkinen 1995; Rwalah 2011). The remaining trial was about the use of ampicillin to prevent pneumonia (Sutrisna 1991).

The trials were conducted in Jordan (Rwalah 2011), France (Autret-Leca 2002), Finland (Heikkinen 1995), and Indonesia (Sutrisna 1991), in private and public health services.

Excluded studies

We excluded 43 studies. The most common reasons for exclusion were as follows:

1. The trial was about specific infections of known bacterial aetiology, such as otitis, streptococcal tonsillo-pharyngitis, pertussis, tuberculosis and other respiratory infections.
2. Antibiotics were not the studied drugs.
3. The studied antibiotic is no longer recommended to be used in children up to 59 months of age.
4. Ages of participants were outside our protocol age range.

5. Multiple publications of the same study.
6. The entire text could not be accessed.

Risk of bias in included studies

The overall risk of bias is included in the [Characteristics of included studies](#) table, presented graphically in [Figure 2](#) and summarised in [Figure 3](#).

Allocation

The four included trials were described as randomised ([Autret-Leca 2002](#); [Heikkinen 1995](#); [Rwalah 2011](#); [Sutrisna 1991](#)). Nevertheless, in three the information about the randomisation process was not sufficient to permit judgement of its adequacy and the methods used to conceal the allocation were not described ([Autret-Leca 2002](#); [Rwalah 2011](#); [Sutrisna 1991](#)).

In one study the randomisation was computer-generated ([Heikkinen 1995](#)). Participants and investigators enrolling participants were not aware of the assignment because the sequentially numbered treatment containers were of identical appearance.

Blinding

Three studies were described as double-blind but the method of blinding was not clearly described. These trials studied the prevention of otitis ([Autret-Leca 2002](#); [Heikkinen 1995](#); [Rwalah 2011](#)). The [Sutrisna 1991](#) trial was a non-blinded study about the prevention of pneumonia.

Incomplete outcome data

There were no missing participants in one study ([Rwalah 2011](#)).

In [Heikkinen 1995](#), 11 of 115 randomised children failed to complete the study: seven in the intervention group and four in the control group. The reasons for this are unclear but they do not seem to be related to clinical motives. We analysed this study according to the ITT principle.

In [Autret-Leca 2002](#), five of 203 children failed to complete the study: one in the intervention group and four in the control group. We analysed this study according to the ITT principle, as presented by the trial authors.

In [Sutrisna 1991](#), there were no missing data but 11 children were excluded due to secondary disorders (four in the treatment group and seven in the control group): they stopped taking ampicillin or paracetamol because they developed diarrhoea (four ampicillin, six control) or allergic reactions (one control). This was the only study considering the 'pneumonia' outcome. In the analysis process, we studied the sample according to the two age groups provided by the authors. Information about exclusions in each age group was not available and we analysed the trial per protocol, as was done by the trial authors.

Selective reporting

We did not identify any possible sources of reporting bias as the reports give insufficient information to reach any conclusion about adequacy.

Other potential sources of bias

We did not identify any other possible sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison](#); [Summary of findings 2](#)

Even though we intended to assess 12 outcomes, we could only assess two: antibiotic compared to control for undifferentiated acute respiratory infections (ARIs) in children younger than five, to prevent otitis and to prevent pneumonia.

Just one of the included trials addressed outcomes related to the adverse effects caused by antibiotics in children with undifferentiated ARI ([Autret-Leca 2002](#)). However, this trial's data could not be analysed as the data were expressed in percentages rather than absolute terms.

Primary outcomes

1. Otitis media

Amoxicillin/clavulanic acid was compared to placebo in children with undifferentiated ARIs and previous episodes of otitis in three included trials with a total of 414 children ([Autret-Leca 2002](#); [Heikkinen 1995](#); [Rwalah 2011](#)). The diagnosis of acute otitis media was based on an assessment of signs and symptoms as well as an otoscopic examination (bulging, opacity or lack of mobility of the tympanic membrane).

There was no statistical evidence of a protective effect of the antibiotic in the occurrence of otitis: risk ratio (RR) 0.70, 95% confidence interval (CI) 0.45 to 1.11 ([Analysis 1.1](#); [Summary of findings for the main comparison](#)).

Considering the characteristics of some of the included studies, we decided to conduct other analyses, although we should emphasise they are only exploratory analyses.

We also separately analysed children from high and low-income countries due to the higher frequency of bacterial complications expected in children from low-income countries. The results were similar and compatible with both benefit and harm in the prevention of otitis: RR 0.67, 95% CI 0.39 to 1.14 in high-income countries ([Analysis 1.2](#)) and RR 0.82, 95% CI 0.34 to 1.94 in low-income regions ([Rwalah 2011](#)).

2. Mastoiditis

Not reported on.

3. Quinsy

Not reported on.

4. Pneumonia

Ampicillin was compared to supportive care (continuation of breastfeeding, clearing of the nose as needed and paracetamol for fever control) in children with undifferentiated ARIs in 889 participants in just one trial ([Sutrisna 1991](#)). The diagnosis of pneumonia was based on the World Health Organization (WHO) criteria for ARI management ([WHO 2012](#)). Although the research was conducted in a low-income region where a bacterial aetiology of ARI could be expected to be more frequent, the intervention

showed no effect: RR 1.05, 95% CI 0.74 to 1.49. We also presented the results separately in two age subgroups, as done by the trial authors. In the same way, a protective effect could not be demonstrated either when patients were analysed together or in two age groups (up to 11 months and from 12 to 58 months). In children up to 11 months of age the RR was 0.96 (95% CI 0.52 to 1.76). In children from 12 to 59 months of age the RR was 1.10 (95% CI 0.71 to 1.69) ([Analysis 1.3](#); [Summary of findings 2](#)).

5. Abscess

Not reported on.

6. Meningitis

Not reported on.

7. Rates of admission to hospital

Not reported on.

8. Death

Not reported on.

Secondary outcomes

1. Diarrhoea

Not reported on.

2. Vomiting

Not reported on.

3. Gastro-intestinal symptoms

Not reported on.

4. Rashes

Not reported on.

DISCUSSION

Undifferentiated acute respiratory infections (ARIs) and infections such as otitis and pneumonia are common in children. Although less frequent, other infections such as mastoiditis and quinsy may be significant and even life-threatening conditions, especially in children up to four years of age. These infections are also a major cause of concern amongst parents and policy makers due to their potential complications, healthcare costs, associated absenteeism from work (parents) and even mortality, especially in socially and economically disadvantaged populations. Moreover, all of these conditions may be under-diagnosed due the smaller anatomy and difficulties of examining young children ([Abdel-Aziz 2010](#); [Schraff 2001](#)).

There are many trials on these topics in the medical literature. However, studies about the common clinical situation in which a physician must decide whether or not to prescribe an antibiotic to a patient presenting with an undifferentiated ARI, in order to avoid potentially life-threatening complications, are less common. This observation is also supported by the contrast between the small number of studies that met the inclusion criteria for this review and the large number of records found in the initial search (i.e. four out of 5167 trials). We also highlight the fact that just one of the included trials addressed outcomes related to the adverse

effects caused by antibiotics in children with undifferentiated ARI ([Autret-Leca 2002](#)). However, the data from this study could not be analysed as they were expressed in percentages rather than absolute terms. The adverse effects of antibiotics should be considered an essential topic when determining the cost-effectiveness of antibiotic prescription.

It has been established that the development of bacterial resistance and the need for new generations of antibiotics for outpatient treatment of infections are major causes of concern globally ([Costelloe 2010](#); [Gjelstad 2013](#)). Furthermore, mortality caused by bacterial respiratory infections is more frequent in low-income countries ([Rudan 2004](#); [Rudan 2008](#)), where limited resources may impair the running of clinical trials. These facts may have contributed to the small number of trials meeting our inclusion criteria.

We included four trials in this review: three investigated the prevention of otitis and one investigated the prevention of pneumonia.

Otitis media is a common infection worldwide. For most children with mild otitis media in high-income countries, an expectant observational approach seems to be justified ([Venekamp 2015](#)). However, there is concern over excessive antibiotic consumption in children in many high-income countries ([Arason 2010](#); [Coco 2009](#); [Kutty 2011](#)). On the other hand, in low-income countries where children have limited access to medical care, suppurative complications and hearing loss are more frequent ([Klein 2000](#); [Vergison 2010](#)). In the studies of otitis in this review, although all patients had a previous history of this infection, it was not stated whether or not they were immunodeficient. Amoxicillin/clavulanic acid was the drug of choice. The results in the three trials were similar and did not provide evidence of a significant benefit of antibiotics in preventing otitis: risk ratio (RR) 0.70, 95% confidence interval (CI) 0.45 to 1.11 ([Analysis 1.1](#)). Although there was no statistical heterogeneity in the three trials, to take into account the characteristics of the studied samples in the selected studies, we conducted some exploratory analyses.

In one trial 11 children failed to complete the study: seven in the intervention group and four in the control group ([Heikkinen 1995](#)). The reasons why children did not complete the study are unclear. A question arose as to whether such drop-outs could modify the results. We verified the best results that could be obtained in a hypothetical situation, conducting an analysis considering the results as if the seven children that did not complete the study who had received the antibiotic did not develop otitis, while incorporating the four in the control group as if they had developed the infection. In this case, a slight statistical protective effect of the antibiotic was displayed: RR 0.64, 95% CI 0.41 to 0.99. However, it should be emphasised that it would be necessary to treat 14 children with ARIs for a seven-day period to prevent one case of otitis (number needed to treat to benefit (NNTB) 14, 95% CI 8 to 50).

We also separately analysed children from high (Finland and France) and low-income countries (Jordan) due to the higher frequency of bacterial complications expected in children from low-income regions. Otitis media was the only outcome that was reported in the trials conducted in both high and low-income countries. The results in the two settings were similar and consistent with both benefit and harm (RR 0.67, 95% CI 0.39 to 1.14 in high-income countries ([Analysis 1.2](#)) and RR 0.70, 95% CI

0.45 to 1.11 in low-income countries [Analysis 1.1](#)). This similarity may seem unexpected due to the higher frequency of bacterial complications in children from low-income countries. However, the small number of studies and sample sizes for this outcome may have influenced the results obtained.

Pneumonia is a common infection in low-income countries. Its annual incidence in these areas is estimated to be 150.7 million new cases, 11 to 20 million (7% to 13%) of which are severe enough to require hospital admission. An estimated nearly 1.2 million children younger than five years died in 2011 from pneumonia ([Izadnegahdar 2013](#)). It has been suggested that more than 95% of all episodes of clinical pneumonia in young children worldwide occur in low-income countries ([Rudan 2004](#)).

We also analysed prevention of pneumonia in one study ([Sutrisna 1991](#)). Ampicillin was the antibiotic studied. Although the research was conducted in a low-income region, where a bacterial aetiology could be expected to be more frequent, the intervention showed no effect. A protective effect could not be demonstrated when patients were analysed together, nor when they were analysed separately in two age groups (up to 11 months and from 12 to 58 months) ([Analysis 1.3](#)). The small number of selected trials for this important cause of childhood death in low-income countries may reflect the limited resources of these regions for conducting clinical trials. It must be emphasised that the comparison is based on just one non-blinded study and the data were analysed per protocol.

Both antibiotic resistance and side effects of antibiotics should be taken into account in further defining the risks and benefits of prescribing these drugs. However, we believe that if we only consider changes in bacterial resistance patterns, the essence of our observed results is unlikely to change in favour of the use of antibiotics to prevent the studied infections, as resistance to antibiotics seems to increase over time ([Del Mar 2012](#)).

Summary of main results

Four trials were included in this review. Three investigated the use of amoxicillin/clavulanic acid compared to placebo to prevent otitis and one investigated ampicillin compared to supportive care to prevent pneumonia.

Amoxicillin/clavulanic acid was compared to placebo to prevent otitis. The estimated reduction in the risk of otitis was compatible with both benefit and harm (RR 0.70, 95% CI 0.45 to 1.11, three trials, 414 selected children, moderate-quality evidence) ([Summary of findings for the main comparison](#)). Methods of random sequence generation and allocation concealment were not clearly stated in two trials. Performance, detection and reporting bias could not be ruled out in three trials.

Ampicillin was compared to supportive care to prevent pneumonia. The estimated reduction in the risk of pneumonia was also compatible with both benefit and harm (RR 1.05, 95% CI 0.74 to 1.49) ([Summary of findings 2](#)). In the one trial looking at pneumonia parents were not blinded, but detection blinding was not clearly stated. Random sequence generation and allocation concealment methods were not clearly stated, and the possibility of reporting bias could not be ruled out.

Harm outcomes could not be analysed as they were expressed only in percentages.

We found no studies that assessed mastoiditis, quinsy, abscess, meningitis, hospital admission or death.

Further research is likely to have an important impact on the estimated effectiveness and may change the obtained results.

Overall completeness and applicability of evidence

The studies dealt with common clinical infections in clinical practice in an age group especially prone to severe secondary complications. Nevertheless, we believe that only limited evidence can be obtained from this review.

The selected trials were conducted on only two continents. Just one of them was produced in the last 10 years. It is possible that changes in the pattern of bacterial resistance and the immune status of paediatric populations has occurred over this period. Some of the possible causes of these changes over time are: inappropriate use of antibiotics, local epidemiological patterns and the implementation of new vaccines ([Coco 2009](#); [Dagan 2008](#)). These facts may limit the external validity of the studies. Furthermore, there were no selected trials from the Americas or Africa, regions where ARIs and their bacterial complications are common. Two of the studies were conducted in private clinics in high-income countries in Europe (318/414 participants) ([Autret-Leca 2002](#); [Heikkinen 1995](#)), where the burden of suppurative complications of undifferentiated ARI is not considered as important as in low-income countries.

Quality of the evidence

We intended to study a common infection: undifferentiated ARI. The objective of our review, to assess the effectiveness and safety of antibiotics in preventing bacterial complications in children aged two to 59 months with undifferentiated ARIs, is a frequent dilemma in clinical practice. The use of antibiotics to prevent suppurative complications does not seem to be rare, whether or not this prescription is considered appropriate. Nevertheless, just four out of the 5167 trials identified by our searches met the inclusion criteria.

We classified the quality of the evidence obtained for the prevention of otitis media and pneumonia as moderate.

We downgraded the evidence for the prevention of otitis media due to some risks of bias. This infection cannot be considered rare but just three trials, including 414 children, met our inclusion criteria. The methods of random sequence generation and allocation concealment were not clearly stated in two trials ([Autret-Leca 2002](#); [Rwalah 2011](#)). Blinding of participants and personnel (performance bias) and outcome assessors (detection bias) was unclear in the three studies ([Autret-Leca 2002](#); [Heikkinen 1995](#); [Rwalah 2011](#)). The reports give insufficient information to make a judgement about the occurrence of reporting bias in all the three studies ([Autret-Leca 2002](#); [Heikkinen 1995](#); [Rwalah 2011](#)).

On the other hand, we think that we should clarify why we did not downgrade Autret-Leca's study for the use of a placebo syrup prepared by a pharmaceutical company ([Autret-Leca 2002](#)). As there was no statistical evidence of a protective effect of the studied antibiotic, we think that this fact did not influence the results.

We believe that further research, especially in other countries, may have an impact on the results.

We also downgraded the evidence for the prevention of pneumonia. We identified risks of bias in the trial studying pneumonia (Sutrisna 1991). This is also a common infection but we included just one single trial, including 889 children. This was a non-blinded study for parents. The presence of detection bias was unclear. The methods of random sequence generation and allocation concealment were not clearly stated. Moreover, there is insufficient information to rule out reporting bias. The reduction in the risk of pneumonia was also compatible with both benefit and harm. Further research is likely to have an important impact on the estimated effectiveness and may change the obtained results.

Potential biases in the review process

In all the included studies the diagnosis of the infections was based on clinical signs and symptoms. We did not include additional tests to identify the aetiological agent of the infections as a selection criteria for the trials. Thus, it is reasonable to suppose that, in some cases, non-bacterial otitis or pneumonia had been wrongly classified as a suppurative complication.

Agreements and disagreements with other studies or reviews

We could not find any other studies with the same objective as this review. However, the question of whether to use antibiotics to prevent infectious complications in children with ARIs has been recognised as a common problem in clinical practice.

Most of the systematic reviews in this area deal more specifically with the site of the infection (otitis, pharyngitis, sinusitis, pneumonia) (Altamimi 2012; Kabra 2013; Venekamp 2015), its aetiology (van Driel 2013), or the choice of immediate or delayed antibiotic use (Spurling 2013). It is not easy to compare this review with these given the differences in objectives and methodologies. The assessment of response to antibiotics in patients with cough and common cold in the Spurling 2013 review could be considered closer to the objectives of our review. Spurling found no benefit from the use of antibiotic therapy for such patients. Despite methodological differences, in our review we also could not find clinical benefits from the use of antibiotics in children with undifferentiated ARI for the prevention of pneumonia and otitis.

AUTHORS' CONCLUSIONS

Implications for practice

There is inadequate evidence to determine the effectiveness of antibiotics in preventing the development of otitis and pneumonia

in children up to five years of age with undifferentiated ARIs. Due to the small number of participants and only moderate quality of evidence, further high-quality research is needed to provide more definitive evidence.

Implications for research

Definitive conclusions may have been impaired by the small number of selected studies and the small number of participants. Further research is necessary to:

1. define the harms or benefits (or both) of prescribing antibiotics to children with undifferentiated ARI in regions where medical assistance is not easily obtained and where a bacterial aetiology is supposed to be more frequent;
2. verify whether possible changes in the characteristics of the aetiological agents, the populations and the antibiotics used in the last 10 years could change the present results;
3. increase knowledge about the phenomenon of antimicrobial resistance and the spread of this resistance in the community when antibiotics are given to this age group;
4. study the use of innovative markers or microbiological techniques to identify children that could benefit from antibiotic use;
5. provide more conclusive recommendations.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Autret-Leca 2002

Methods	RCT
Participants	Children at risk of AOM Age range: 3 months to 3 years of age
Interventions	Amoxicillin/clavulanic acid or placebo
Outcomes	Otitis
Notes	Children at risk of AOM

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised but information about the randomisation process was insufficient to permit judgement of adequacy or inadequacy
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blind, but the method of blinding was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as double-blind, but the method of blinding was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data are balanced in numbers across the groups

Autret-Leca 2002 (Continued)

Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement of adequacy or inadequacy
Other bias	Unclear risk	A pharmaceutical company prepared the placebo syrup used in the trial

Heikkinen 1995

Methods	RCT
Participants	Children at risk of AOM Age range: 1 to 4 years of age
Interventions	Amoxicillin/clavulanic acid or placebo
Outcomes	Otitis
Notes	Children at risk of AOM

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation sequence was described as randomised and generated by a computer
Allocation concealment (selection bias)	Low risk	Participants and investigators enrolling participants could not foresee assignment because of sequentially numbered drug containers of identical appearance
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blind but the method of blinding was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as double-blind but the method of blinding was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for missing outcome data are unclear but do not seem to be related to clinical motives
Selective reporting (reporting bias)	Unclear risk	The report gives insufficient information to permit judgement of adequacy or inadequacy
Other bias	Low risk	The trial appears to be free of other sources of bias

Rwalah 2011

Methods	RCT
Participants	Children at risk of AOM Age range: up to 4 years of age

Rwalah 2011 (Continued)

Interventions	Amoxicillin/clavulanic acid 40 mg/kg/day or placebo
Outcomes	Otitis
Notes	Children at risk of AOM

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised but there was insufficient information about the sequence generation process to permit judgment of adequacy or inadequacy
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised but the method used to conceal the allocation was not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The trial was described as double-blind but the method of blinding was not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The trial was described as double-blind but the method of blinding was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing participants
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement of adequacy or inadequacy
Other bias	Low risk	The trial appears to be free of other sources of bias

Sutrisna 1991

Methods	RCT
Participants	Children up to 5 years of age
Interventions	Ampicillin: 25 to 30 mg/kg per dose, every 6 hours, during 5 days and supportive care or just supportive care
Outcomes	Pneumonia
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was described as randomised, but there was insufficient information about the sequence generation process to permit judgement of adequacy or inadequacy

Sutrisna 1991 (Continued)

Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but the method used to conceal the allocation was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding was not clearly stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing outcome data. 11 children were excluded because of secondary disorders during the study
Selective reporting (reporting bias)	Unclear risk	There is insufficient information to permit judgement of adequacy or inadequacy
Other bias	Unclear risk	The trial appears to be free of other sources of bias

AOM: acute otitis media

RCT: randomised clinical trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ackerman 1968	Tetracycline was one of the studied antibiotics; nowadays it is not recommended for the age range in our protocol
Arroll 2008	Review
Betend 1972	Trial is not about undifferentiated acute respiratory infections
Bloomfield 2004	Trial conducted in hospitalised children with respiratory syncytial virus infection
Bovier-Lapierre 1971	Trial is not about undifferentiated acute respiratory infections
Carr 1973	There is no placebo or non-treatment control group in this trial
Castello 1981	Not a RCT
De Mattia 1986	Comparison between 2 antibiotics. Ages of participants are not clearly stated
De Sario 1986	Study is not about undifferentiated respiratory infections
Easton 2010	Not a RCT
Gjelstad 2013	It is an article about medical education
Gordon 1974	Data about the effects of antibiotic compared to control in relieving symptoms, preventing complications or causing adverse events were not provided

Study	Reason for exclusion
Gronås 1971	Trial is a comparison of 2 antibiotics for respiratory infections probably caused by <i>Haemophilus influenzae</i>
Guerrier 1972	Ages of participants were outside our protocol age range
Gupta 1977	Comparison among 3 antibiotics; there is no placebo or non-treatment control group
Hardy 1956	Data for participants in our protocol age range were not available
He 2006	The entire text could not be accessed
Hennes 1982	Study is a comparison among antibiotics; there is no placebo or non-treatment control group
Higashi 2014	Ages of participants were outside our protocol age range
Kundu 1976	Ages of participants were outside our protocol age range
Lake 1971	Ages of participants were outside our protocol age range
Lexomboon 1971	Data about the effects of antibiotics compared to control in relieving symptoms, preventing complications and causing adverse events in children included in our protocol age range were not available
Limson 1972	Ages of participants were outside our protocol age range
Lines 1973	Trial is a comparison between 2 antibiotics
Little 1997	Ages of participants were outside our protocol age range
Maeda 1999	Data for children included specifically in our protocol age range were not available
Masbernard 1979	Ages of participants were outside our protocol age range
McGuinness 1986	Study is a comparison among antibiotics; no placebo or non-treatment control group
Newell 1970	Trial is not about undifferentiated acute respiratory tract infection
Oggero 1985	Trial is a comparison between 2 antibiotics
Pan 2000	Ages of participants were outside our protocol age range
Price 1975	Trial is not about undifferentiated acute respiratory tract infections
Ratjen 2013	An article about cystic fibrosis
Reinert 1991	Data for children up to 5 years of age were not available
Rentsch 1980	Not a RCT. Ages of participants were outside our protocol age range
Roper 1970	Ages of participants were outside our protocol age range
Taylor 1977	Trial was not about undifferentiated respiratory infections. Laboratory tests were used to exclude children with infections of bacterial aetiology

Study	Reason for exclusion
Todd 1981	There are insufficient data for the sample age range and for the outcomes that are the subject of this review
Varricchio 2006	In this trial 2 antibiotics are compared; there was no non-treatment or placebo control group
Varricchio 2008	Trial about culture-proven acute bacterial infection
Windorfer 1980	Comparison between 2 antibiotics; no placebo or non-treatment control group
Zwart 2003	No subgroup analyses for our protocol age range
Zwart 2004	Ages of participants were outside our protocol age range

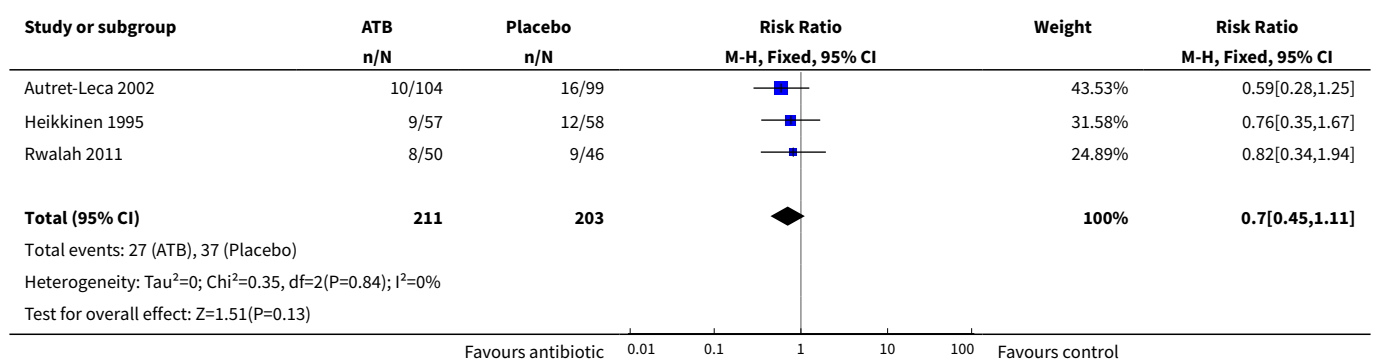
RCT: randomised controlled trial

DATA AND ANALYSES

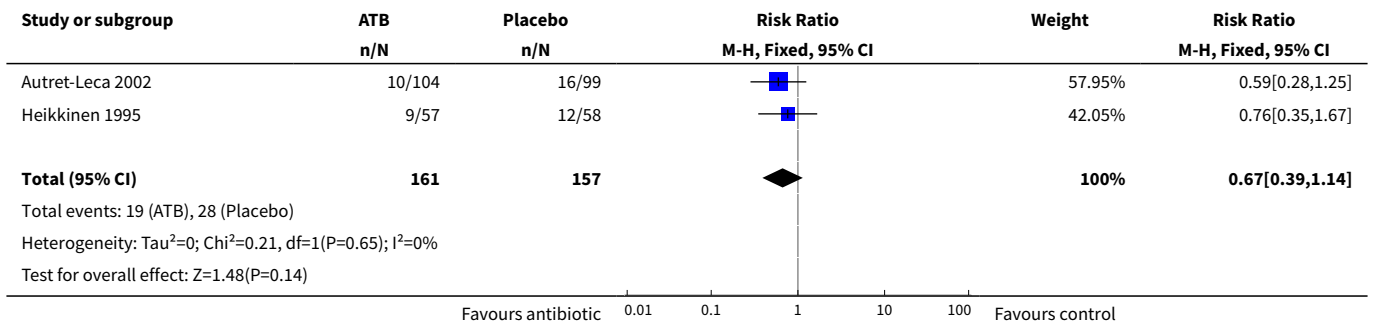
Comparison 1. Antibiotic compared to control in the treatment of ARI in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Otitis	3	414	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.45, 1.11]
2 Otitis - high-income countries	2	318	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.39, 1.14]
3 Pneumonia	1	889	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.74, 1.49]
3.1 Up to 11 months old	1	326	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.52, 1.76]
3.2 12 to 58 months old	1	563	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.71, 1.69]

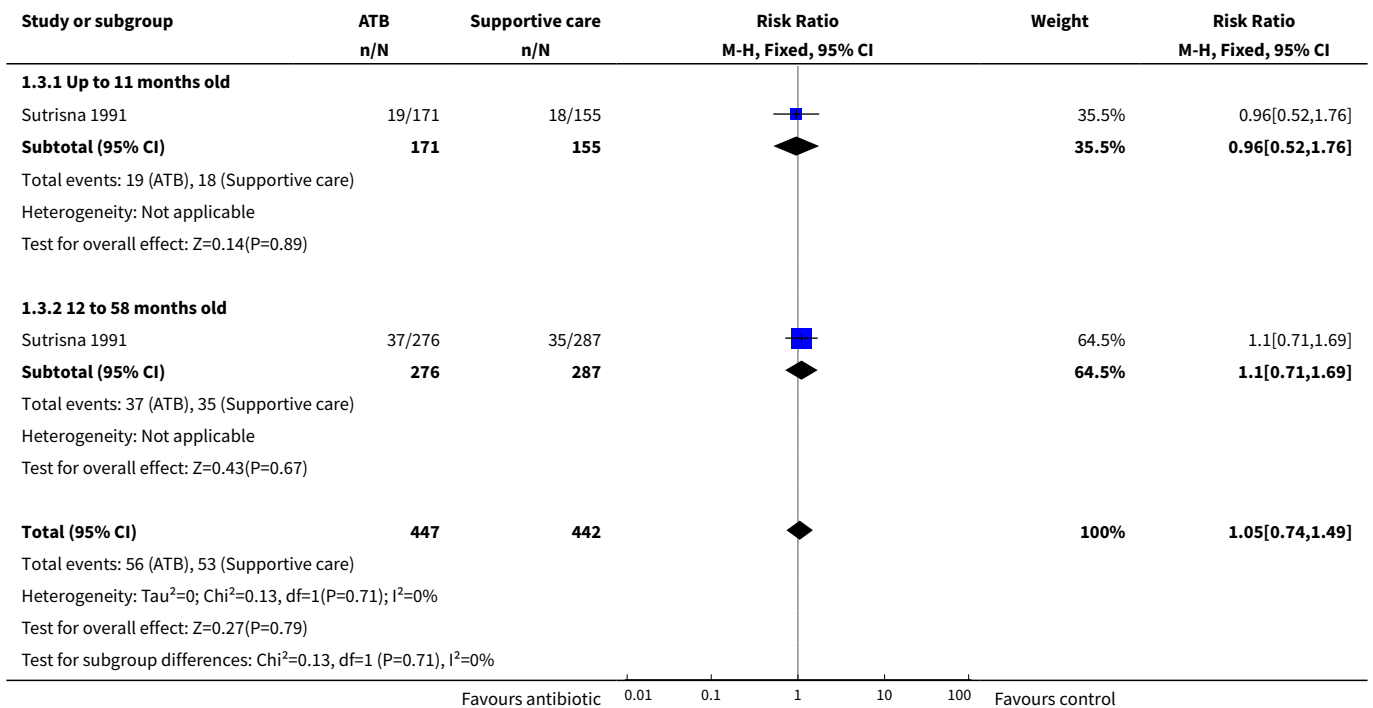
Analysis 1.1. Comparison 1 Antibiotic compared to control in the treatment of ARI in children, Outcome 1 Otitis.



Analysis 1.2. Comparison 1 Antibiotic compared to control in the treatment of ARI in children, Outcome 2 Otitis - high-income countries.



Analysis 1.3. Comparison 1 Antibiotic compared to control in the treatment of ARI in children, Outcome 3 Pneumonia.



APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE (Ovid)

- 1 exp Respiratory Tract Infections/
- 2 respiratory tract infection*.tw.
- 3 respiratory infection*.tw.
- 4 (urti or uri or ari).tw.
- 5 Nasopharyngitis/
- 6 nasopharyngit*.tw.

7 exp Sinusitis/
 8 sinusit*.tw.
 9 rhinitis/
 10 rhinit*.tw.
 11 rhinosinusit*.tw.
 12 Pharyngitis/
 13 pharyngit*.tw.
 14 sore throat*.tw.
 15 Tonsillitis/
 16 tonsillit*.tw.
 17 exp Laryngitis/
 18 laryngit*.tw.
 19 croup*.tw.
 20 tracheitis/
 21 tracheit*.tw.
 22 Epiglottitis/
 23 epiglottit*.tw.
 24 Common Cold/
 25 common cold*.tw.
 26 coryza.tw.
 27 exp Otitis Media/
 28 otitis media.tw.
 29 (AOM or OME).tw.
 30 Cough/
 31 cough*.tw.
 32 Influenza, Human/
 33 (influenza* or flu).tw.
 34 exp Bronchitis/
 35 (bronchit* or bronchiolit*).tw.
 36 exp Pneumonia/
 37 pneumon*.tw.
 38 or/1-37
 39 exp Anti-Bacterial Agents/
 40 antibiotic*.tw.
 41 (cephalosporin* or cefadroxil* or cephalixin* or cephaloridine* or cephalothin* or cephapirin* or cefazolin* or cephradine* or cefaclor* or cefoxitin* or cefprozil* or cefuroxime* or cefdinir* or cefixime* or cefpodoxime* or ceftibuten or ceftriaxone* or cefotaxime*).tw.
 42 (penicillin* or methicillin* or oxacillin* or ampicillin* or amoxicillin*).tw.
 43 (macrolide* or erythromycin* or clarithromycin* or azithromycin* or dirithromycin* or roxithromycin* or troleandomycin*).tw.
 44 (aminoglycoside* or amikacin* or gentamicin* or kanamycin* or neomycin* or tobramycin*).tw.
 45 (cloramphenicol* or sulfonamide* or erythromycin* or trimethoprim*).tw.
 46 or/39-45
 47 38 and 46
 48 Infant/
 49 (infant* or infancy or baby* or babies).tw.
 50 exp Child/
 51 (child* or schoolchild* or school age* or preschool* or kid or kids or toddler* or boy* or girl*).tw.
 52 Pediatrics/
 53 (pediatric* or paediatric*).tw.
 54 52 or 50 or 53 or 49 or 51 or 48
 55 54 and 47

Appendix 2. Embase.com search strategy

1. 'respiratory tract infection'/exp
2. 'respiratory tract infection':ti,ab OR 'respiratory tract infections':ti,ab
3. 'respiratory infection':ti,ab OR 'respiratory infections':ti,ab OR urti:ti,ab OR uri:ti,ab OR ari:ti,ab
4. 'rhinopharyngitis'/exp
5. nasopharyngit*:ti,ab OR rhinopharyngit*:ti,ab
6. 'sinusitis'/exp

7. sinusit*:ti,ab
8. 'rhinitis'/de
9. rhinit*:ti,ab
10. 'rhinosinusitis'/exp
11. rhinosinusit*:ti,ab
12. 'pharyngitis'/exp
13. pharyngit*:ti,ab
14. 'sore throat'/exp
15. 'tonsillitis'/de
16. tonsillit*:ti,ab
17. 'laryngitis'/de
18. 'croup'/exp OR 'laryngotracheobronchitis'/exp
19. laryngit*:ti,ab OR croup*:ti,ab OR laryngotracheobronchit*:ti,ab
20. 'tracheitis'/exp
21. tracheit*:ti,ab
22. 'epiglottitis'/exp
23. epiglottit*:ti,ab
24. 'common cold'/exp
25. 'common cold':ti,ab OR 'common colds':ti,ab OR coryza*:ti,ab
26. 'otitis media'/exp
27. 'otitis media':ti,ab OR aom:ti,ab OR ome:ti,ab
28. 'coughing'/exp
29. cough*:ti,ab
30. 'influenza'/exp
31. flu*:ti,ab OR influenza*:ti,ab
32. 'bronchitis'/exp
33. bronchit*:ti,ab OR bronchiolit*:ti,ab
34. 'pneumonia'/exp
35. pneumon*:ti,ab
36. 'sore throat':ti,ab OR 'sore throats':ti,ab
37. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #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 OR #22 OR #23 O
 R #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR
 #31 OR #32 OR #33 OR #34 OR #35 OR #36
38. 'antibiotic agent'/exp
39. antibiotic*:ti,ab OR 'anti biotic':ti,ab OR 'antibiotics':ti,ab
40. (cephalosporin*:ti,ab OR cefadroxil*:ti,ab OR cephalixin*:ti,ab OR cephaloridine*:ti,ab OR cephalothin*:ti,ab OR cephapirin*:ti,ab OR
 cefazolin*:ti,ab OR cephradine*:ti,ab OR cefaclor*:ti,ab OR cefoxitin*:ti,ab OR cefprozil*:ti,ab OR cefuroxime*:ti,ab OR cefdinir*:ti,ab OR
 cefixime*:ti,ab OR cefpodoxime*:ti,ab OR ceftibuten:ti,ab OR ceftriaxone*:ti,ab OR cefotaxime*:ti,ab)
41. (penicillin*:ti,ab OR methicillin*:ti,ab OR oxacillin*:ti,ab OR ampicillin*:ti,ab OR amoxicillin*:ti,ab)
42. (macrolide*:ti,ab OR erythromycin*:ti,ab OR clarithromycin*:ti,ab OR azithromycin*:ti,ab OR dirithromycin*:ti,ab OR
 roxithromycin*:ti,ab OR troleandomycin*:ti,ab)
43. (aminoglycoside*:ti,ab OR amikacin*:ti,ab OR gentamicin*:ti,ab OR kanamycin*:ti,ab OR neomycin*:ti,ab OR tobramycin*:ti,ab)
44. (cloramphenicol*:ti,ab OR sulfonamide*:ti,ab OR erythromycin*:ti,ab OR trimethoprim*:ti,ab)
45. #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44
46. 'infant'/exp
47. (infant*:ti,ab OR infancy*:ti,ab OR baby*:ti,ab OR babies:ti,ab)
48. 'child'/exp
50. 'pediatrics'/exp
51. pediatric*:ti,ab OR paediatric*:ti,ab
52. (child*:ti,ab OR schoolchild*:ti,ab OR preschool*:ti,ab OR kid:ti,ab OR kids:ti,ab OR toddler*:ti,ab
 OR boy*:ti,ab OR girl*:ti,ab) OR 'school age':ti,ab OR 'school aged':ti,ab OR 'school ages':ti,ab
53. #46 OR #47 OR #48 OR #50 OR #51 OR #52
54. #37 AND #45 AND #53
55. 'crossover procedure'/exp
56. 'double blind procedure'/exp
57. 'randomized controlled trial'/exp
58. 'single blind procedure'/exp
59. (random*:ti,ab OR factorial*:ti,ab OR crossover*:ti,ab OR placebo*:ti,ab OR assign*:ti,ab OR allocat
 :ti,ab OR volunteer:ti,ab) OR 'double blind':ti,ab OR 'double blinded':ti,ab OR 'double blinding':ti,ab OR 'single blind':ti,ab OR 'single
 blinded':ti,ab OR 'single blinding':ti,ab

60. #55 OR #56 OR #57 OR #58 OR #59

61. #54 AND #60

WHAT'S NEW

Date	Event	Description
5 August 2015	New citation required but conclusions have not changed	Our conclusions remain unchanged.
5 August 2015	New search has been performed	This review was updated in August 2015. We retrieved 616 new studies but none met our selection criteria. We excluded three new trials (Gjelstad 2013 ; Higashi 2014 ; Ratjen 2013).

CONTRIBUTIONS OF AUTHORS

Márcia G Alves Galvão (MG), Marilene AR Crispino Santos (MS) and Antonio JL Alves da Cunha (AC) were responsible for the conception of this protocol. They also approved this document for publication.

MG and MS selected trials and extracted data. AC was appointed as an arbitrator to resolve disagreements between MG and MS on the selection of the trials.

MG drafted the review. MS supervised the day-to-day work. MS and AC commented on the review critically for its content.

DECLARATIONS OF INTEREST

Márcia G Alves Galvão: none known.

Marilene Augusta Rocha Crispino Santos: none known.

Antonio JL Alves da Cunha: none known.

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Internal sources

- The authors declare that no funding was received for this systematic review, Other.

External sources

- The authors declare that no funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After reading the included articles we decided to conduct another analysis. In one trial ([Heikkinen 1995](#)), 11 children failed to complete the study: seven in the intervention group and four in the control group. The reasons why the children did not complete the study are unclear. We simulated the best-case scenario for the antibiotic effect, conducting an analysis taking into account the best results that could have been found with antibiotic treatment if these 11 children had completed the study. As such, we considered what the results would have been if the seven children who did not complete the study that had received treatment had not developed otitis. On the other hand, we also considered that the four patients in the control group that did not finish the study did develop the infection.

Furthermore, some of the specific outcomes that we intended to study could not be analysed because they were not reported in the studies (mastoiditis, quinsy, abscess, meningitis, admission to hospital and death).

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Amoxicillin-Potassium Clavulanate Combination [*therapeutic use]; Ampicillin [*therapeutic use]; Anti-Bacterial Agents [*therapeutic use]; Otitis [*prevention & control]; Pneumonia [*prevention & control]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [complications] [drug therapy]; Suppuration [drug therapy]

MeSH check words

Child, Preschool; Humans