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Antibiotics for otitis media with effusion in children (Review)

Venekamp RP, Burton MJ, van Dongen TMA, van der Heijden GJ, van Zon A, Schilder AGM

Venekamp RP, Burton MJ, van Dongen TMA, van der Heijden GJ, van Zon A, Schilder AGM.
Antibiotics for otitis media with effusion in children.
Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD009163.
DOI: 10.1002/14651858.CD009163.pub3.

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[Intervention Review]

Antibiotics for otitis media with effusion in children

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Editorial group: Cochrane ENT Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2016.

Citation: Venekamp RP, Burton MJ, van Dongen TMA, van der Heijden GJ, van Zon A, Schilder AGM. Antibiotics for otitis media with effusion in children. *Cochrane Database of Systematic Reviews* 2016, Issue 6. Art. No.: CD009163. DOI: 10.1002/14651858.CD009163.pub3.

ABSTRACT

Background

Otitis media with effusion (OME) is characterised by an accumulation of fluid in the middle ear behind an intact tympanic membrane, without the symptoms or signs of acute infection. Since most cases of OME will resolve spontaneously, only children with persistent middle ear effusion and associated hearing loss potentially require treatment. Previous Cochrane reviews have focused on the effectiveness of ventilation tube insertion, adenoidectomy, nasal autoinflation, antihistamines, decongestants and corticosteroids in OME. This review, focusing on the effectiveness of antibiotics in children with OME, is an update of a Cochrane review published in 2012.

Objectives

To assess the benefits and harms of oral antibiotics in children up to 18 years with OME.

Search methods

The Cochrane ENT Information Specialist searched the ENT Trials Register; Central Register of Controlled Trials (CENTRAL 2016, Issue 3); PubMed; Ovid EMBASE; CINAHL; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 14 April 2016.

Selection criteria

Randomised controlled trials comparing oral antibiotics with placebo, no treatment or therapy of unproven effectiveness in children with OME.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane.

Main results

Twenty-five trials (3663 children) were eligible for inclusion. Two trials did not report on any of the outcomes of interest, leaving 23 trials (3258 children) covering a range of antibiotics, participants, outcome measures and time points for evaluation. Overall, we assessed most studies as being at low to moderate risk of bias.

We found moderate quality evidence (six trials including 484 children) that children treated with oral antibiotics are more likely to have complete resolution at two to three months post-randomisation (primary outcome) than those allocated to the control treatment (risk ratio (RR) 2.00, 95% confidence interval (CI) 1.58 to 2.53; number needed to treat to benefit (NNTB) 5). However, there is evidence (albeit of

low quality; five trials, 742 children) indicating that children treated with oral antibiotics are more likely to experience diarrhoea, vomiting or skin rash (primary outcome) than those allocated to control treatment (RR 2.15, 95% CI 1.29 to 3.60; number needed to treat to harm (NNTH) 20).

In respect of the secondary outcome of complete resolution at *any* time point, we found low to moderate quality evidence from five meta-analyses, including between two and 14 trials, of a beneficial effect of antibiotics, with a NNTB ranging from 3 to 7. Time periods ranged from 10 to 14 days to six months.

In terms of other secondary outcomes, only two trials (849 children) reported on hearing levels at two to four weeks and found conflicting results. None of the trials reported data on speech, language and cognitive development or quality of life. Low quality evidence did not show that oral antibiotics were associated with a decrease in the rate of ventilation tube insertion (two trials, 121 children) or in tympanic membrane sequelae (one trial, 103 children), while low quality evidence indicated that children treated with antibiotics were less likely to have acute otitis media episodes within four to eight weeks (five trials, 1086 children; NNTB 18) and within six months post-randomisation (two trials, 199 children; NNTB 5). It should, however, be noted that the beneficial effect of oral antibiotics on acute otitis media episodes within four to eight weeks was no longer significant when we excluded studies with high risk of bias.

Authors' conclusions

This review presents evidence of both benefits and harms associated with the use of oral antibiotics to treat children up to 16 years with OME. Although evidence indicates that oral antibiotics are associated with an increased chance of complete resolution of OME at various time points, we also found evidence that these children are more likely to experience diarrhoea, vomiting or skin rash. The impact of antibiotics on short-term hearing is uncertain and low quality evidence did not show that oral antibiotics were associated with fewer ventilation tube insertions. Furthermore, we found no data on the impact of antibiotics on other important outcomes such as speech, language and cognitive development or quality of life.

Even in situations where clear and relevant benefits of oral antibiotics have been demonstrated, these must always be carefully balanced against adverse effects and the emergence of bacterial resistance. This has specifically been linked to the widespread use of antibiotics for common conditions such as otitis media.

PLAIN LANGUAGE SUMMARY

Antibiotics for otitis media with effusion ('glue ear') in children

Review question

This review compared the effects of oral antibiotics against placebo, no treatment or other therapies in children with otitis media with effusion (OME) or 'glue ear'.

Background

Glue ear is one of the most common conditions of early childhood. Glue ear means that there is fluid in the middle ear space behind the eardrum. This may cause hearing difficulties that may in turn affect children's behaviour, language and progress at school. In approximately one in three children with glue ear, bacteria are identified in the middle ear fluid. Therefore, people have suggested that antibiotics may be beneficial in children with glue ear.

Study characteristics

This review included evidence available up to 14 April 2016. In total 25 studies (3663 children) were eligible for inclusion. Two studies did not report on any of the outcomes of interest, leaving 23 studies (3258 children). Overall, we assessed most studies as being at low to moderate risk of bias. In the 23 studies many different antibiotics were used and the children were of different ages and had suffered from glue ear for various lengths of time. They looked at the benefits at various time points after the treatment was given.

Key results

The most important outcomes that we measured were the difference in the proportion of children who no longer had glue ear two to three months after the treatment was started and adverse effects of antibiotics (diarrhoea, vomiting or skin rash).

We found moderate quality evidence (six trials including 484 children) that children treated with oral antibiotics are more likely to have glue ear resolved two to three months after the treatment was started than those allocated to control treatment. The number of children needed to treat for one beneficial outcome (NNTB) was five. However, there is evidence (albeit of low quality; five trials, 742 children) indicating that children treated with oral antibiotics are more likely to experience diarrhoea, vomiting or skin rash than those allocated to control treatment. The number of children needed to treat for one harmful outcome (NNTH) was 20.

In respect of the secondary outcome of having glue ear resolved at *any* time point, we found low to moderate quality evidence from five of our analyses where we combined data from studies (meta-analyses), which included between two and 14 studies, of a beneficial effect of antibiotics, with a NNTB ranging from three to seven. Time periods ranged from 10 to 14 days to six months.

In terms of other secondary outcomes, only two trials (849 children) reported on hearing levels at two to four weeks and found conflicting results. None of the trials reported data on speech, language and cognitive development or quality of life. Low quality evidence did not show that oral antibiotics were associated with fewer ventilation tube (grommet) insertions (two trials, 121 children) or in adverse consequences for the tympanic membrane (ear drum) (one trial, 103 children). Low quality evidence indicated that children treated with oral antibiotics were less likely to have acute otitis media (ear infection) episodes within four to eight weeks (five trials, 1086 children; NNTB 18) and within six months after treatment was started (two trials, 199 children; NNTB 5). It should however be noted that the beneficial effect of oral antibiotics on ear infection episodes within four to eight weeks was no longer significant when studies with high risk of bias were excluded.

Quality of the evidence

Moderate quality evidence is available that children with glue ear do benefit from oral antibiotics in terms of resolving glue ear at various time points and reducing acute otitis media episodes during follow-up compared with control treatment. Low quality evidence is available that children treated with oral antibiotics are more likely to experience diarrhoea, vomiting and skin rash than those receiving the control treatment. Currently only two trials have assessed the impact of oral antibiotics on hearing and these showed conflicting results (low quality evidence). Low quality evidence did not show that oral antibiotics were associated with fewer ventilation tube insertions or in adverse consequences for the tympanic membrane.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Antibiotics compared to placebo, no treatment or therapy of unproven effectiveness for otitis media with effusion in children

Antibiotics compared to placebo, no treatment or therapy of unproven effectiveness for otitis media with effusion in children

Patient or population: children with otitis media with effusion
Setting: community, primary care, secondary care and tertiary care
Intervention: antibiotics
Comparison: placebo, no treatment or therapy of unproven effectiveness

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control treatment	Risk with antibiotics				
Complete resolution of OME at 2 to 3 months	Study population		RR 2.00 (1.58 to 2.53)	484 (6 RCTs)	⊕⊕⊕⊖ **moderate** [1]	The NNTB based on the study population risk was 1/(493-247)*1000 = 4.07
	247 per 1000	493 per 1000 (390 to 624)				
Adverse effects	Study population		RR 2.15 (1.29 to 3.60)	742 (5 RCTs)	⊕⊕⊖⊖ **low** [2]	The NNTH based on the study population risk was 1/(97-45)*1000 = 19.23
	45 per 1000	97 per 1000 (54 to 149)				
Complete resolution of OME at 2 to 4 weeks	Study population		RR 1.98 (1.47 to 2.67)	2091 (14 RCTs)	⊕⊕⊖⊖ **low** [2]	The NNTB based on the study population risk was 1/(403-203)*1000 = 5.00
	203 per 1000	403 per 1000 (299 to 543)				
Complete resolution of OME at more than 6 months	Study population		RR 1.75 (1.41 to 2.18)	606 (5 RCTs)	⊕⊕⊖⊖ **low** [2]	The NNTB based on the study population risk was 1/(445-255)*1000 = 5.26
	255 per 1000	445 per 1000 (359 to 555)				
Insertion of ventilation tubes	Study population		RR 0.90 (0.46 to 1.78)	121 (2 RCTs)	⊕⊕⊖⊖ **low** [3]	—
	185 per 1000	167 per 1000 (85 to 330)				
Tympanic membrane sequelae	Study population		RR 0.42 (0.18 to 1.01)	103 (1 RCT)	⊕⊕⊖⊖ **low** [4]	—

	275 per 1000	115 per 1000 (49 to 277)

*__The risk in the intervention group__ (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).

CI: confidence interval; **NNTB:** number needed to treat to benefit; **NNTH:** number needed to treat to harm; **OME:** otitis media with effusion; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]We downgraded the evidence from high to moderate quality due to study limitations (risk of bias).
[2]We downgraded the evidence from high to low quality due to study limitations (risk of bias) and inconsistency of effect estimates across individual trials.
[3]We downgraded the evidence from high to low quality due to study limitations (risk of bias) and imprecise effect estimates across individual trials.
[4]We downgraded the evidence from high to low quality due to concerns around directness of evidence: one trial included participants particularly at risk for suppurative otitis media (Australian Aboriginal children in rural Australia) and had a limited number of children, leading to an imprecise effect estimate.

BACKGROUND

Description of the condition

Symptoms, prevalence and aetiology

Otitis media with effusion (OME) or 'glue ear' is one of the most common diseases of early childhood. OME is characterised by an accumulation of fluid in the middle ear behind an intact tympanic membrane, without the symptoms or signs of acute infection (Gates 2002; Shekelle 2002).

The potential absence of symptoms of OME makes it difficult to estimate its true prevalence, but in the first year of life more than 50% of children will experience an episode of OME, increasing to more than 60% by two years of age (Casselbrant 2003).

When OME is newly detected, natural resolution (i.e. disappearance of the fluid from the middle ear space) within three months is seen in 28% of children. Rates of improvement or spontaneous resolution in children with OME observed after an episode of acute otitis media (AOM) are much higher (Rosenfeld 2003). However, recurrence of OME is also common, with an estimated rate of 50% within 24 months (Teele 1989).

In most cases, OME causes mild hearing impairment of short duration. When experienced in early life and when episodes of (bilateral) OME persist or recur, the associated hearing loss may be significant and have a negative impact on speech development and behaviour (Gouma 2011; Roberts 2004; Sabo 2003; Shekelle 2002).

Although the pathophysiology of OME is not fully understood, both middle ear inflammation and Eustachian tube dysfunction are likely to be contributory factors (Rovers 2004).

Description of the intervention

Since most cases of OME will resolve spontaneously, only children with persistent middle ear effusion and associated hearing loss potentially require treatment. To that end there are two management options: surgical and non-surgical. There are two Cochrane reviews addressing different surgical interventions: ventilation tubes (grommets) (Browning 2010), and adenoidectomy (van den Aardweg 2010). The combination of the two is addressed in an individual patient data meta-analysis (Boonacker 2014). The following non-surgical interventions have been addressed in different Cochrane reviews: antihistamines and/or decongestants (Griffin 2011), intranasal and oral corticosteroids (Simpson 2011), and nasal autoinflation (Perera 2013). A variety of antibiotics directed at the microbial pathogens causing upper respiratory tract infections are being used and are considered in this review.

How the intervention might work

The rationale for using antibiotics in OME is the potential bacterial origin of the disease; a bacterial pathogen is identified in the middle ear fluid of approximately one in three children with OME (Poetker 2005). Successful eradication of bacteria may promote faster resolution of middle ear fluid and prevention of secondary complications. However, not all OME cases are of bacterial origin and therefore the potential benefits of antibiotics need to be balanced both against the well-recognised adverse effects and the increased risk of bacterial resistance (Costelloe 2010; ECDC 2011; Gillies 2015; Laxminarayan 2013).

Why it is important to do this review

In 2004, Rosenfeld reviewed the effects of antibiotic therapy in OME and concluded that there is evidence for a short-term benefit, but longer-term benefits are uncertain (Rosenfeld 2004). Mandel et al came to a similar conclusion in their review (Mandel 2004). After 2004, the effectiveness of antibiotics in the management of OME had not been reviewed systematically until the original publication of this review (van Zon 2012). This is an update of that review.

OBJECTIVES

To assess the benefits and harms of oral antibiotics in children up to 18 years with OME.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). We excluded quasi- and cluster-RCTs. If cross-over trials were available, we only included those where data from the first phase were available.

Types of participants

Children aged 18 years or under with a diagnosis of unilateral or bilateral OME at time of randomisation. The clinical diagnosis of OME had to be made by tympanometry alone or in combination with otoscopy (including pneumatic otoscopy and otomicroscopy). We excluded studies of children with ventilation tubes present, those with chronic suppurative otitis media, known immunodeficiency, Down syndrome or craniofacial anomalies, including cleft palate.

Types of interventions

Intervention

Oral antibiotics (of all types and courses of any duration).

Control

Placebo, no treatment or therapy of unproven effectiveness (antihistamines, decongestants, mucolytics and intranasal corticosteroids). We excluded studies in which one antibiotic was compared with another.

We analysed antihistamines, decongestants, mucolytics and intranasal corticosteroids as the same comparator as placebo and no treatment as they are not proven to be effective in children with OME (Griffin 2011; Pignataro 1996; Simpson 2011).

Participants were allowed to receive additional medical therapies provided such adjunct interventions were the same in the treatment and in the control groups and that the additional therapies were one of those of unproven effectiveness (see above).

Types of outcome measures

We analysed the outcomes listed below in the review, but we did not use them as a basis for including or excluding studies.

Primary outcomes

- Complete resolution of OME (complete treatment success) at two to three months post-randomisation.

This is defined as resolution of OME in the affected ear in children with unilateral OME at randomisation and resolution of OME in both ears in children with bilateral OME at randomisation; in either case, the diagnosis having been made by tympanometry alone or in combination with otoscopy.

- Adverse effects, specifically diarrhoea, vomiting or skin rash.

Secondary outcomes

- Complete resolution of OME (complete treatment success) at all possible time points.
- Hearing level.
- Language and speech development.
- Cognitive development.
- Quality of life.
- Insertion of ventilation tubes.
- Tympanic membrane sequelae.
- AOM episodes.

Search methods for identification of studies

The Cochrane ENT Information Specialist conducted systematic searches for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions. The date of the search was 14 April 2016.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Trials Register (searched 14 April 2016);
- the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 3);
- PubMed (1946 to 14 April 2016);
- Ovid EMBASE (1974 to 2016 week 15);
- Ovid CAB Abstracts (1910 to 2016 week 13);
- EBSCO CINAHL (1982 to 14 April 2016);
- LILACS, lilacs.bvsalud.org (searched 14 April 2016);
- KoreaMed (searched via Google Scholar 14 April 2016);
- IndMed, www.indmed.nic.in (searched 14 April 2016);
- PakMediNet, www.pakmedinet.com (searched 14 April 2016);
- Web of Knowledge, Web of Science (1945 to 14 April 2016);
- ClinicalTrials.gov (searched via the Cochrane Register of Studies 14 April 2016);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), www.who.int/ictrp (searched 14 April 2016);
- ISRCTN, www.isrctn.com (searched 14 April 2016);
- Google Scholar, scholar.google.co.uk (searched 14 April 2016);
- Google, www.google.com (searched 14 April 2016).

In searches prior to 2015, we also searched BIOSIS Previews 1926 to February 2012.

The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, the Information Specialist searched PubMed, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials.

Data collection and analysis

This review is based on a published protocol (van Zon 2011). Any differences between the published protocol and the (update of) the review have been listed in the Differences between protocol and review section.

Selection of studies

One review author independently screened titles and abstracts obtained from the database searches. Two review authors reviewed the full text of the potentially relevant titles and abstracts against the inclusion and exclusion criteria. We resolved any disagreements by discussion.

Data extraction and management

Two review authors independently extracted study characteristics and outcomes from the included studies using standardised data extraction forms. Any disagreements were resolved by discussion. When information was insufficient, we contacted trial authors in an attempt to obtain further information.

Assessment of risk of bias in included studies

Two authors independently assessed the methodological quality of the included trials and resolved any disagreements by discussion.

We used the Cochrane 'Risk of bias' tool, which involves describing each bias domain as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

We expressed dichotomous outcomes as a risk ratio (RR) with accompanying 95% confidence intervals (CIs). For continuous outcomes (i.e. mean hearing loss) we proposed to calculate mean differences (MD) and their corresponding 95% CIs.

Unit of analysis issues

We identified one double-blind, cross-over trial. This trial was, however, excluded since results were only reported after treatment with both sulfisoxazole and placebo (i.e. data from the first phase were not available).

Dealing with missing data

In case of missing data, we tried to contact the trial authors to provide additional information.

Assessment of heterogeneity

We considered heterogeneity both clinically and statistically. We assessed clinical heterogeneity of the included trials by reviewing for potential differences between the trials in the types of participants recruited, interventions or control used, and how outcomes were measured or reported (or both).

We assessed statistical heterogeneity with visual inspection of forest plots and using the Chi^2 test (with a significance level set at P value < 0.10) and the I^2 statistic, with I^2 values over 50% suggesting substantial heterogeneity (Handbook 2011).

Where there was substantial statistical heterogeneity, we carried out pre-specified subgroup analyses and conducted sensitivity analyses based on the risk of bias (see Subgroup analysis and investigation of heterogeneity; Sensitivity analysis). Assessments of potential differences in effect sizes between subgroups were based on the Chi^2 tests for heterogeneity between subgroups and with visual inspection of forest plots. If none of these analyses completely resolved statistical heterogeneity then we employed a random-effects (DerSimonian and Laird) model to provide a more conservative effect estimate.

Assessment of reporting biases

For each included trial, we searched the internet and ClinicalTrials.gov (http://clinicaltrials.gov/) for available study protocols. Furthermore, we planned to consider reporting biases using a funnel plot if a sufficient number of trials was identified (n > 20).

Data synthesis

We analysed the data by using an available case analysis according the intention-to-treat (ITT) principle. In multi-arm studies we only used data from the group treated with antibiotics and those from the control group. If antibiotics were prescribed to more than one group, and no potentially effective additional treatments were given, we combined data from these groups.

For dichotomous data, we calculated the RR with 95% CI using the Mantel-Haenszel method with a fixed-effect (I^2 values < 50%) or random-effects model. In addition, we calculated the number needed to treat to benefit (NNTB) or number needed to treat to harm (NNTH) based on the average risks of the control groups in the included studies ('study population') (Handbook 2011).

Subgroup analysis and investigation of heterogeneity

We planned to consider the following subgroup analyses if sufficient data were available:

- age (< 2 years versus ≥ 2 years);
- duration of OME prior to study entry (< 3 months versus ≥ 3 months);
- definition of resolution of OME (tympanogram A versus A and C1 versus A, C1 and C2);
- laterality of OME (bilateral OME versus uni- or bilateral OME);
- type of control intervention (placebo versus other); and
- duration of antibiotic treatment (< 4 weeks versus ≥ 4 weeks).

Sensitivity analysis

We performed a sensitivity analysis in which trials with high risk of bias were excluded. We defined high risk of bias as a high risk of allocation concealment or attrition bias.

GRADE and 'Summary of findings' table

We used the GRADE approach to rate the overall quality of evidence for each listed outcome, and to draw conclusions about the quality of evidence. There are four possible ratings: high, moderate, low and very low.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We included a 'Summary of findings' table that contains what we felt to be the seven most important outcomes: complete resolution of OME at two to three months; adverse effects; complete resolution of OME at two to four weeks; complete resolution of OME at more than six months; insertion of ventilation tubes; tympanic membrane sequelae

RESULTS

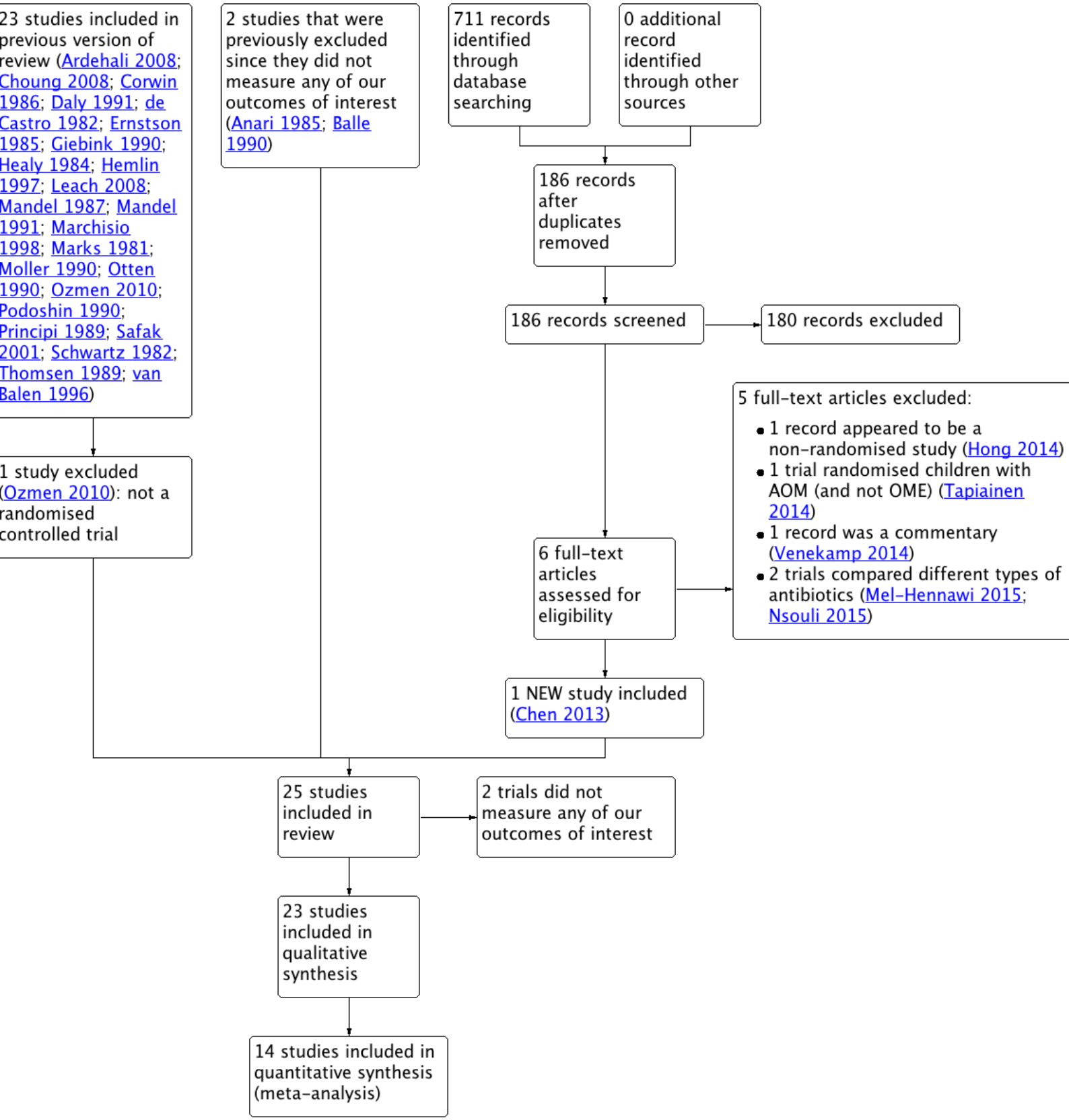
Description of studies

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

Results of the search

This is an update of a Cochrane review first published in 2012 (van Zon 2012). In the first version of our review, 23 trials were included. For this 2016 review, one additional trial was suitable for inclusion. Furthermore, we included two studies that were previously excluded on the basis that they did not report any of our outcomes of interest and we excluded one study that was previously included on the basis that this was not a randomised controlled trial. We therefore included 25 trials in this 2016 review (Figure 1). We did not identify any ongoing trials.

Figure 1. Study flow diagram.



Included studies

Details of included studies can be found in the Characteristics of included studies table.

Design

All 25 included trials were parallel-group design trials. Seven (28%) were open-label trials, three (12%) were investigator-blinded and 15 (60%) were double-blinded.

Participants and setting

The mean age of the included children was 4.7 years and 54% were boys. Tympanometry was used in all trials and the majority used a type B (60%) or type B or C2 (24%) tympanogram to define OME. At baseline, the mean duration of OME was 10.6 weeks and 73% of children had bilateral disease.

The majority of trials (72%) were performed in secondary care.

Interventions

The types of antibiotics most commonly used were amoxicillin (six trials), trimethoprim-sulfamethoxazole (TMP-SMX; six trials) and amoxicillin/clavulanic acid (five trials). Treatment duration varied across trials, but in the majority treatment duration was 10 to 14 days (60%) or four weeks (24%) (Table 1). The comparator was placebo in 52%. In four trials (16%) children in both the antibiotic and comparator group also received intranasal corticosteroids, an antihistamine, a decongestant or a combination of both.

Outcome measures

Two trials did not report on any of the outcomes of interest, leaving 23 trials (3258 children) that reported on at least one (Figure 1).

The type of tympanogram used to define resolution of OME varied across trials, but most trials used a type A, C1 or C2 (48%), type A or C1 (22%) or type A tympanogram (17%).

Excluded studies

We excluded a total of 42 studies; see Characteristics of excluded studies.

Risk of bias in included studies

Details of the 'Risk of bias' assessment of the included trials are summarised in a 'Risk of bias' graph (Figure 2) and summary (Figure 3).

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

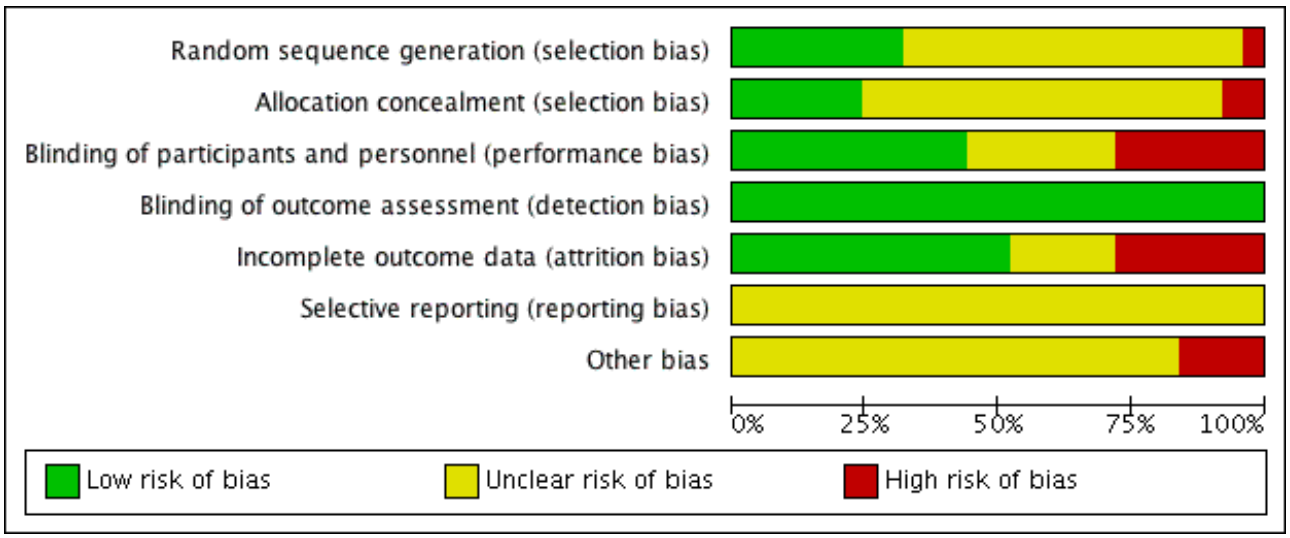


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

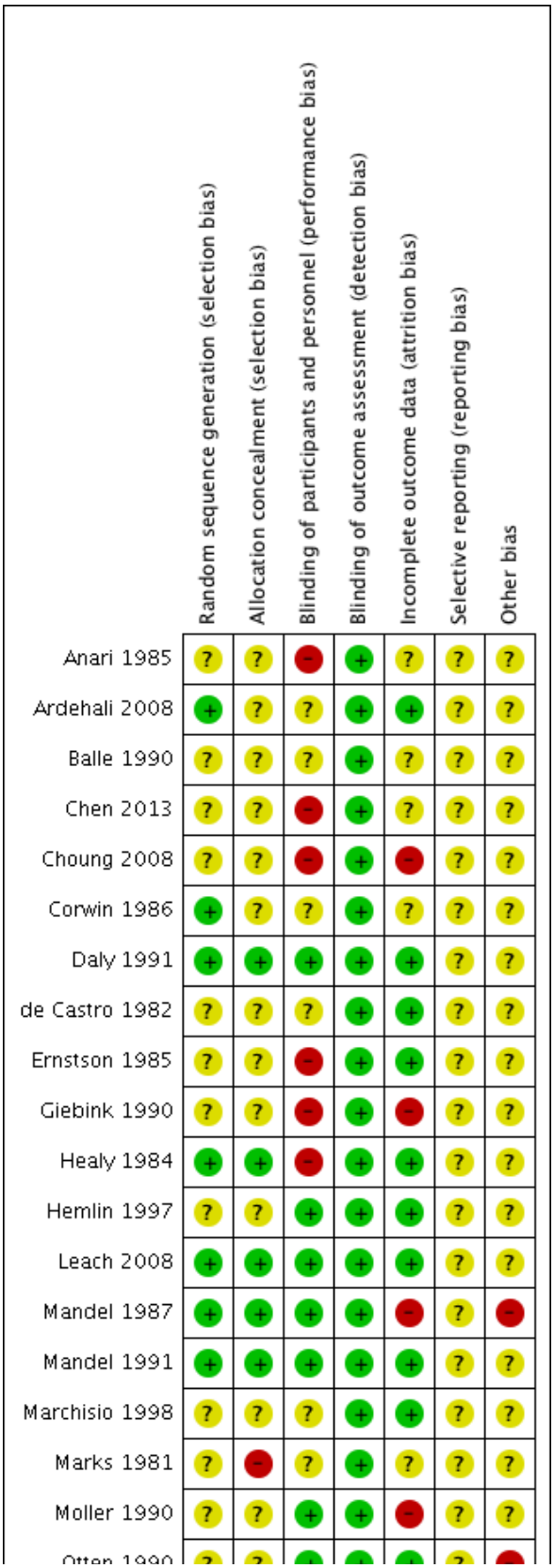
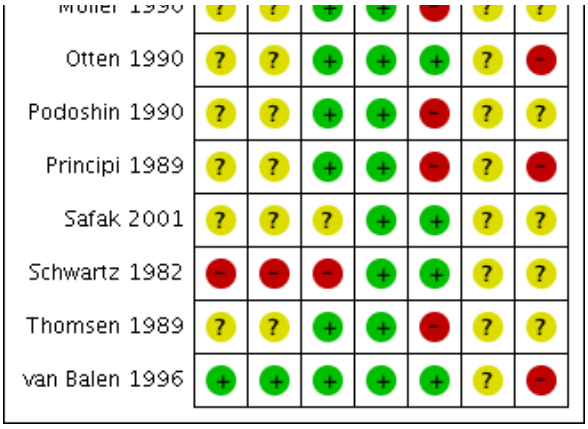


Figure 3. (Continued)



Allocation

The method of random sequence generation was adequately described in eight trials (32%), unclear in 16 trials (64%) and judged inadequate in one trial (4%).

Concealment of allocation was adequately described in six trials (24%), unclear in 18 trials (72%) and judged inadequate in one trial (4%).

Blinding

We judged the risk of bias for blinding of participants and personnel to be low in 11 trials (44%), unclear in seven trials (28%) and high in seven trials (28%). All included studies had a low risk of bias for blinding of outcome assessment; resolution of OME was in all studies based on tympanometry, an objective outcome measure.

Incomplete outcome data

We judged the risk of bias for incomplete outcome data to be low in 13 trials (52%), unclear in five trials (20%) and high in seven trials (28%).

Selective reporting

We could not retrieve any of the trial protocols and could not determine the risk of selective outcome reporting bias.

Other potential sources of bias

We judged the risk of other potential sources of bias to be unclear in 21 trials (84%) and high in four trials (16%).

Effects of interventions

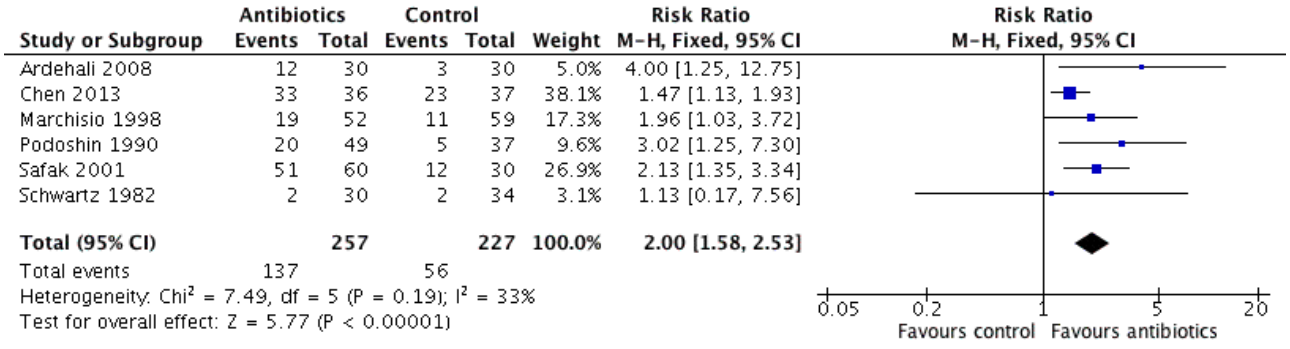
See: **Summary of findings for the main comparison** Antibiotics compared to placebo, no treatment or therapy of unproven effectiveness for otitis media with effusion in children

Primary outcomes

Complete resolution of otitis media with effusion (OME) (complete treatment success) at two to three months post-randomisation

We combined data from six trials (523 randomised children; 484 (93%) included in analysis). Children treated with oral antibiotics were more likely to have complete resolution of OME at two to three months post-randomisation than those allocated to control treatment (risk ratio (RR) 2.00, 95% confidence interval (CI) 1.58 to 2.53; $I^2 = 33\%$, fixed-effect model, number needed to treat to benefit (NNTB) 5) (Analysis 1.1; Figure 4). We did not find evidence that the effects of antibiotics differed among subgroups for this outcome.

Figure 4. Forest plot of comparison: 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, outcome: 1.1 Complete resolution of OME at 2 to 3 months.



In the sensitivity analysis, where we excluded studies at high risk of bias, the result was comparable with the effect observed in our

main analysis (RR 1.92, 95% CI 1.51 to 2.44; I^2 = 44%, fixed-effect model) (Analysis 2.1).

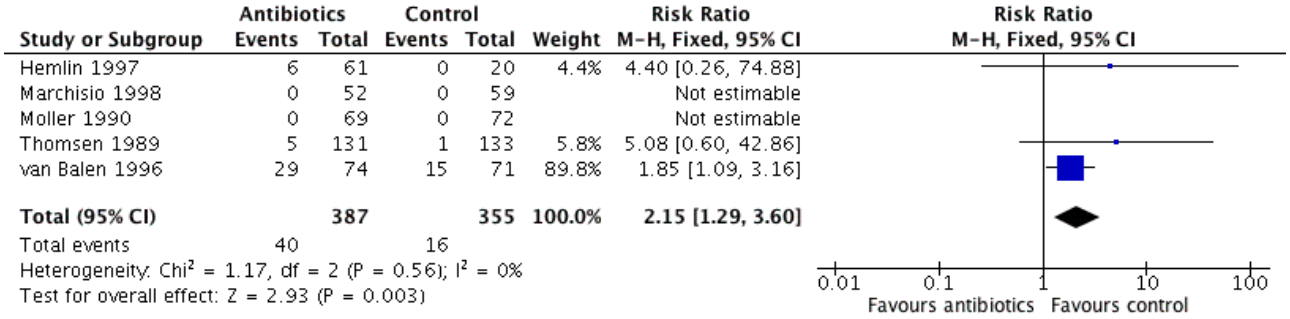
Quality of the evidence

We judged the evidence for this outcome to be of moderate quality; we downgraded it from high to moderate quality due to study limitations (risk of bias).

Adverse effects, specifically diarrhoea, vomiting or skin rash

We combined data from five trials (775 randomised children; 742 (96%) included in analysis). Children treated with oral antibiotics were more likely to experience adverse effects than those allocated to control treatment (RR 2.15, 95% CI 1.29 to 3.60; I^2 = 0%, fixed-effect model; NNTH 20) (Analysis 1.2; Figure 5).

Figure 5. Forest plot of comparison: 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, outcome: 1.2 Adverse effects.



In the sensitivity analysis, where we excluded studies at high risk of bias, the result was comparable with the effect observed in our main analysis (RR 1.97, 95% CI 1.16 to 3.35, I^2 = 0%, fixed-effect model) (Analysis 2.2).

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to study limitations (risk of bias) and inconsistency of effect estimates across individual trials.

Secondary outcomes

Complete resolution of OME (complete treatment success) at all possible time points

The duration of antibiotic treatment varied between studies (Table 1). The following analyses look at complete resolution of OME, initially at fixed times post-randomisation *irrespective* of the duration of treatment (analyses a and b). The remaining analyses look at the same outcomes at time points that also coincide with the end of treatment (analyses c to f).

a) Complete resolution of OME at two to four weeks (short-term)

We combined data from 14 trials (2253 randomised children; 2091 (93%) included in analysis). Children treated with oral antibiotics were more likely to have complete resolution of OME at two to four weeks post-randomisation than those allocated to control treatment (RR 1.98, 95% CI 1.47 to 2.67; I^2 = 71%, random-effects model; NNTB 5) (Analysis 1.3). We found no evidence that the effects of antibiotics differed among subgroups for this outcome.

In the sensitivity analysis, where we excluded studies at high risk of bias, the effect of antibiotics was somewhat larger than the effect observed in our main analysis (RR 2.58, 95% CI 1.60 to 4.17; I^2 = 76%, random-effects model) (Analysis 2.3).

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to study limitations (risk of bias) and inconsistency of effect estimates across individual trials.

b) Complete resolution of OME at more than six months (long-term)

We combined data from five trials (668 randomised children; 606 (91%) included in analysis). Children treated with oral antibiotics were more likely to have complete resolution of OME at more than six months post-randomisation than those allocated to control treatment (RR 1.75, 95% CI 1.41 to 2.18; I^2 = 32%, fixed-effect model; NNTB 6) (Analysis 1.4). We did not find evidence that the effects of antibiotics differed among subgroups for this outcome.

In the sensitivity analysis, where we excluded studies at high risk of bias, the result was comparable with the effect observed in our main analysis (RR 2.13, 95% CI 1.30 to 3.50, I^2 = 48%, fixed-effect model) (Analysis 2.4).

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to study limitations (risk of bias) and inconsistency of effect estimates across individual trials.

c) Complete resolution of OME at end of treatment (10 to 14 days treatment)

For this outcome, we could use data from six trials (1231 randomised children; 1129 (92%) included in analysis). In this analysis one of the subgroup analyses showed a significant subgroup difference: children with persistent OME at study entry were more likely to have complete resolution of OME at the end of the treatment period of 10 to 14 days when treated with oral antibiotics than those with OME of any duration (RR 4.03, 95% CI 2.13 to 7.61; I^2 = 0%, fixed-effect model; NNTB 4 versus RR 1.83, 95%

CI 1.38 to 2.44; I^2 = 0%, fixed-effect model; NNTB 7, respectively) (Analysis 1.5).

In the sensitivity analysis, where we excluded studies at high risk of bias, the results were comparable with the effect estimates observed in our main analysis (Analysis 2.5).

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to study limitations (risk of bias) and imprecise effect estimates across subgroups.

d) Complete resolution of OME at end of treatment (four weeks treatment)

We combined data from four trials (534 randomised children; 479 (90%) included in analysis). Children treated with oral antibiotics were more likely to have complete resolution of OME at the end of the four-week treatment period than those allocated to control treatment (RR 3.28, 95% CI 1.37 to 7.87; I^2 = 79%, random-effects model; NNTB 3) (Analysis 1.6). We found no evidence that the effects of antibiotics differed among subgroups for this outcome.

In the sensitivity analysis, where we excluded studies at high risk of bias, the effect of antibiotics was larger than the effect observed in our main analysis, but with a wider confidence interval (RR 9.19, 95% CI 4.29 to 19.70; I^2 = 0%, fixed-effect model) (Analysis 2.6).

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to study limitations (risk of bias) and inconsistency of effect estimates across individual trials.

e) Complete resolution of OME at end of treatment (three months treatment)

We combined data from two trials (150 randomised children; 150 (100%) included in analysis). Children treated with oral antibiotics were more likely to have complete resolution of OME at the end of the three-month treatment period than those allocated to control treatment (RR 2.10, 95% CI 1.39 to 3.17; I^2 = 44%, fixed-effect model; NNTB 4) (Analysis 1.7). We did not deem subgroup and sensitivity analyses to be useful because of the low number of trials and included children.

Quality of the evidence

We judged the evidence for this outcome to be of moderate quality; we downgraded it from high to moderate quality due to imprecise effect estimates across individual trials.

f) Complete resolution of OME at end of treatment (six months treatment)

We combined data from two trials (203 randomised children; 196 (97%) included in analysis). Oral antibiotics were associated with an increased chance of complete resolution of OME at the end of the six-month treatment period, but the effect was not statistically significant (RR 2.81, 95% CI 0.29 to 27.50; I^2 = 64%, random-effects model) (Analysis 1.8). We did not deem subgroup and sensitivity analyses to be useful because of the low number of trials and included children.

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to study limitations (risk of bias) and imprecise effect estimates across individual trials.

Hearing level

Two studies reported hearing level based on speech recognition thresholds at baseline and after two or four weeks follow-up.

At two weeks, Mandel 1991 reported a "statistically significant" difference in mean speech recognition threshold between the antibiotic and placebo groups: left ears 14.2 dB HL versus 18.5 dB HL and right ears 14.0 dB HL versus 18.7 dB HL, respectively. At four weeks, a "significant difference" was found between the antibiotic and placebo groups only in the right ears (12.6 dB HL versus 17.2 dB HL). The number of ears analysed was not reported and insufficient data were available to calculate the mean difference (MD) and 95% CI.

At four weeks, Mandel 1987 reported no statistically significant differences in the mean speech recognition threshold between the antibiotic and placebo groups: 14.9 dB HL versus 16.7 dB HL, respectively.

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to inconsistency of effect estimates across individual trials and incomplete outcome reporting.

Language and speech development

None of the trials reported data on language and speech development.

Cognitive development

None of the trials reported data on cognitive development.

Quality of life

None of the trials reported data on quality of life.

Insertion of ventilation tubes

We combined data from two trials (144 randomised children; 121 (84%) included in analysis). Oral antibiotics were not associated with a decrease in the proportion of children who had received ventilation tubes compared with control treatment (RR 0.90, 95% CI 0.46 to 1.78; I^2 = 0%, fixed-effect model) (Analysis 1.9). We did not deem subgroup and sensitivity analyses to be useful because of the low number of trials and included children.

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to risk of study limitations (risk of bias) and imprecise effect estimates across individual trials.

Tympanic membrane sequelae

For this outcome, data from one trial (103 randomised children; 103 (100%) included in analysis) were available (Leach 2008). In this trial, amoxicillin given for six months was associated with a

reduced risk for any tympanic membrane perforation during follow-up as compared with placebo, but the effect was not statistically significant (RR 0.42, 95% CI 0.18 to 1.01) (Analysis 1.10).

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to concerns around directness of evidence and imprecision. The trial included a limited number of participants particularly at risk of suppurative otitis media (Australian Aboriginal children in rural Australia).

Acute otitis media (AOM) episodes

Several studies looked for episodes of AOM in two different time 'windows': in the first period of up to four to eight weeks and up to six months.

AOM episodes within four to eight weeks

We combined data from five trials (1158 randomised children; 1086 (94%) included in analysis). Children treated with oral antibiotics were less likely to experience AOM episodes within four to eight weeks compared with those allocated control treatment (RR 0.60, 95% CI 0.42 to 0.85; I^2 = 0%, fixed-effect model; NNTB 18) (Analysis 1.11). We did not find evidence that the effects of antibiotics differed among subgroups.

In the sensitivity analysis, where we excluded studies at high risk of bias, the effect of antibiotics was no longer statistically significant (RR 0.70, 95% CI 0.37 to 1.31) (Analysis 2.7).

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to study limitations (risk of bias) and imprecise effect estimates across individual trials.

AOM episodes within six months

We combined data from two trials (203 randomised children; 199 (98%) included in analysis). Children treated with oral antibiotics were less likely to experience AOM episodes within six months compared with those allocated control treatment (RR 0.56, 95% CI 0.40 to 0.80; I^2 = 61%, random-effects model; NNTB 5) (Analysis 1.12). We did not deem subgroup and sensitivity analyses to be useful because of the low number of trials and included children.

Quality of the evidence

We judged the evidence for this outcome to be of low quality; we downgraded it from high to low quality due to study limitations (risk of bias) and inconsistency of effect estimates across individual trials.

DISCUSSION

Summary of main results

We included 25 trials (3663 children), evaluating a range of antibiotics, in a variety of different participants (varying in a number of ways including severity of disease). Several different outcome measures and time points for evaluation were used. Overall, we assessed most studies as being at low risk of bias and the quality of the evidence to be moderate.

We found moderate quality evidence that children with otitis media with effusion (OME) treated with oral antibiotics are more likely to have complete resolution at two to three months post-randomisation (primary outcome) than those allocated to control treatment. However, there is evidence (albeit of low quality) indicating that children treated with oral antibiotics are more likely to experience diarrhoea, vomiting or skin rash (primary outcome) than those allocated to the control treatment.

Whilst resolution of the middle ear effusion in OME – and the restoration of a ventilated middle ear cleft – is undoubtedly desirable, for an individual patient it is important to know that this is associated with an improvement in hearing. This is an assumption that is often made and this does not seem to be an unreasonable one. However, when the impact of antibiotics on short-term hearing is actually evaluated in clinical trials, some uncertainty remains. We only identified low quality evidence relating to this outcome: that evidence is sparse and the results were inconclusive. Furthermore, we did not identify any trials that looked at speech, language and cognitive development or quality of life.

Overall completeness and applicability of evidence

We believe that the studies included in this review include a comprehensive range of participants with a broad spectrum of disease severity. Studies also cover several different antibiotics, periods of treatment, outcome measures and follow-up times. As such, the overall degree of completeness is high and the studies are sufficient to address the objectives of the review.

'High-risk' children (those at increased risk of speech, language or learning problems and their consequences) are often excluded from OME trials. However, we found nothing to make us suspect that these children would particularly benefit from antibiotics.

Quality of the evidence

The quality of the evidence of the different outcomes varied from moderate to low, mainly due to concerns about study limitations (risk of bias), inconsistency and imprecision.

Potential biases in the review process

Since we used an extensive search strategy without language or publication restrictions, it is unlikely that we have missed relevant studies. In this 2016 update, we were able to retrieve the full text of the two studies that were previously classified as 'studies awaiting classification' (Hozawa 2001; Yin 2002). Neither of these studies met our inclusion criteria. Data extraction and quality assessment were both undertaken by two authors independently and we strictly adhered to the instructions of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

Agreements and disagreements with other studies or reviews

The results of our systematic review are consistent with the evidence underpinning the latest US guidelines (AAFP 2004) and the meta-analysis by Rosenfeld 2004. Neither publication recommends antibiotics for treating children with OME.

Our review differs from previous publications in the following ways:

- We have included four trials published since 2004 (Ardehali 2008; Chen 2013; Choung 2008; Leach 2008).
- We have not only included trials with placebo as comparator, but also trials comparing antibiotics to no treatment or therapies of unproven effectiveness.
- We have included trials in which a prophylactic antibiotic dose was used in the treatment group (de Castro 1982; Principi 1989; Thomsen 1989).

AUTHORS' CONCLUSIONS

Implications for practice

This review presents evidence of both benefits and harms associated with the use of antibiotics to treat children up to 16 years with otitis media with effusion (OME). Although evidence indicates that oral antibiotics are associated with an increased chance of complete resolution of OME at various time points, we also found evidence that these children are more likely to experience diarrhoea, vomiting or skin rash. The impact of antibiotics on short-term hearing is uncertain and low quality evidence did not show that oral antibiotics were associated with fewer ventilation tube insertions. Furthermore, we found no data on the impact of antibiotics on other important outcomes such as speech, language and cognitive development or quality of life.

Even in situations where clear and relevant benefits of antibiotics have been demonstrated, these must always be carefully balanced against the adverse effects and the emergence of bacterial resistance. Immediate adverse effects of antibiotics such as gastrointestinal upset and skin rash are common (Gillies 2015), and the emergence of bacterial resistance has specifically been linked to the widespread use of antibiotics for common conditions such as otitis media (Costelloe 2010; ECDC 2011; Laxminarayan 2013).

Implications for research

We included 25 studies covering a comprehensive range of pharmacological interventions, participants (with disease of varying degrees of severity), outcome measures and follow-up. We believe that further research will not provide added value to our current findings.

However, since the demonstrable benefits of both surgery and medical therapies in OME are limited, children with OME-related hearing loss that are at risk of speech and language and learning problems deserve special attention. Further research to evaluate the effectiveness of alternative strategies in these children in particular is necessary.

ACKNOWLEDGEMENTS

We acknowledge the work of Maroeska Rovers in the early stages of the protocol and the assistance received from the staff at the Cochrane ENT editorial base.

We thank Samantha Faulkner for her support with the search strategy and searches for the 2016 update, and Gemma Sandberg and Bianca Kramer for their help with the searches for the original publication of the review.

We thank Iain Swan for commenting on the 2016 update of this review.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to Cochrane ENT. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Anari 1985

Methods	**Allocation:** randomised **Design:** parallel groups, open-label

Anari 1985 *(Continued)*

Participants	**Number:** 141 children (127 children included in analysis) **Age (mean):** 4.6 years **Gender (%):** 52% boys, 48% girls **Duration of OME at baseline (mean):** unknown; OME had to last for at least 12 weeks **Laterality of disease at baseline (%):** unknown **Setting:** secondary care, Karlskrona, Sweden **Eligibility criteria:** 1. Children below 12 years of age 2. OME in one or both ears, which lasted for at least 3 months, diagnosed by otomicroscopy (fluid behind intact ear drum) and type B tympanogram **Exclusion criteria:** children with cleft palate, children treated with antibiotics because of upper respiratory tract infection during the observation period
Interventions	**Intervention group 1:** cefaclor 20 mg/kg/day in 2 divided doses for 10 days prior to surgery; n = 46 **Intervention group 2:** cefaclor 20 mg/kg/day in a single dose 0.4 to 4 hours before surgery; n = 50 **Comparator group:** no treatment; n = 45 **Use of additional interventions:** all children were placed on the waiting list for surgery
Outcomes	**Primary outcome:** nasopharyngeal cultures collected during surgery
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 14/141 children (10%) **Participants lost to follow-up in Tx1 group:** 14/46 children (30%) **Participants lost to follow-up in Tx2 group:** 0/50 children (0%) **Participants lost to follow-up in control group:** 0/45 children (0%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded, objective primary outcome (nasopharyngeal culture)

Anari 1985 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10% participants lost to follow-up, all in treatment group
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: imbalance (age) Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: no information provided

Ardehali 2008

Methods	**Allocation:** randomised **Design:** parallel groups, investigator-blinded
Participants	**Number:** 90 children (no patients were excluded; 60 children were eligible for inclusion in this review) **Age (mean):** 5.4 years **Gender (%):** 51% boys, 49% girls **Duration of OME at baseline (mean):** unknown; OME had to last for at least 12 weeks **Laterality of disease at baseline (%):** unknown **Setting:** secondary care, Teheran, Iran **Eligibility criteria:** 1. Children aged 2 to 12 years 2. Chronic OME that lasted for at least 3 months documented by clinical examination by 2 separate ENT surgeons and type B or C2 tympanogram in at least one ear without clinical signs and symptoms of active infection that were refractory to 3 periods of antibacterial treatment **Exclusion criteria:** past medical history of disorders that are known to be associated with an increased prevalence of recurrent otitis media, otitis media with effusion with unknown aetiology such as Down Syndrome, cleft palate, neurodevelopmental delay, patients with genetic or congenital palate, craniofacial malformations, previous ventilation tubes or adenoidectomy, immunodeficiency, cholesteatoma, sensorineural hearing loss or other medical conditions (renal, liver or cardiac illnesses)
Interventions	**Intervention group 1:** amoxicillin-clavulanic acid 40 mg/kg/day in 3 divided doses (maximum 750 mg/day) for 3 months; n = 30 **Intervention group 2:** cisapride 1 mg/kg/day for 3 months; n = 30; *this group was not included in our analyses* **Comparator group:** no treatment for 3 months; n = 30 **Use of additional interventions:** none described

Ardehali 2008 *(Continued)*

Outcomes	**Primary outcome:** complete resolution of OME at 3 months based on clinical examination and tympanometry (type A or C1 tympanogram) assessed by 2 unique independent ENT surgeons blinded to participant group assignment **Secondary outcome:** adverse effects All patients were followed up every month for 3 months
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 0/90 children (0%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single-blind; only personnel were blinded during treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome determined by 2 unique ENT surgeons blinded to assignment. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: no information provided

Balle 1990

Methods	**Allocation:** randomised **Design:** parallel groups, double-blind
Participants	**Number:** 264 children (221 children included in analysis) **Age (mean):** ? (range 1 to 10 years)

Balle 1990 *(Continued)*

	Gender (%): 52% boys, 48% girls **Duration of OME at baseline (mean):** unknown; OME had to last for at least 12 weeks **Laterality of disease at baseline (%):** unknown **Setting:** secondary care, Copenhagen, Denmark **Eligibility criteria:** 1. Children aged 1 to 10 years 2. OME defined as type B or C2 tympanogram in one or both ears for at least 3 months **Exclusion criteria:** allergy to penicillin
Interventions	**Intervention group:** amoxicillin-clavulanic acid for 4 weeks (children aged 1 to 5: 5 ml 3 times a day and children 6 to 10: 7.5 ml 3 times a day); n = 131 **Comparator group:** placebo; n = 133 **Use of additional interventions:** no concomitant medication other than analgesics was allowed during the treatment period
Outcomes	**Primary outcome:** nasopharyngeal cultures collected prior to and after termination of treatment and every month for the next 11 months
Funding sources	Astra Medical company supplied the antibiotic and supported the study
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 43/264 children (16%) **Participants lost to follow-up in Tx group:** 22/131 children (17%) **Participants lost to follow-up in control group:** 21/133 children (16%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blind; no further information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blind. Objective primary outcome (nasopharyngeal culture).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16% participants lost to follow-up

Balle 1990 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: not permitted other than analgesics Compliance with treatment: assessed from contents of the returned medication bottles

Chen 2013

Methods	**Allocation:** randomised **Design:** parallel groups, open-label
Participants	**Number:** 84 children (73 followed up for 12 weeks) **Age (mean):** 5.6 years **Gender (%):** 58% boys, 42% girls **Duration of OME at baseline (mean):** 1.5 weeks **Laterality of disease at baseline (%):** 45% bilateral disease **Setting:** secondary care, ENT department in the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China **Eligibility criteria:** 1. Children aged 3 to 14 years 2. OME with a duration of less than 3 months defined as aural fullness, hearing loss or tinnitus together with integrity, invagination or fluid level of tympanic membrane at otoscopy and tympanometry (type B or C2 tympanogram) **Exclusion criteria:** suppurative otitis media, tympanic membrane perforation, adenoid hypertrophy, tumour, severe systemic diseases and allergy or intolerance to macrolides
Interventions	**Intervention group:** clarithromycin; first week 15 mg/kg/day divided in 2 doses followed by 5 to 8 mg/kg/day divided in 4 doses until the tympanogram was type A; n = 42 **Comparator group:** no antibiotics (intranasal corticosteroids only); n = 42 **Use of additional interventions:** all participants were prescribed intranasal corticosteroids (type of corticosteroid not described)
Outcomes	**Primary outcome:** complete resolution of OME at 3 months based on tympanometry (type A tympanogram) **Secondary outcomes:** hearing levels, number of ventilation insertions because of treatment failure, adverse effects All patients were followed up every 2 weeks with hearing and tympanometry. Routine nasal endoscopy was performed to exclude possible nasal diseases.
Funding sources	The study was supported by grants from National Basis Research Program of China, National Natural Science fund of China and Key Nature Fund of Guangdong Province

Chen 2013 *(Continued)*

Declaration of interest	None declared
Notes	**Participants lost to follow-up total:** 11/84 children (13%) **Participants lost to follow-up in antibiotic group:** 6/42 children (14%) **Participants lost to follow-up in control group:** 5/42 children (12%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: all participants were prescribed intranasal corticosteroids Compliance with treatment: quote "all the rest patients completed the entire course of treatment"

Choung 2008

Methods	**Allocation:** randomised **Design:** parallel groups, open-label
Participants	**Number:** 100 children (83 followed up for a mean period of 6.9 weeks) **Age (mean):** 5.8 years **Gender:** 68% boys, 32% girls **Duration of OME at baseline (mean):** 10.5 weeks

Choung 2008 *(Continued)*

	Laterality of disease at baseline (%): 81% bilateral disease **Setting:** tertiary care, ENT department Ajou University Hospital, Suwon, Korea **Eligibility criteria:** 1. Children aged 5 months to 12 years 2. OME diagnosed by pneumatic otoscopy, tympanometry and pure tone audiometry. Children needed to have a type B, C1 or C2 tympanogram and a hearing loss greater than 25 dB on pure tone audiometry **Exclusion criteria:** children with AOM and fever or otalgia, children with cleft palates, developmental difficulties, contraindications to medications
Interventions	Duration of treatment: 2 weeks **Intervention group 1:** amoxicillin-clavulanic acid syrup 1 cc/kg; n = ? (n = 16 included in analysis) **Intervention group 2:** amoxicillin-clavulanic acid syrup 1 cc/kg plus prednisolone 1 mg/kg; n = ? (n = 18 included in analysis); *this group was not included in our analyses* **Intervention group 3:** amoxicillin-clavulanic acid syrup 1 cc/kg plus ebastine 0.2 cc/kg; n = ? (n = 15 included in analysis) **Intervention group 4:** amoxicillin-clavulanic acid syrup 1 cc/kg plus prednisolone 1 mg/kg plus ebastine 0.2 cc/kg; n = ? (n = 17 included in analysis); *this group was not included in our analyses* **Comparator group:** mucolytic ivy leaf extract; n = ? (n = 17 included in analysis) **Use of additional interventions:** not described
Outcomes	**Primary outcomes:** complete resolution of OME at 6 months by pneumatic otoscopy, pure tone audiometry and tympanometry (type A tympanogram) and VT insertion (hearing loss greater than 40 dB, bilateral OME for more than 3 months, unilateral OME for more than 6 months) All patients were followed up every 2 weeks with pure tone audiometry and tympanometry. Children with hearing loss less than 40 dB and bilateral OME were observed for 3 months and those with hearing loss less than 40 dB and unilateral OME were observed for 6 months.
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 17/100 children (17%); no further information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Low risk	Not blinded. Primary outcome based on objective tympanometry.

Choung 2008 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Total of randomised children per subgroup not reported 17 randomised children were not used for analysis; only 16 children were reported as lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: no information provided

Corwin 1986

Methods	**Allocation:** randomised **Design:** parallel groups, investigator-blinded
Participants	**Number:** 149 children (131 followed up for 1 month) **Age (median):** 3.4 years **Gender:** unknown **Duration of OME at baseline (mean):** unknown **Laterality of disease at baseline (%):** 46% bilateral disease **Setting:** secondary care, Department of Pediatrics SUNY Upstate Medical Center, New York, USA **Eligibility criteria:** 1. Children aged 5 months to 16 years 2. Persistent MEE at 1 month after diagnosis of AOM defined otoscopically as immobile or minimally mobile tympanic membrane, which was in neutral or retracted position and had a grey or opalescent colour. In children over 2 years of age the diagnosis was confirmed with tympanometry. **Exclusion criteria:** history of 3 or more AOM episodes during previous year, antibiotic prophylaxis, chronic middle ear effusion
Interventions	**Intervention group:** erythromycin ethylsuccinate 50 mg/kg/day and sulfisoxizole 150 mg/kg/day for 10 days; n = 75 **Comparator group:** no treatment; n = 74 **Use of additional interventions:** children with repeat episodes of acute otitis media prior to the follow-up visit were treated with antibiotics; no further information provided
Outcomes	**Primary outcome:** complete resolution of OME at 1 month based on pneumatic otoscopy and tympanometry (no further details provided on the definition of complete OME resolution)
Funding sources	No information provided

Corwin 1986 *(Continued)*

Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 18/149 children (12%) **Participants lost to follow-up in antibiotic group:** 9/75 children (12%) **Participants lost to follow-up in control group:** 9/74 children (12%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Single-blind; only personnel were blinded during treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome determined by nurse practitioners blinded to assignment. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: no information provided

Daly 1991

Methods	**Allocation:** randomised, stratified on 3 prognostic variables (age at first episode, day-care attendance, duration of otitis media with effusion) **Design:** parallel groups, double-blind
Participants	**Number:** 42 children (42 followed up for 1 month) **Age (mean):** 2.8 years **Gender:** 60% boys, 40% girls **Duration of OME at baseline (mean):** 6.4 weeks **Laterality of disease at baseline (%):** 100% bilateral disease

Daly 1991 *(Continued)*

	Setting: secondary care, suburban multispecialty clinic, Minneapolis, USA **Eligibility criteria:** 1. Children aged 6 months to 8 years 2. 2 or more physician-documented AOM episodes in previous 18 months 3. Last documentation of AOM or OME no more than 4 weeks prior to enrolment 4. Appropriate antibiotic treatment for the most recent acute otitis media episode 5. Immunisations appropriate for age 6. Bilateral OME based on an algorithm using findings from otoscopy and tympanometry and one or both of the following: day-care attendance for at least 15 hours a week with 5 or more children or otitis media with effusion for at least 4 weeks at enrolment as documented in the medical record **Exclusion criteria:** allergy to trimethoprim, sulfonamides, ampicillin, amoxicillin or oral corticosteroids, significant chronic disease of kidney, heart, liver or immune system, hypertension, ventilation tubes, concomitant infection or varicella exposure in the preceding 3 weeks without a previous history of varicella
Interventions	**Intervention group:** TMP-SMX 8 mg and 40 mg/day in 2 doses for 2 weeks; n = 21 **Comparator group:** placebo for 2 weeks; n = 21 **Use of additional interventions:** children who experienced AOM during the treatment phase were discontinued from study medication and treated with amoxicillin 40 mg/kg/day divided into 3 daily doses for 10 days
Outcomes	**Primary outcome:** complete resolution of OME at 1 month based on pneumatic otoscopy and tympanometry (type A, C1 or C2 tympanogram) **Secondary outcome:** adverse effects
Funding sources	Active and placebo drugs were provided by Burroughs Wellcome Co. and The Upjohn Company. The work was supported in parts by grants from The Upjohn Company, Burroughs Wellcome Co., Minnesota Medical Foundation and the Park Nicollet Medical Center Research Foundation.
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 0/42 children (0%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation scheme to achieve balanced assignment Group assignment was determined by the study identification number
Allocation concealment (selection bias)	Low risk	The allocation scheme was unknown to the research nurse and examining physicians and allocation was performed by the clinic pharmacy (pharmacy-controlled)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, placebo-controlled fashion. Placebos were similar in taste and appearance to the active drugs.

Daly 1991 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, placebo-controlled fashion. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children lost to follow-up (and no cross-overs)
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: 89% in both groups as measured by diary, bottle method and serum assay for sulfamethoxazole

de Castro 1982

Methods	**Allocation:** randomised **Design:** parallel groups, double-blind
Participants	**Number:** 30 children (30 followed up for 1 month) **Age (mean):** unknown (range 3 to 6 years) **Gender:** 63% boys, 37% girls **Duration of OME at baseline (mean):** unknown **Laterality of disease at baseline (%):** unknown **Setting:** all children were living in a home for abused and/or neglected children, St. Louis, USA 1. Children aged 3 to 6 years 2. Bilateral otitis media with effusion of any duration based on otoscopy, pure tone audiometry and tympanometry (type B, C1 or C2 tympanogram) **Exclusion criteria:** none
Interventions	**Intervention group:** sulfisoxazole 40 mg/kg/day for 4 weeks; n = 15 **Comparator group:** placebo for 4 weeks; n = 15 **Use of additional interventions:** no information provided
Outcomes	**Primary outcome:** complete resolution of OME at 1 month based on otoscopy, pure tone audiometry and tympanometry (type A tympanogram)
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 0/30 children (0%)

de Castro 1982 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blinded, but insufficient information provided on how blinding was ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blinded. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: no information provided Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: quote "compliance with treatment was excellent (96.2%)"

Ernstson 1985

Methods	**Allocation:** randomised **Design:** parallel groups, open-label
Participants	**Number:** 91 children (91 followed up for median 3 weeks (range 2 to 5)) **Age (mean):** 4.7 years **Gender:** 49% boys, 51% girls **Duration of OME at baseline (mean):** unknown **Laterality of disease at baseline (%):** 70% bilateral disease **Setting:** secondary care, Karlskrona, Sweden **Eligibility criteria:** 1. Children aged 12 years and below 2. Chronic OME (> 3 months) in one or both ears diagnosed by otomicroscopy showing fluid behind an intact ear drum and tympanometry (type B tympanogram)

Ernstson 1985 *(Continued)*

	Exclusion criteria: children with cleft palate, upper respiratory tract infection during the period of observation, antibiotics in previous 4 weeks
Interventions	**Intervention group:** cefaclor 20 mg/kg/day in 2 doses for the last 10 days prior to the day scheduled for surgery; n = 46 **Comparator group:** untreated for the time from the decision to operate to the day appointed for surgery; n = 45 **Use of additional interventions:** children that had not healed in both ears at day of surgery underwent myringotomy with or without insertion of ventilation tubes. No further information provided.
Outcomes	**Primary outcome:** complete resolution of OME at 3 weeks (range 2 to 5 weeks) based on otomicroscopy and tympanometry (type A or C1 tympanogram) **Secondary outcome:** proportion of children with a relapse after complete resolution of OME at 10 to 27 months (median 20 months)
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 0/91 children (0%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: imbalance (gender) Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: no information provided

Giebink 1990

Methods	**Allocation:** randomised **Design:** parallel groups, open-label
Participants	**Number:** 76 children (72 included in analysis) **Age (mean):** 3.8 years **Gender:** 60% boys, 40% girls **Duration of OME prior at baseline (mean):** 9.5 weeks **Laterality of disease at baseline (%):** unknown **Setting:** secondary care, Minneapolis, USA **Eligibility criteria:** 1. Children aged 10 months to 8 years 2. 3 or more otitis media episodes within the previous 18 months 3. An episode of AOM or asymptomatic OME diagnosed 10 to 28 days before entry 4. Completion of at least 10 days of antimicrobial treatment for the most recent AOM episode 5. OME documented by otoscopy and tympanometry at entry and 3 and 6 weeks after entry (children entered the study 6 weeks before they were randomised) **Exclusion criteria:** history of adverse reactions to sulfonamides, presence of ventilation tubes, acute otitis media
Interventions	**Intervention group:** TMP-SMX suspension 8 mg and 40 mg/kg/day in 2 doses for 4 weeks; n = ? (n = 20 included in analysis) **Intervention group 2:** ibuprofen suspension 24 mg/kg/day in 4 doses for 2 weeks; n = ? (n = 15 included in analysis); *this group was not included in our analyses* **Intervention group 3:** prednisone tablets 1 mg/kg/day in 2 doses for 7 days, followed by 0.5 mg/kg/day in 2 doses for 4 days, followed by 0.12 mg/kg/day in 1 dose for 3 days; n = ? (n = 18 included in analysis); *this group was not included in our analyses* **Comparator group:** no treatment; n = ? (n = 19 included in analysis) **Use of additional interventions:** no other medications, including antihistamines, decongestants and antipyretics, were prescribed; parents were advised not to use any other medication, including over-the-counter preparations, during the 4 weeks after randomisation
Outcomes	**Primary outcome:** complete resolution of OME at 2 and 4 weeks after randomisation based on an algorithm in which results from pneumatic otoscopy, middle ear muscle reflex and impedance audiometry were used (type A, C1 or C2 tympanogram) **Secondary outcome:** treatment failure (OME in at least one ear at both the 2- and 4-week post-randomisation visits or continuous OME for 10 weeks during follow-up after initially resolving OME), AOM relapse within 8 weeks after randomisation, insertion of ventilation tubes, OME duration, hearing levels, adverse effects * Data on insertion of ventilation tubes and hearing levels not suitable for inclusion in this review
Funding sources	Supported in parts by grants from the Robert Wood Johnson Foundation, The Upjohn Company and Burroughs Wellcome Company and a programme project grant (8P50-CD-00133) from the National Institute of Deafness and Other Communicative Disorders

Giebink 1990 *(Continued)*

Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 4/76 children (5%); no further information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	High risk	Total of randomised children per subgroup not reported 5% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no other medication prescribed, parents were advised not to use any medication during the 4 weeks after randomisation Compliance with treatment: high compliance rates; monitored by parental diary and by measuring the remaining medication after treatment

Healy 1984

Methods	**Allocation:** randomised **Design:** parallel groups, open-label
Participants	**Number:** 200 children (189 included in analysis) **Age (mean):** unknown (range 2 to 5 years) **Gender:** 61% boys, 39% girls **Duration of OME prior at baseline (mean):** unknown; OME had to last for at least 6 weeks **Laterality of disease at baseline (%):** 79% bilateral disease **Setting:** secondary care, Boston, USA **Eligibility criteria:**

Healy 1984 *(Continued)*

	1. Children aged 2 to 5 years 2. OME for at least 6 weeks documented by pneumatic otoscopy, middle ear muscle reflex and tympanometry (type B, C1 or C2 tympanogram) **Exclusion criteria:** history of ENT surgery, middle ear abnormality such as adhesive otitis media, tympanic membrane perforation or cholesteatoma, facial anomalies or congenital syndromes, upper respiratory infection in previous 4 weeks, systemic illness such as cystic fibrosis, acute suppurative otitis media, sinusitis, a strong family history of allergy or history of having received medical therapy of their MEE within the previous 4 weeks (including sympathomimetic amines, antihistamines or antibiotics)
Interventions	**Intervention group:** TMP-SMX suspension 8 mg and 40 mg/kg/day in 2 doses for 4 weeks; n = 100 **Comparator group:** observation; n = 100 **Use of additional interventions:** not described
Outcomes	**Primary outcome:** complete resolution of OME at 4 weeks after randomisation based on pneumatic otoscopy, middle ear muscle reflex and tympanometry (type A tympanogram) **Secondary outcomes:** complete or partial resolution of OME at 4 weeks, AOM at 4 weeks
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 11/200 children (6%) **Participants lost to follow-up in antibiotic group:** 4/100 children (4%) **Participants lost to follow-up in control group:** 7/100 children (7%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The author would simply call a disinterested person who would pull a previously randomly arranged card that would show the word either "control" or "antibiotic"
Allocation concealment (selection bias)	Low risk	Allocation concealment was ensured as a disinterested person performed the randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced

Healy 1984 *(Continued)*

	Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: high compliance rates; monitored by parental administration of the medication on a daily calendar and investigation of the bottles returned by parents

Hemlin 1997

Methods	**Allocation:** randomised (3:3:1 ratio) **Design:** parallel groups, double-blind, double-dummy
Participants	**Number:** 142 children (140 included in analysis) **Age (mean):** 5.3 years **Gender:** 62% boys, 38% girls **Duration of OME prior at baseline (mean):** unknown; OME had to last for at least 12 weeks **Laterality of disease at baseline (%):** 86% bilateral disease **Setting:** secondary care, Karolinska Hospital, Sweden **Eligibility criteria:** 1. Children aged 2 to 12 years 2. Unilateral or bilateral OME for at least 3 months documented by otomicroscopy and tympanometry (type B tympanogram in at least one of the ears) **Exclusion criteria:** severe underlying disease, immunologic deficiency, cleft palate, known or suspected allergy to penicillins or cephalosporins, a history of an antibacterial treatment within the prior 4 weeks, previous inclusion in the study
Interventions	**Intervention group:** cefexime suspension 8 mg/kg/day in 2 doses for 10 days; n = 62 **Intervention group 2:** cefexime 8 mg/kg/day in 2 doses for 10 days + betamethasone 6 mg single dose at day 10; n = 60; *this group was not included in our analyses* **Comparator group:** placebo suspension for 10 days + placebo tablet at day 10; n = 20 **Use of additional interventions:** antimicrobial agents other than the study drugs were not allowed but any other medications considered necessary for the patient's welfare were allowed
Outcomes	**Primary outcome:** partial or complete resolution of OME at 2 to 11 days after completion of the trial (days 12 to 21) based on otomicroscopy and tympanometry defined as a normal middle ear status (type A, C1 or C2 tympanogram) in at least one ear (in case of bilateral OME at baseline) or both ears (in case of unilateral OME at baseline) **Secondary outcomes:** OME relapses at 6 weeks and 6 months, adverse effects
Funding sources	ASTRA AB supplied the drugs and patient registration forms and assisted in data-analysis
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 2/142 children (1%) **Participants lost to follow-up in antibiotic group:** 1/62 children (2%)

Hemlin 1997 *(Continued)*

Participants lost to follow-up in control group: 0/20 children (0%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The drugs were dispensed double-blind by a double-dummy technique"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Unclear whether they used ITT analysis Formal sample size calculations were performed Use of co-interventions: antimicrobial agents other than the study drugs were not allowed but any other medications considered necessary for the patient's welfare were allowed Compliance with treatment: compliance was determined (described in materials and methods), but not presented in manuscript

Leach 2008

Methods	**Allocation:** randomised (block-randomisation) **Design:** parallel groups, double-blind
Participants	**Number:** 103 children (103 included in analysis) **Age (mean):** 3.7 months **Gender:** 52% boys, 48% girls **Duration of OME prior at baseline (mean):** unknown **Laterality of disease at baseline (%):** unknown **Setting:** Aboriginal community located 70 km from Darwin, Australia **Eligibility criteria:** 1. Children below 12 months of age

Leach 2008 *(Continued)*

	2. Unilateral or bilateral OME documented by pneumatic otoscopy and tympanometry (type B tympanogram) **Exclusion criteria:** prematurity (< 34 weeks), chronic infection requiring prophylactic antibiotic therapy, craniofacial abnormalities or immune deficiency syndromes
Interventions	**Intervention group:** amoxicillin 50 mg/kg/day in 2 doses for 24 weeks; n = 52 (n = 52 included in analysis) **Comparator group:** placebo for 24 weeks; n = 51 (n = 51 included in analysis) **Use of additional interventions:** intercurrent illnesses were managed according to local community treatment guidelines
Outcomes	**Primary outcome:** complete resolution of OME at 2 consecutive monthly visits based on pneumatic otoscopy and tympanometry (type A, C1 or C2 tympanogram) **Secondary outcomes:** complete resolution of OME at 6 months, AOM at 6 months, tympanic membrane sequelae (perforation) at 6 months Infants were examined monthly over the 24-week intervention period or until "treatment success" (complete resolution of OME at 2 consecutive monthly visits) was documented
Funding sources	The NHMRC and the Menzies School of Research funded the authors
Declaration of interest	None declared
Notes	**Participants lost to follow-up total:** 2/103 children (2%); all 103 children were included in analyses **Participants lost to follow-up in antibiotic group:** 0/52 children (0%) **Participants lost to follow-up in control group:** 2/51 children (4%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block-randomisation (n = 7) stratified by age (< 6 months versus > 6 months) using computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Quote: "Allocation to placebo or amoxicillin, and the use and size of block-randomisation was concealed from investigators until data collection was completed."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "Blinding was achieved by using a placebo similar in packaging, colour, consistency and smell to amoxicillin suspension."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% of children lost to follow-up; all randomised children were included in analyses
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk

Leach 2008 *(Continued)*

Other bias	Unclear risk	Baseline characteristics: balanced except for mean birth weight ITT analysis was used Formal sample size calculations were performed Use of co-interventions: intercurrent illnesses were managed according to local community treatment guidelines Compliance with treatment: no information provided

Mandel 1987

Methods	**Allocation:** randomised (block-randomisation) **Design:** parallel groups, double-blind, double-dummy
Participants	**Number:** 518 children (474 included in analysis at 4 weeks) **Age (mean):** unknown (range 7 months to 12 years) **Gender:** 64% boys, 36% girls **Duration of OME prior at baseline (mean):** unknown **Laterality of disease at baseline (%):** 69% bilateral disease **Setting:** secondary care, Children's Hospital of Pittsburgh Otitis Media Research Center **Eligibility criteria:** 1. Children aged 7 months to 12 years 2. Unilateral or bilateral OME documented by otoscopy, middle ear muscle reflex and tympanometry **Exclusion criteria:** congenital craniofacial malformations, systemic illness, history of ENT surgery, structural middle ear abnormality, hearing loss not attributable to MEE, severe upper airway obstruction, AOM, acute or chronic sinusitis, history of treatment with sympathomimetic amines or antihistamines during the prior 30 days, history or hypersensitivity to any form of penicillin
Interventions	**Intervention group:** amoxicillin 40 mg/kg/day in 3 doses for 2 weeks plus placebo 4 times daily for 4 weeks; n = ? (n = 160 included in analysis) **Intervention group 2:** amoxicillin 40 mg/kg/day in 3 doses for 2 weeks plus pseudoephedrine hydrochloride and chlorpheniramine maleate 1.0 and 0.09 mg/kg 4 times daily for 4 weeks (decongestant-antihistamine); n = ? (n = 158 included in analysis) **Comparator group:** placebo in 3 doses for 2 weeks plus placebo 4 times daily for 4 weeks; n = ? (n = 156 included in analysis) **Use of additional interventions:** acute symptomatic episodes (fever, ear pain or both) were treated with an antimicrobial agent other than amoxicillin for 10 days with the originally assigned decongestant-antihistamine or its placebo
Outcomes	**Primary outcome:** complete resolution of OME at 4 weeks based on otoscopy, middle ear muscle reflex and tympanometry (type A, C1 or C2 tympanogram) **Secondary outcomes:** complete resolution of OME at 2 weeks, partial or complete resolution of OME at 4 weeks, AOM at 4 weeks, OME recurrences at 4 weeks and 3 months, adverse effects, hearing levels based on speech recognition thresholds
Funding sources	The Otitis Media Research Center is supported by a grant from the National Institute of Neurological and Communicative Disorders and Stroke, National Institute of Health

Mandel 1987 *(Continued)*

Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 44/518 children (8%); no further information provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block-randomisation (n = 3) stratified by 24 subgroups
Allocation concealment (selection bias)	Low risk	Quote: "Within each subgroup, subjects were randomly assigned in a double-blind fashion (in blocks of three) to one of the following three groups: ..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "The amoxicillin placebo was similar in appearance and taste to the active medication… The corresponding placebo was identical in appearance and similar in taste to the active medication (decongestant-antihistamine)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	High risk	Total of randomised children per subgroup not reported 8% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information to permit a judgement of low or high risk
Other bias	High risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: additional antimicrobial treatment for AOM or other conditions was given in 36 children (18 in the control group), no other co-interventions described Compliance with treatment: information on compliance provided; 77% to 91% of children received at least 75% of the assigned medication

Mandel 1991

Methods	**Allocation:** randomised (block randomisation) **Design:** parallel groups, double-blind
Participants	**Number:** 331 children (310 included in analysis at 4 weeks) **Age (mean):** unknown (range 7 months to 12 years) **Gender:** 56% boys, 44% girls **Duration of OME prior at baseline (mean):** unknown **Laterality of disease at baseline (%):** 71% bilateral disease **Setting:** secondary care, Children's Hospital of Pittsburgh Otitis Media Research Center

Mandel 1991 *(Continued)*

	Eligibility criteria: 1. Children aged 7 months to 12 years 2. Unilateral or bilateral OME documented by otoscopy, middle ear muscle reflex and tympanometry **Exclusion criteria:** congenital craniofacial malformations, systemic illness, history of ENT surgery, structural middle ear abnormality, hearing loss not attributable to MEE, severe upper airway obstruction, AOM, acute or chronic sinusitis, history of treatment with sympathomimetic amines or antihistamines during the prior 30 days, history or hypersensitivity to any form of penicillin
Interventions	**Intervention group:** erythromycin-sulfisoxazole 50 and 150 mg/kg/day in 4 doses for 2 weeks; n = 84 **Intervention group 2:** cefaclor 40 mg/kg/day in 3 doses for 2 weeks; n = 83 **Intervention group 3:** amoxicillin 40 mg/kg/day in 3 doses for 2 weeks; n = 83 **Comparator group:** placebo either in 3 or 4 doses for 2 weeks; n = 81 **Use of additional interventions:** AOM episodes were treated with an antimicrobial agent differing in colour from the participant's originally assigned medication for 10 days
Outcomes	**Primary outcome:** complete resolution of OME at 2 and 4 weeks based on otoscopy, middle ear muscle reflex and tympanometry (type A, C1 or C2 tympanogram) **Secondary outcomes:** partial or complete resolution of OME at 4 weeks, AOM at 2 and 4 weeks, OME recurrences at 16 weeks, adverse effects, hearing levels based on speech recognition thresholds
Funding sources	The study was supported in part by grants from the National Institute of Health, Eli Lilly Company (supplied cefaclor) and Ross Laboratories (supplied erythromycin-sulfisoxazole)
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 21/331 children (6%) **Participants lost to follow-up in erythromycin-sulfisoxazole group:** 4/84 children (5%) **Participants lost to follow-up in cefaclor group:** 5/83 children (6%) **Participants lost to follow-up in amoxicillin group:** 6/83 children (7%) **Participants lost to follow-up in control group:** 6/81 children (7%) **Participants lost to follow-up in combined antibiotic group:** 15/250 children (6%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation (n = 4) stratified by 6 subgroups
Allocation concealment (selection bias)	Low risk	Quote: "The medication assigned was unknown to the study physician and to the parent"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "... to receive a placebo that was color-matched and similar in taste to erythromycin-sulfisoxazole (white), cefaclor (purple), or amoxicillin (pink)… All assigned medications were dispensed with parents and physicians blinded as to their content."
Blinding of outcome assessment (detection bias)	Low risk	Double-blind. Primary outcome based on objective tympanometry.

Mandel 1991 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	6% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced ITT analysis were used Formal sample size calculations were performed Use of co-interventions: additional antimicrobial treatment for AOM was given in 35 children (10 in the control group); no other co-interventions described Compliance with treatment: information on compliance provided; 92% to 96% of children received the assigned medication

Marchisio 1998

Methods	**Allocation:** randomised **Design:** parallel groups, investigator-blinded
Participants	**Number:** 120 children (111 included in analysis at 4 and 8 weeks) **Age (mean):** unknown (range 5 to 7 years) **Gender:** 58% boys, 42% girls **Duration of OME prior at baseline (mean):** unknown; OME had to last for at least 12 weeks **Laterality of disease at baseline (%):** 70% bilateral disease **Setting:** community, 11 primary schools in different regions of Italy **Eligibility criteria:** 1. Children aged 7 months to 12 years 2. Unilateral or bilateral OME for 12 weeks documented by otoscopy and tympanometry (type B tympanogram) **Exclusion criteria:** hypersensitivity to a beta-lactam drug, antibiotic therapy in prior 4 weeks, concomitant upper respiratory infection that would preclude evaluation of response to study medication
Interventions	**Intervention group:** ceftibuten (cephalosporin) 9 mg/kg/day in 1 dose for 2 weeks; n = 58 **Comparator group:** no treatment (only nasal saline drops were allowed); n = 62 **Use of additional interventions:** not described
Outcomes	**Primary outcome:** complete resolution of OME at 4 and 8 weeks based on otoscopy and tympanometry (type A, C1 or C2 tympanogram) **Secondary outcomes:** partial or complete resolution of OME at 4 and 8 weeks, adverse effects
Funding sources	The study was supported in part by Recordati SpA, Italy, which supplied ceftibuten

Marchisio 1998 *(Continued)*

Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 9/120 children (8%) **Participants lost to follow-up in ceftibuten group:** 6/58 children (10%) **Participants lost to follow-up in control group:** 3/62 children (5%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Local randomisation list". No further information provided.
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Investigator-blinded; parents were aware of the allocated treatment, investigators were blinded to treatment assignment during follow-up
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator-blinded. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Due to protocol violations 9 children were excluded from analysis. As far as outcome is concerned, all children returned for scheduled follow-up visits. 8% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: only nasal saline drops were allowed in the control group Compliance with treatment: no information provided

Marks 1981

Methods	**Allocation:** randomised **Design:** parallel groups, double-blind
Participants	**Number:** 59 children (51 included in analysis at 4 to 6 weeks) **Age (mean):** 6.2 years **Gender:** 56% boys, 44% girls **Duration of OME prior at baseline (mean):** unknown

Marks 1981 *(Continued)*

	Laterality of disease at baseline (%): unknown **Setting:** unclear, London, UK **Eligibility criteria:** 1. Children below 12 years of age 2. Unilateral or bilateral OME documented by otoscopy, audiometry (audiogram had to show a 15 dB air/bone gap or greater) and tympanometry (type B tympanogram) **Exclusion criteria:** none
Interventions	**Intervention group:** TMP-SMX 5 ml 3 times daily for 4 weeks; n = 30 **Comparator group:** Dimotapp elixir (decongestant); n = 29 **Use of additional interventions:** not described
Outcomes	**Primary outcome:** partial or complete resolution of OME at 4 to 6 weeks based on otoscopy, audiometry (audiogram had to show a 15 dB air/bone gap or greater) and tympanometry (type A, C1 or C2 tympanogram)
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 8/59 children (14%) **Participants lost to follow-up in cotrimoxazole group:** 5/30 children (17%) **Participants lost to follow-up in control group:** 3/29 children (10%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	High risk	Alternative allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blinded, but insufficient information provided on how blinding was ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blinded. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Did not perform ITT analysis

Marks 1981 *(Continued)*

	No formal sample size calculations were performed
	Use of co-interventions: not allowed
	Compliance with treatment: no information provided

Moller 1990

Methods	**Allocation:** randomised **Design:** parallel groups, double-blind
Participants	**Number:** 147 children (141 included in analysis at 4 weeks) **Age (median):** 5 years **Gender:** 56% boys, 44% girls **Duration of OME prior at baseline (mean):** unknown; OME had to last for at least 12 weeks **Laterality of disease at baseline (%):** 100% bilateral disease **Setting:** secondary care, Bergen, Norway **Eligibility criteria:** 1. Children aged 1 to 15 years 2. Bilateral OME for at least 3 months documented by otomicroscopy, pure tone hearing tests and tympanometry (type B tympanogram) 3. Candidates for ventilation tubes **Exclusion criteria:** no AOM in prior 3 months, no antibiotic use in prior 3 months, no obstructive adenoid tissue
Interventions	**Intervention group:** erythromycin 50 mg/kg/day divided into 2 doses for 14 days; n = ? (n = 69 included in analysis) **Comparator group:** placebo for 14 days; n = ? (n = 72 included in analysis) **Use of additional interventions:** not described
Outcomes	**Primary outcome:** complete resolution of OME at 4 weeks based on otomicroscopy, pure tone hearing tests and tympanometry (type A, C1 or C2 tympanogram) **Secondary outcome:** adverse effects
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 6/147 children (4%) Quote: "six patients were unable to continue due to intercurrent disease or an unwillingness to participate". No further information provided.

Risk of bias

Bias	Authors' judgement	Support for judgement

Moller 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The drugs were administered double blind… dispensed by the hospital pharmacist in two daily doses…"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Primary outcome objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	High risk	Total of randomised children per subgroup not reported 4% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Protocol not available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: no information provided Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: no information provided

Otten 1990

Methods	**Allocation:** randomised **Design:** parallel groups, double-blind
Participants	**Number:** 141 children (139 included in analysis at 6, 12 and 26 weeks) **Age (mean):** unknown (range 3 to 10 years) **Gender:** 57% boys, 43% girls **Duration of OME prior at baseline (mean):** unknown **Laterality of disease at baseline (%):** unknown **Setting:** secondary care, Leiden, The Netherlands **Eligibility criteria:** 1. Children aged 3 to 10 years 2. Unilateral or bilateral OME documented by pneumatic otoscopy, otomicroscopy and tympanometry (type B or C2 tympanogram) 3. Chronic rhinosinusitis: purulent rhinitis for at least 3 months and radiological abnormalities of the maxillary sinus in the form of opacity or mucosal swelling **Exclusion criteria:** signs of chronic lower respiratory tract infections, nasal allergies, allergies to amoxicillin, totally obstructive adenoids, Down syndrome

Otten 1990 *(Continued)*

Interventions	**Intervention group:** amoxicillin 250 mg 3 times daily for 10 days + xylometazoline hydrochloride nose drops 0.5%; n = 38 **Intervention group 2:** amoxicillin 250 mg 3 times daily for 10 days + xylometazoline hydrochloride nose drops 0.5% + drainage of the maxillary sinus; n = 35 **Intervention group 3:** placebo 3 times daily for 10 days + physiological saline nasal drops 0.5% + drainage of the maxillary sinus; n = 30 **Comparator group:** placebo 3 times daily for 10 days + physiological saline nasal drops 0.5%; n = 38 **Use of additional interventions:** in cases in which the upper respiratory tract infection or OME was not cured within 12 weeks or parents did not wish their children to remain in the study supplementary treatment could be given
Outcomes	**Primary outcome:** complete resolution of OME at 26 weeks based on pneumatic otoscopy, otomicroscopy and tympanometry (type A or C1 tympanogram)
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 2/141 children (1%) **Participants lost to follow-up in antibiotic group:** 1/73 children (1%) **Participants lost to follow-up in control group:** 1/68 children (1%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The medication could be given on a double-blind basis; the drainage could not"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	High risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed

Otten 1990 *(Continued)*

	Use of co-interventions: possibility of supplemental treatment when OME or an upper respiratory tract infection was still present after 12 weeks Compliance with treatment: no information provided

Podoshin 1990

Methods	**Allocation:** randomised **Design:** parallel groups, double-blind
Participants	**Number:** 150 children (136 included in analysis at 8 weeks) **Age (mean):** 6.8 years **Gender:** 53% boys, 47% girls **Duration of OME prior at baseline (mean):** unknown; OME had to last for at least 8 weeks **Laterality of disease at baseline (%):** unknown **Setting:** secondary care, Haifa, Israel **Eligibility criteria:** 1. Children aged 3 to 8 years 2. Unilateral or bilateral OME for at least 2 months documented by pneumatic otoscopy and tympanometry (type B tympanogram) **Exclusion criteria:** signs of fluid lines, air bubbles or yellow fluid
Interventions	**Intervention group:** amoxicillin 50 mg/kg/day + placebo for 2 weeks; n = 50 **Intervention group 2:** amoxicillin 50 mg/kg/day + prednisone 1 mg/kg/day (dosage was reduced by 5 mg every 2 days) for 2 weeks; n = 50; *this group was not included in our analyses* **Comparator group:** placebo + placebo; n = 50 **Use of additional interventions:** not described
Outcomes	**Primary outcome:** complete resolution of OME at 2 months based on pneumatic otoscopy and tympanometry (type A tympanogram) **Secondary outcome:** improvement of OME at 2 months based on pneumatic otoscopy and tympanometry (type C1 or C2 tympanogram)
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 14/150 children (9%) **Participants lost to follow-up in antibiotic group:** 1/50 children (2%) **Participants lost to follow-up in control group:** 13/50 children (26%)

Risk of bias

Bias	Authors' judgement	Support for judgement

Podoshin 1990 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind fashion. Quote: "The amoxicillin, prednisone, and placebo…was given to the treating physician"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	High risk	9% of children lost to follow-up; 2% in antibiotic group versus 26% in placebo group
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced ITT analysis were used No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: no information provided

Principi 1989

Methods	**Allocation:** randomised **Design:** parallel groups, double-blind
Participants	**Number:** 100 children (93 included in analysis at 6 months) **Age (mean):** unknown (range 9 months to 5 years) **Gender:** 55% boys, 45% girls **Duration of OME prior at baseline (mean):** unknown **Laterality of disease at baseline (%):** 81% bilateral disease **Setting:** tertiary care, Milan, Italy **Eligibility criteria:** 1. Children aged 9 months to 5 years 2. Unilateral or bilateral OME documented by otoscopy and tympanometry (type B tympanogram) 3. 3 or more AOM episodes in the prior 6 months as confirmed by otoscopy and tympanometry with the last episode occurring between 15 days and 2 months prior to enrolment **Exclusion criteria:** cleft palate, Down syndrome, immunodeficiency, history or allergic reactions to any of the study drugs

Principi 1989 *(Continued)*

Interventions	**Intervention group:** amoxicillin 20 mg/kg/day once daily for 6 months; n = 34 **Intervention group 2:** TMP-SMX 12 mg/kg/day once daily for 6 months; n = 33 **Comparator group:** placebo once daily for 6 months; n = 33 **Use of additional interventions:** AOM episodes were treated with cefaclor (prophylaxis was discontinued) for 10 days. If acute signs persisted tympanocentesis was performed and another antimicrobial drug was prescribed based on the sensitivity of the isolated pathogen. If another infectious disease requiring antibiotic treatment occurred, prophylaxis was stopped and the more appropriate treatment instituted. A child was discharged from the study in case of 2 AOM episodes within a 2-month period.
Outcomes	**Primary outcome:** complete resolution of OME at 6 months based on otoscopy and tympanometry (type A, C1 or C2 tympanogram) **Secondary outcome:** adverse effects and AOM at 6 months
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 7/100 children (7%) **Participants lost to follow-up in antibiotic group:** 3/67 children (4%) **Participants lost to follow-up in control group:** 4/33 children (12%) 1 child in each antibiotic group had no OME at randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... the placebo was similar in appearance to one of the active drugs."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	High risk	7% of children lost to follow-up; 4% in antibiotic group versus 12% in placebo group
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	High risk	Baseline characteristics: balanced Did not perform ITT analysis No formal sample size calculations were performed

Principi 1989 *(Continued)*

	Use of co-interventions: antibiotic treatment in case of AOM episodes or other infectious disease requiring antibiotic treatment Compliance with treatment: compliance with medication was good in 97% (32/33) of children with amoxicillin, in 94% (31/33) of those receiving sulfamethoxazole and trimethoprim, and in 97% (29/30) of children who received placebo

Safak 2001

Methods	**Allocation:** randomised **Design:** parallel groups, double-blind
Participants	**Number:** 90 children (90 included in analysis) **Age (mean):** 5.8 years **Gender:** 49% boys, 51% girls **Duration of OME prior at baseline (mean):** unknown; OME had to last for at least 4 weeks **Laterality of disease at baseline (%):** unknown **Setting:** secondary care, Ankara, Turkey **Eligibility criteria:** 1. Children aged 2 to 13 years 2. Unilateral or bilateral OME for at least 4 weeks documented by pneumatic otoscopy and tympanometry (type B tympanogram) 3. No previous medication in prior 3 months **Exclusion criteria:** severe septal deviation, totally obstructive adenoid hypertrophy, allergic signs
Interventions	**Intervention group:** azithromycin 10 mg/kg/day once daily for 3 days, repeated for up to 12 weeks; n = 30 **Intervention group 2:** azithromycin 10 mg/kg/day once daily for 3 days for the first week; this dose was then repeated for 1 day a week for up to 12 weeks; n = 30 **Comparator group:** pseudoephedrine hydrochloride (decongestant) 4 mg/kg 3 daily for 12 weeks; n = 30 **Use of additional interventions:** not described
Outcomes	**Primary outcome:** complete resolution of OME at 1, 2 and 3 months based on pneumatic otoscopy and tympanometry (type A tympanogram) **Secondary outcome:** improvement of OME at 1, 2 and 3 months based on pneumatic otoscopy and tympanometry (type C1 or C2 tympanogram)
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 0/90 children (0%)
Risk of bias	

Safak 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be double-blinded, but insufficient information provided on how blinding was ensured
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated to be double-blinded. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Unclear whether they used ITT analysis No formal sample size calculations were performed Use of co-interventions: no information provided Compliance with treatment: no information provided

Schwartz 1982

Methods	**Allocation:** randomised **Design:** parallel groups, open-label
Participants	**Number:** 69 children (64 included in analysis at 4 weeks) **Age (mean):** 3.6 years **Gender:** 60% boys, 40% girls **Duration of OME prior at baseline (mean):** unknown **Laterality of disease at baseline (%):** unknown **Setting:** secondary care, Washington, USA **Eligibility criteria:** 1. Persistent unilateral or bilateral OME documented by pneumatic otoscopy and tympanometry (type B tympanogram) 2. Recent AOM episode within 15 days of enrolment 3. Previous amoxicillin treatment for at least 10 days **Exclusion criteria:** none described

Schwartz 1982 *(Continued)*

Interventions	**Intervention group:** TMP-SMX 4 mg/kg/day once daily for 2 weeks; n = 33 **Comparator group:** no treatment; n = 36 **Use of additional interventions:** neither decongestants nor antihistamines were prescribed
Outcomes	**Primary outcome:** complete resolution of OME at 2, 4, 6 weeks and 3 months based on pneumatic otoscopy and tympanometry (type A, C1 or C2 tympanogram) **Secondary outcome:** AOM at 2 and 4 weeks
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 5/69 children (7%) **Participants lost to follow-up in antibiotic group:** 3/33 children (9%) **Participants lost to follow-up in control group:** 2/36 children (6%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternative allocation
Allocation concealment (selection bias)	High risk	Alternative allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced, except for gender Did not perform ITT analysis No formal sample size calculations were performed Use of co-interventions: no other medication prescribed Compliance with treatment: not tested

Thomsen 1989

Methods	**Allocation:** randomised **Design:** parallel groups, double-blind
Participants	**Number:** 264 children (221 included in analysis) **Age (mean):** unknown (range 1 to 10 years) **Gender:** 52% boys, 48% girls **Duration of OME prior at baseline (mean):** unknown; OME had to last for at least 12 weeks **Laterality of disease at baseline (%):** unknown **Setting:** secondary care, Hellerup, Denmark **Eligibility criteria:** 1. Children aged 1 to 10 years 2. Unilateral or bilateral OME for at least 3 months documented by tympanometry (type B or C2 tympanogram) In children with bilateral disease, a ventilation tube was inserted in the right ear whereas the left ear was included in the study **Exclusion criteria:** allergy to penicillin
Interventions	**Intervention group:** amoxicillin-clavulanic acid 25/6.25 mg/ml for 4 weeks (1 to 5 years: 5 ml 3 times daily; 6 to 10: 7.5 ml 3 times daily); n = 131 **Comparator group:** placebo for 4 weeks; n = 133 **Use of additional interventions:** no concomitant medications other than antipyretic or analgesic were allowed during the treatment period
Outcomes	**Primary outcome:** complete resolution of OME at 4 weeks based on tympanometry (type A or C1 tympanogram) **Secondary outcome:** adverse effects at 4 weeks, time with abnormal tympanogram at 12 months
Funding sources	No information provided
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 43/264 children (16%) **Participants lost to follow-up in antibiotic group:** 22/131 children (17%) as described in text of manuscript; 20/131 (15%) as extracted from Table 6 **Participants lost to follow-up in control group:** 21/133 children (16%) as described in text of manuscript; 23/131 (17%) as extracted from Table 6

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described

Thomsen 1989 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All medications were dispensed in a double-blind fashion"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	High risk	16% of children lost to follow-up; discrepancies between numbers provided in text and table
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Did not perform ITT analysis No formal sample size calculations were performed Use of co-interventions: no concomitant medications other than antipyretic or analgesic were allowed during the treatment period Compliance with treatment: parental records and bottle method were used, but actual compliance rates were not reported

van Balen 1996

Methods	**Allocation:** randomised **Design:** parallel groups, double-blind
Participants	**Number:** 162 children (153 included in analysis) **Age (mean):** unknown (range 6 months to 6 years) **Gender:** 52% boys, 48% girls **Duration of OME prior at baseline (mean):** unknown; OME had to last for at least 12 weeks **Laterality of disease at baseline (%):** 100% bilateral disease **Setting:** primary care, Utrecht, the Netherlands **Eligibility criteria:** 1. Children aged 6 months to 6 years 2. Bilateral OME for at least 3 months documented by otoscopy and tympanometry (type B or C2 tympanogram) **Exclusion criteria:** antibiotic treatment in prior 4 weeks, penicillin allergy, compromised immunity, referral to an ENT surgeon at time of inclusion, craniofacial abnormalities, Down syndrome, cystic fibrosis
Interventions	**Intervention group:** amoxicillin-clavulanic acid 20/5 mg/kg divided into 3 daily doses for 2 weeks + xylometazoline 0.25% nose drops (decongestant) 3 times daily; n = 82 **Comparator group:** placebo for 2 weeks + xylometazoline 0.25% nose drops (decongestant) 3 times daily; n = 80

van Balen 1996 *(Continued)*

	Use of additional interventions: general practitioners were free in their choice of treatment at the 2-week follow-up visit
Outcomes	**Primary outcome:** complete resolution of OME at 2 weeks based on otoscopy and tympanometry (type A or C1 tympanogram) **Secondary outcome:** partial or complete resolution of OME at 2 weeks, adverse effects at 2 weeks
Funding sources	SmithKline Beecham supplied the study drug (Augmentin) and placebo and Zyma Geigy the nose drops (Otrivin). The study was supported by the Netherlands Organisation for Scientific Research
Declaration of interest	No information provided
Notes	**Participants lost to follow-up total:** 9/162 children (6%) **Participants lost to follow-up in antibiotic group:** 3/82 children (4%) **Participants lost to follow-up in control group:** 6/80 children (8%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised block randomisation (n = 4)
Allocation concealment (selection bias)	Low risk	Quote: "The suspensions were dispensed to participating general practitioners in a double-blind fashion with computerised four-block randomisation."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "...placebo with same colour and taste..." Quote: "Throughout the study, doctor and patient remained blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Primary outcome based on objective tympanometry.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% of children lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	High risk	Baseline characteristics: significantly more males in the placebo group, which also showed to be a significant prognostic factor in this study Did not perform ITT analysis No formal sample size calculations were performed Use of co-interventions: no concomitant medications other than antipyretic or analgesic were allowed during the treatment period Compliance with treatment: measured by examination of the diaries and measurement of suspension that remained in the bottle, 90% of all patients took the medication for at least 10 days

AOM: acute otitis media

ENT: ear, nose and throat
ITT: intention-to-treat
MEE: middle ear effusion
OME: otitis media with effusion
RCT: randomised controlled trial
Rx: prescription
TMP-SMX: trimethoprim-sulfamethoxazole
Tx: treatment
VT: ventilation tube

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

Study	Reason for exclusion
Balle 1998	INTERVENTIONS One antibiotic was compared with another antibiotic (amoxicillin/clavulanic acid versus penicillin V)
Berman 1987	INTERVENTIONS Antibiotics were compared with antibiotics in combination with corticosteroids (sulfamethoxazole with and without prednisone)
Berman 1990	INTERVENTIONS Antibiotics were compared with antibiotics in combination with corticosteroids (TMP-SMX with and without prednisone)
Bojanovic 1999	Only published in abstract form - no full-text publication
Cantekin 1991	Reanalysis of data originally published by Mandel and co-workers (Mandel 1987)
Chan 1988	INTERVENTIONS One antibiotic was compared with another antibiotic (amoxicillin/clavulanic acid versus amoxicillin trihydrate)
Combs 2004	PARTICIPANTS Children were randomised on the basis of AOM; not all children were diagnosed with OME at the time of randomisation
Donaldson 1990	INTERVENTIONS One antibiotic (cefaclor) was used in all groups (different dosage)
Eiden 1997	ALLOCATION Not a randomised controlled trial
Ernstson 1985a	ALLOCATION Not a randomised controlled trial
Fontanel 1998	ALLOCATION Not a randomised controlled trial
Fujita 1994	PARTICIPANTS

Study	Reason for exclusion
	Adults were also included (participants aged 10 to 20 years)
Gates 1986	ALLOCATION Not a randomised controlled trial
Goodey 1975	ANALYSIS Ears instead of patients were used as the unit of analysis
Heary 1990	Only published in abstract form - no full-text publication
Hong 2014	ALLOCATION Not a randomised controlled trial
Howie 1971	PARTICIPANTS Children were randomised on the basis of otitis media in general; not all children were diagnosed with OME at the time of randomisation
Hozawa 2001	ALLOCATION Not a randomised controlled trial
Karlidag 2002	ANALYSIS Ears instead of patients were used as the unit of analysis
Mandel 1996	INTERVENTIONS One antibiotic was compared with another antibiotic (ceftibuten versus amoxicillin)
Mandel 2002	INTERVENTIONS Antibiotics were compared with antibiotics in combination with corticosteroids (amoxicillin with or without prednisolone)
Margas 2004	Only published in abstract form - no full-text publication
Mel-Hennawi 2015	INTERVENTIONS Two antibiotics were compared with another antibiotic (clarithromycin, metronidazole (and lansoprazole) versus amoxicillin/clavulanic acid)
Nsouli 2015	INTERVENTIONS One antibiotic was compared with another antibiotic (clarithromycin versus amoxicillin/clavulanic acid)
Ortega 2005	INTERVENTIONS Antibiotics were compared with antibiotics in combination with AM3 (immunoferon)
Ozmen 2010	ALLOCATION Not a randomised controlled trial
Pestalozza 1992	PARTICIPANTS

Study	Reason for exclusion
	Children were randomised on the basis of otitis media in general; not all children were diagnosed with OME at the time of randomisation
Puhakka 1985	PARTICIPANTS Diagnosis of OME was made without performing tympanometry
Rosenfeld 1995	ALLOCATION Not a randomised controlled trial
Roydhouse 1991	ALLOCATION Not a randomised controlled trial
Schloss 1988	Only published in abstract form - no full-text publication
Schwartz 1980	INTERVENTIONS Antibiotics were compared with antibiotics in combination with corticosteroids (sulfisoxazole with and without corticosteroids)
Schwartz 1982a	PARTICIPANTS All otitis-prone children were included; just a small number of children had OME at the time of randomisation
Sundberg 1984	ALLOCATION Not a randomised controlled trial
Tapiainen 2014	PARTICIPANTS Children were randomised on the basis of AOM (and not OME)
Thomsen 1997	INTERVENTIONS One antibiotic was compared with another antibiotic (penicillin V versus amoxicillin/clavulanic acid)
Tracy 1998	INTERVENTIONS Prophylactic antibiotics were compared with prophylactic antibiotics in combination with intranasal corticosteroids (amoxicillin 20 mg/kg twice a day with or without addition of intranasal corticosteroids)
Unlu 2005	Only published in abstract form - no full-text publication
Varsano 1985	ANALYSIS Double-blind, cross-over trial; we were not able to separate the effect of the intervention of interest as the results were only reported after treatment with both sulfisoxazole and placebo
Venekamp 2014	ALLOCATION Not a randomised controlled trial
Yin 2002	INTERVENTIONS One antibiotic was compared with another antibiotic (cefaclor versus roxithromycin)

Study	Reason for exclusion
Zocconi 1994	ALLOCATION Not a randomised controlled trial

AOM: acute otitis media
OME: otitis media with effusion
Rx: prescription
TMP-SMX: trimethoprim-sulfamethoxazole

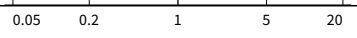
DATA AND ANALYSES

Comparison 1. Antibiotics versus placebo, no treatment or therapy of unproven effectiveness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete resolution of OME at 2 to 3 months	6	484	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.58, 2.53]
2 Adverse effects	5	742	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.29, 3.60]
3 Complete resolution of OME at 2 to 4 weeks	14	2091	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.47, 2.67]
4 Complete resolution of OME at more than 6 months	5	606	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.41, 2.18]
5 Complete resolution of OME at end of treatment (10 to 14 days)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Duration of OME prior to study entry < 3 months	4	885	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.38, 2.44]
5.2 Duration of OME prior to study entry ≥ 3 months	2	244	Risk Ratio (M-H, Fixed, 95% CI)	4.03 [2.13, 7.61]
6 Complete resolution of OME at end of treatment (4 weeks)	4	479	Risk Ratio (IV, Random, 95% CI)	3.28 [1.37, 7.87]
7 Complete resolution of OME at end of treatment (3 months)	2	150	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [1.39, 3.17]
8 Complete resolution of OME at end of treatment (6 months)	2	196	Risk Ratio (M-H, Random, 95% CI)	2.81 [0.29, 27.50]
9 Insertion of ventilation tubes	2	121	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.46, 1.78]
10 Tympanic membrane sequelae	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.18, 1.01]
11 AOM within 4 to 8 weeks	5	1086	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.42, 0.85]
12 AOM within 6 months	2	199	Risk Ratio (IV, Fixed, 95% CI)	0.56 [0.40, 0.80]

Analysis 1.1. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 1 Complete resolution of OME at 2 to 3 months.

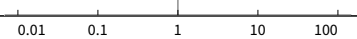
Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ardehali 2008	12/30	3/30		5.04%	4[1.25,12.75]
Chen 2013	33/36	23/37		38.09%	1.47[1.13,1.93]
Marchisio 1998	19/52	11/59		17.3%	1.96[1.03,3.72]
Podoshin 1990	20/49	5/37		9.57%	3.02[1.25,7.3]
Safak 2001	51/60	12/30		26.86%	2.13[1.35,3.34]
Schwartz 1982	2/30	2/34		3.15%	1.13[0.17,7.56]
Total (95% CI)	**257**	**227**		**100%**	**2[1.58,2.53]**
Total events: 137 (Antibiotics), 56 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.49, df=5(P=0.19); I^2=33.29%					
Test for overall effect: Z=5.77(P<0.0001)					



Favours control — Favours antibiotics

Analysis 1.2. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 2 Adverse effects.

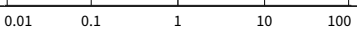
Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hemlin 1997	6/61	0/20		4.38%	4.4[0.26,74.88]
Marchisio 1998	0/52	0/59			Not estimable
Moller 1990	0/69	0/72			Not estimable
Thomsen 1989	5/131	1/133		5.82%	5.08[0.6,42.86]
van Balen 1996	29/74	15/71		89.8%	1.85[1.09,3.16]
Total (95% CI)	**387**	**355**		**100%**	**2.15[1.29,3.6]**
Total events: 40 (Antibiotics), 16 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.17, df=2(P=0.56); I^2=0%					
Test for overall effect: Z=2.93(P=0)					



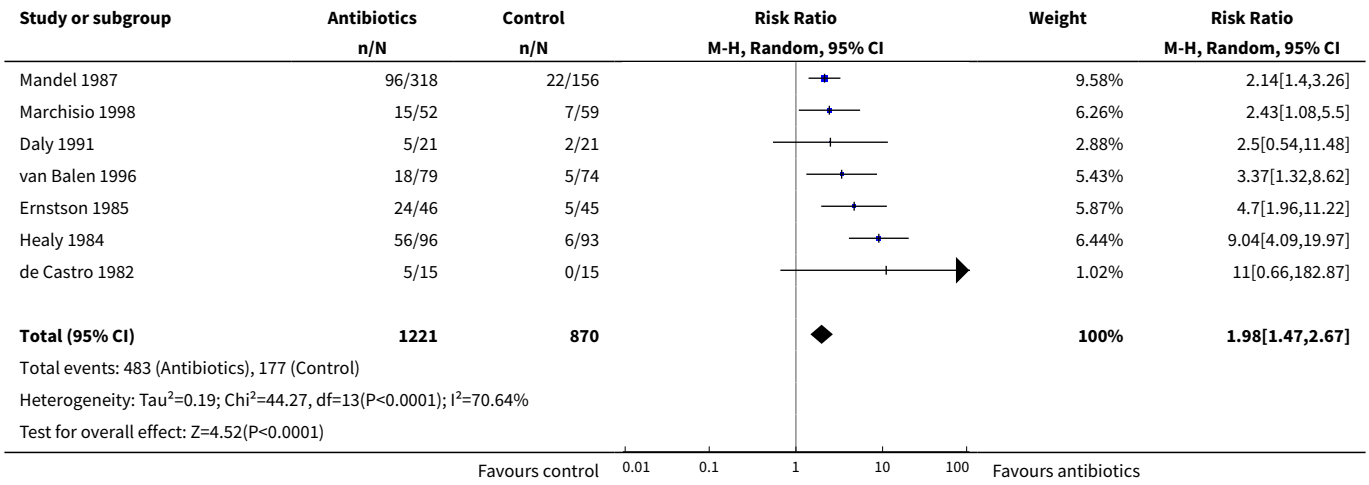
Favours antibiotics — Favours control

Analysis 1.3. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 3 Complete resolution of OME at 2 to 4 weeks.

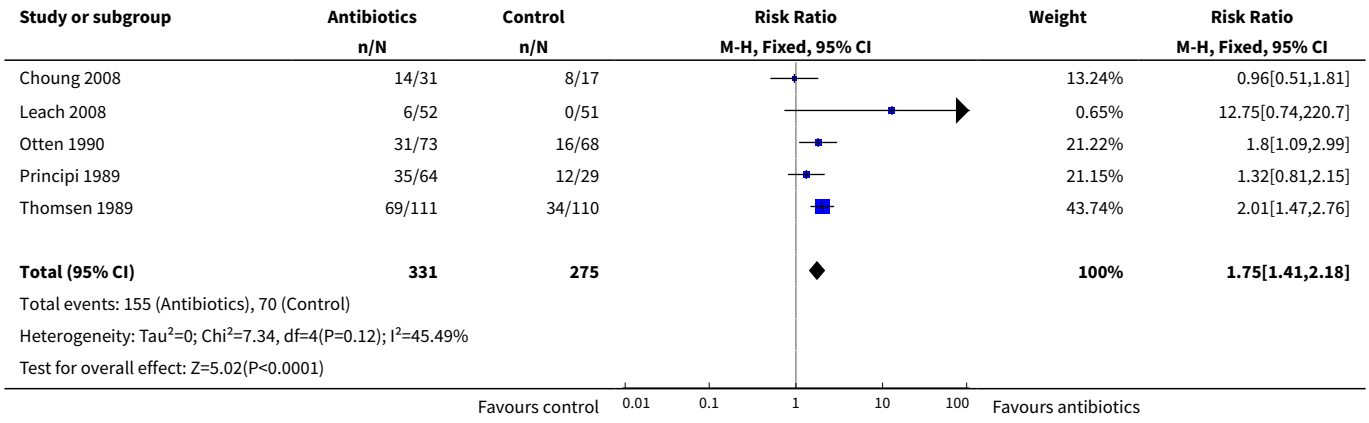
Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Moller 1990	12/69	19/72		7.63%	0.66[0.35,1.25]
Mandel 1991	69/235	20/75		9.55%	1.1[0.72,1.68]
Schwartz 1982	19/33	15/36		9.02%	1.38[0.85,2.24]
Corwin 1986	33/66	22/65		9.62%	1.48[0.97,2.24]
Giebink 1990	10/20	6/19		6.42%	1.58[0.72,3.5]
Safak 2001	52/60	14/30		9.81%	1.86[1.25,2.76]
Thomsen 1989	69/111	34/110		10.47%	2.01[1.47,2.76]



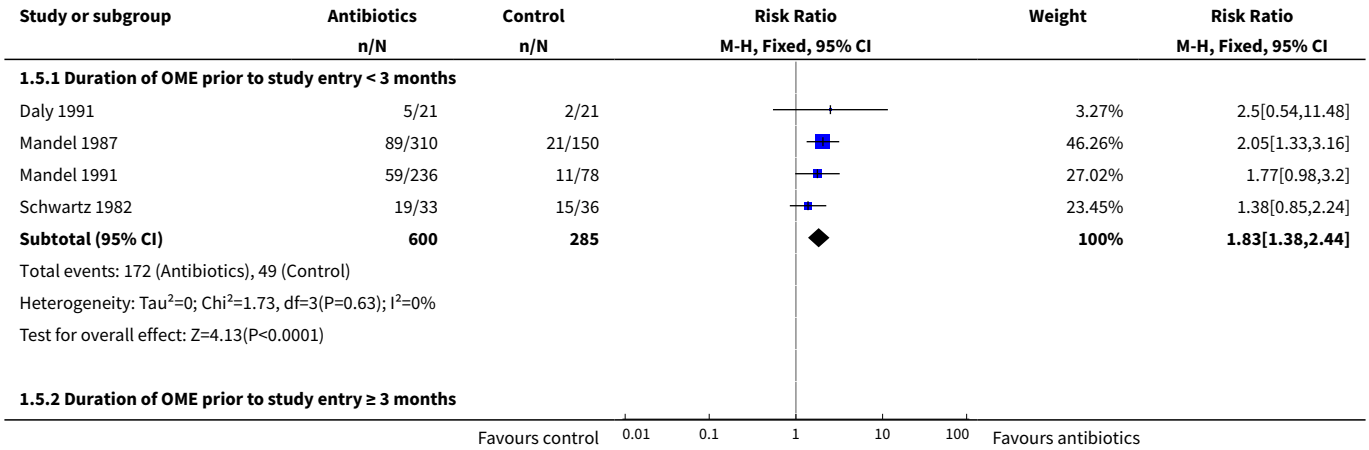
Favours control — Favours antibiotics

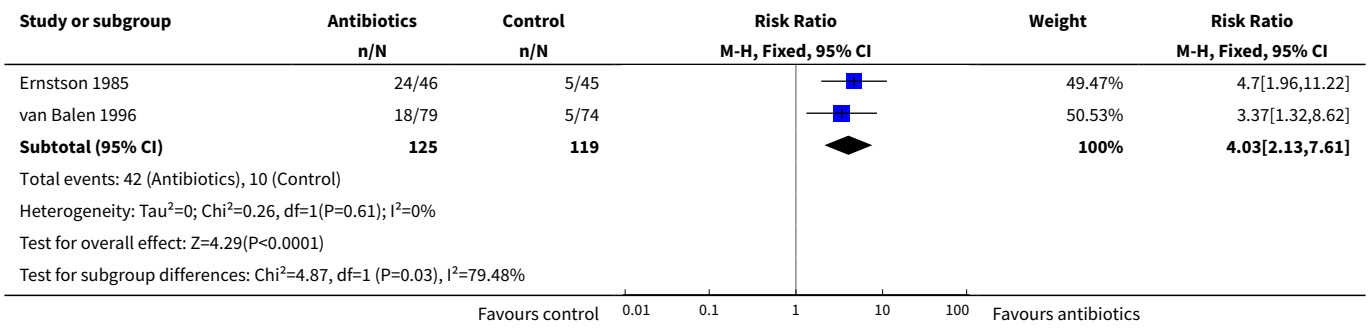


Analysis 1.4. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 4 Complete resolution of OME at more than 6 months.

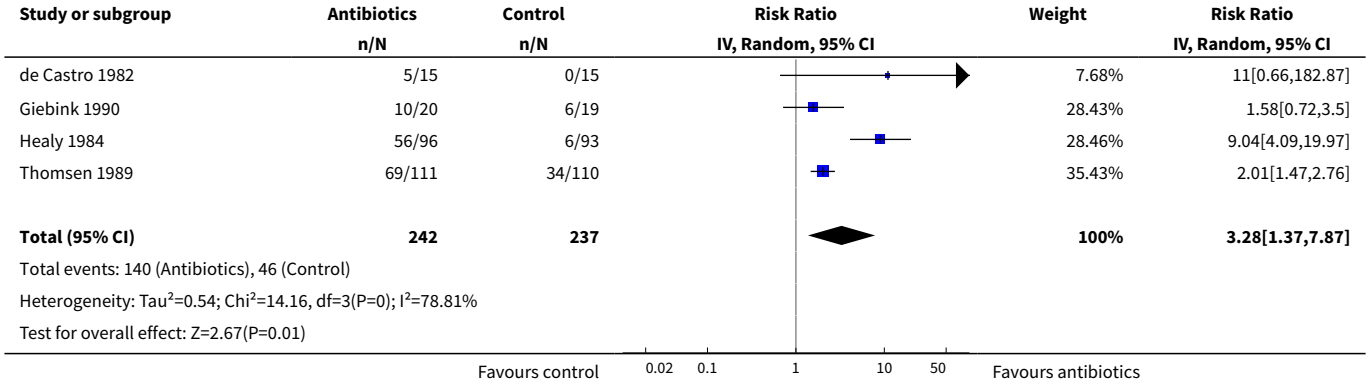


Analysis 1.5. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 5 Complete resolution of OME at end of treatment (10 to 14 days).

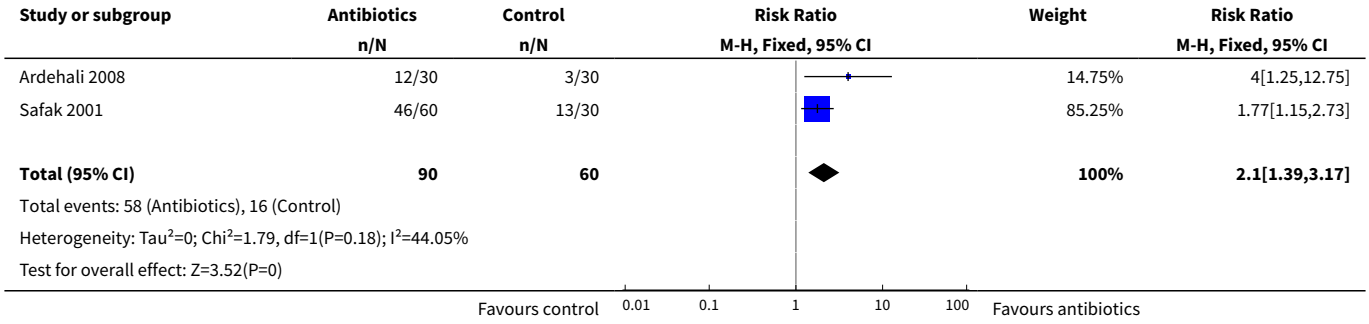




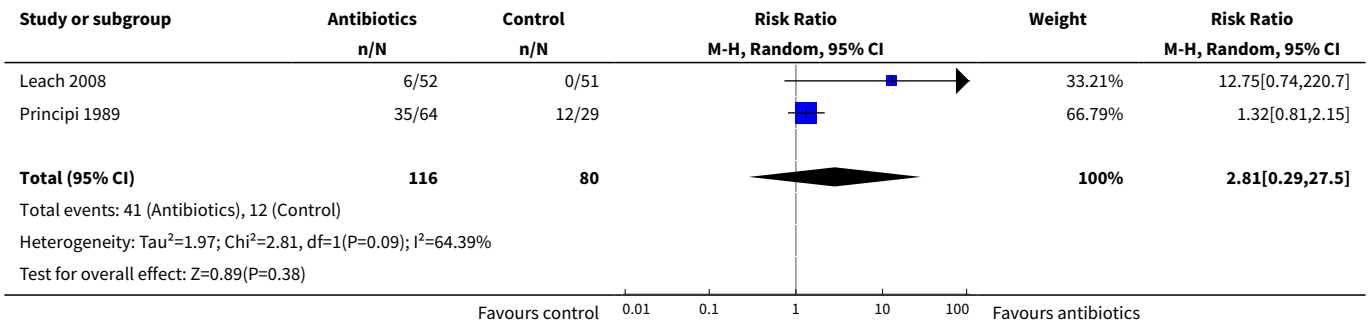
Analysis 1.6. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 6 Complete resolution of OME at end of treatment (4 weeks).



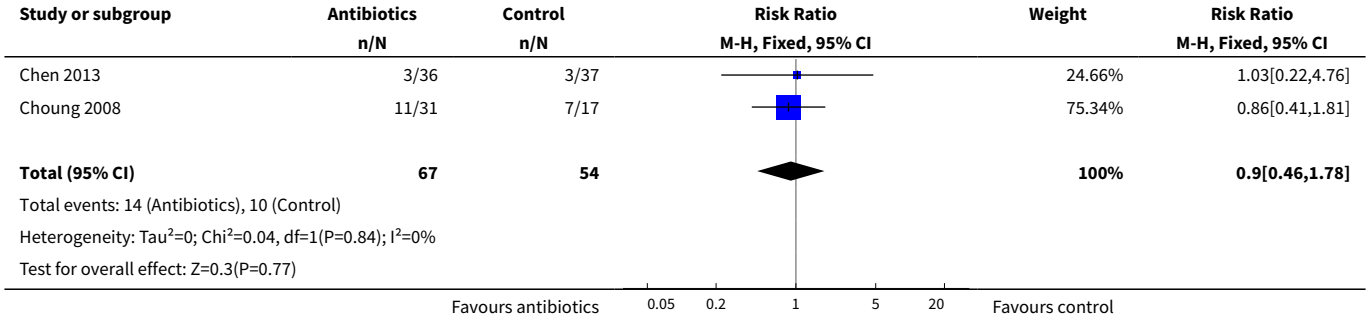
Analysis 1.7. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 7 Complete resolution of OME at end of treatment (3 months).



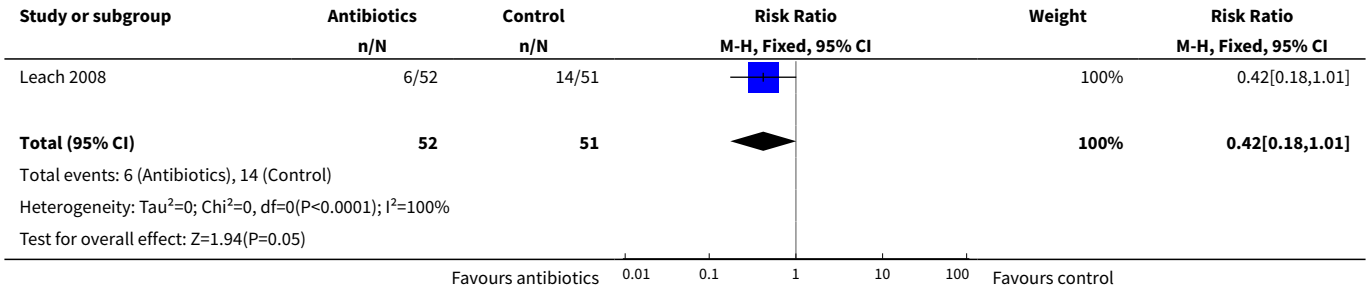
Analysis 1.8. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 8 Complete resolution of OME at end of treatment (6 months).



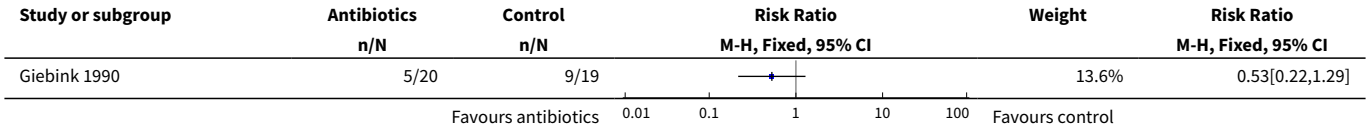
Analysis 1.9. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 9 Insertion of ventilation tubes.

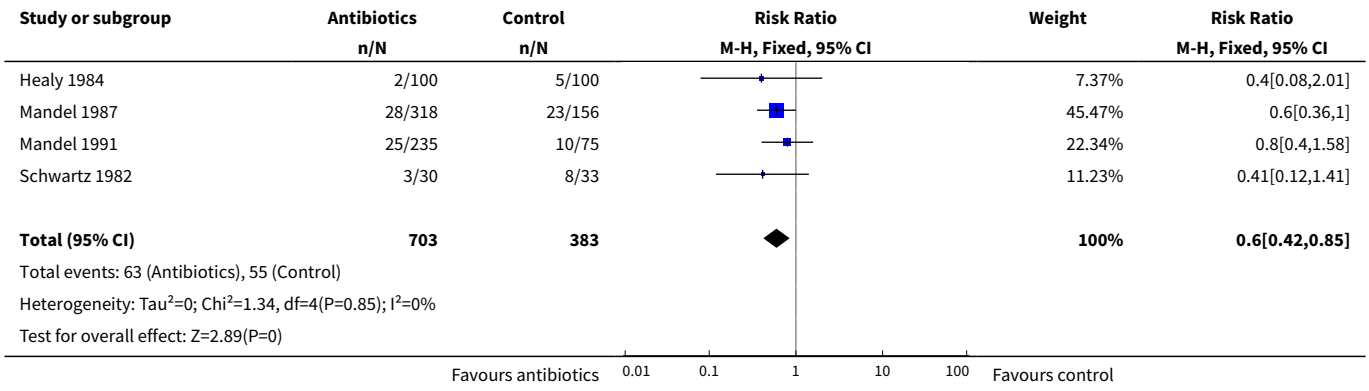


Analysis 1.10. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 10 Tympanic membrane sequelae.

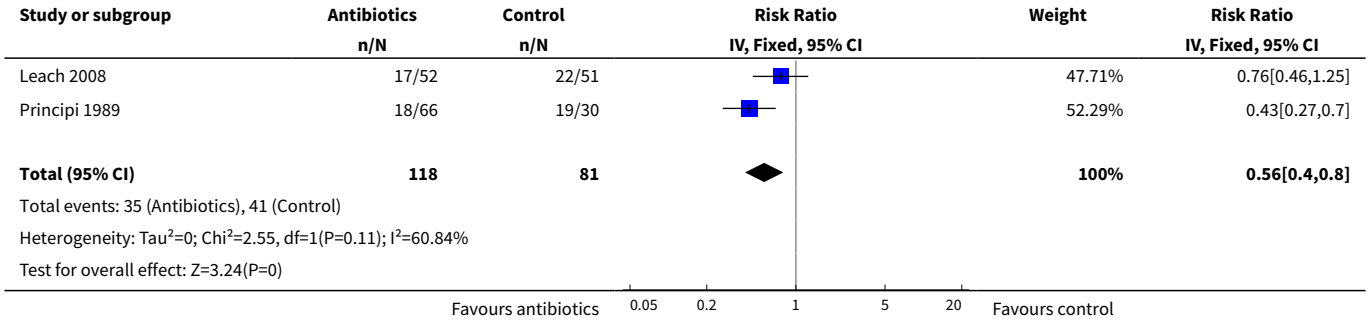


Analysis 1.11. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 11 AOM within 4 to 8 weeks.





Analysis 1.12. Comparison 1 Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 12 AOM within 6 months.



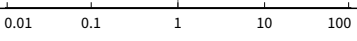
Comparison 2. Sensitivity analysis - Antibiotics versus placebo, no treatment or therapy of unproven effectiveness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete resolution of OME at 2 to 3 months	4	334	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.51, 2.44]
2 Adverse effects	3	337	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [1.16, 3.35]
3 Complete resolution of OME at 2 to 4 weeks	9	1147	Risk Ratio (M-H, Random, 95% CI)	2.58 [1.60, 4.17]
4 Complete resolution of OME at more than 6 months	2	244	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [1.30, 3.50]
5 Complete resolution of OME at end of treatment (10 to 14 days)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Duration of OME prior to study entry < 3 month	2	356	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.07, 3.21]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.2 Duration of OME prior to study entry ≥ 3 months	2	244	Risk Ratio (M-H, Fixed, 95% CI)	4.03 [2.13, 7.61]
6 Complete resolution of OME at end of treatment (4 weeks)	2	219	Risk Ratio (M-H, Fixed, 95% CI)	9.19 [4.29, 19.70]
7 AOM within 4 to 8 weeks	2	510	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.37, 1.31]

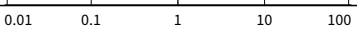
Analysis 2.1. Comparison 2 Sensitivity analysis - Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 1 Complete resolution of OME at 2 to 3 months.

Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ardehali 2008	12/30	3/30		5.77%	4[1.25,12.75]
Chen 2013	33/36	23/37		43.63%	1.47[1.13,1.93]
Marchisio 1998	19/52	11/59		19.82%	1.96[1.03,3.72]
Safak 2001	51/60	12/30		30.77%	2.13[1.35,3.34]
Total (95% CI)	**178**	**156**		**100%**	**1.92[1.51,2.44]**
Total events: 115 (Antibiotics), 49 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.37, df=3(P=0.15); I^2=44.18%					
Test for overall effect: Z=5.3(P<0.0001)					



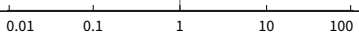
Analysis 2.2. Comparison 2 Sensitivity analysis - Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 2 Adverse effects.

Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hemlin 1997	6/61	0/20		4.65%	4.4[0.26,74.88]
Marchisio 1998	0/52	0/59			Not estimable
van Balen 1996	29/74	15/71		95.35%	1.85[1.09,3.16]
Total (95% CI)	**187**	**150**		**100%**	**1.97[1.16,3.35]**
Total events: 35 (Antibiotics), 15 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.36, df=1(P=0.55); I^2=0%					
Test for overall effect: Z=2.52(P=0.01)					



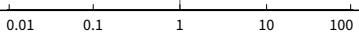
Analysis 2.3. Comparison 2 Sensitivity analysis - Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 3 Complete resolution of OME at 2 to 4 weeks.

Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Corwin 1986	33/66	22/65		15.4%	1.48[0.97,2.24]
Daly 1991	5/21	2/21		6.31%	2.5[0.54,11.48]
de Castro 1982	5/15	0/15		2.49%	11[0.66,182.87]
Ernstson 1985	24/46	5/45		11.06%	4.7[1.96,11.22]
Healy 1984	56/96	6/93		11.81%	9.04[4.09,19.97]
Mandel 1991	69/235	20/75		15.33%	1.1[0.72,1.68]
Marchisio 1998	15/52	7/59		11.58%	2.43[1.08,5.5]
Safak 2001	52/60	14/30		15.58%	1.86[1.25,2.76]
van Balen 1996	18/79	5/74		10.45%	3.37[1.32,8.62]
Total (95% CI)	**670**	**477**		**100%**	**2.58[1.6,4.17]**
Total events: 277 (Antibiotics), 81 (Control)					
Heterogeneity: Tau^2=0.34; Chi^2=33.15, df=8(P<0.0001); I^2=75.87%					
Test for overall effect: Z=3.88(P=0)					



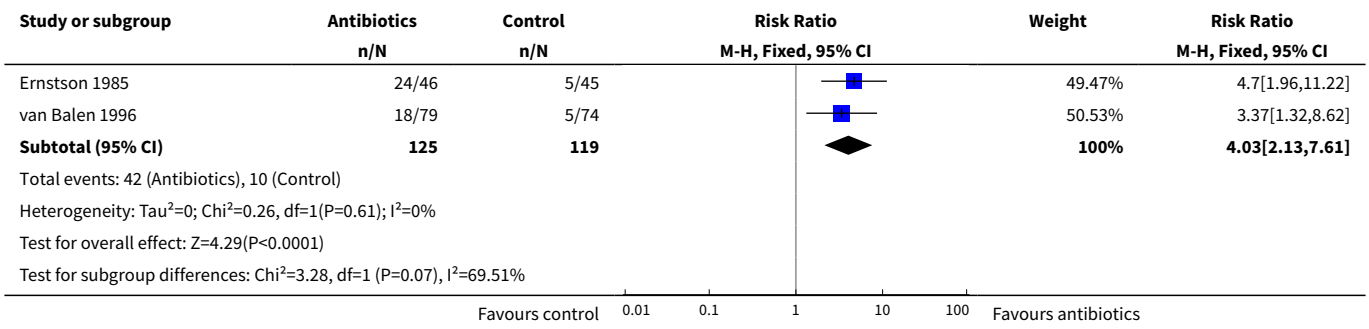
Analysis 2.4. Comparison 2 Sensitivity analysis - Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 4 Complete resolution of OME at more than 6 months.

Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Leach 2008	6/52	0/51		2.96%	12.75[0.74,220.7]
Otten 1990	31/73	16/68		97.04%	1.8[1.09,2.99]
Total (95% CI)	**125**	**119**		**100%**	**2.13[1.3,3.5]**
Total events: 37 (Antibiotics), 16 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.93, df=1(P=0.17); I^2=48.06%					
Test for overall effect: Z=2.98(P=0)					

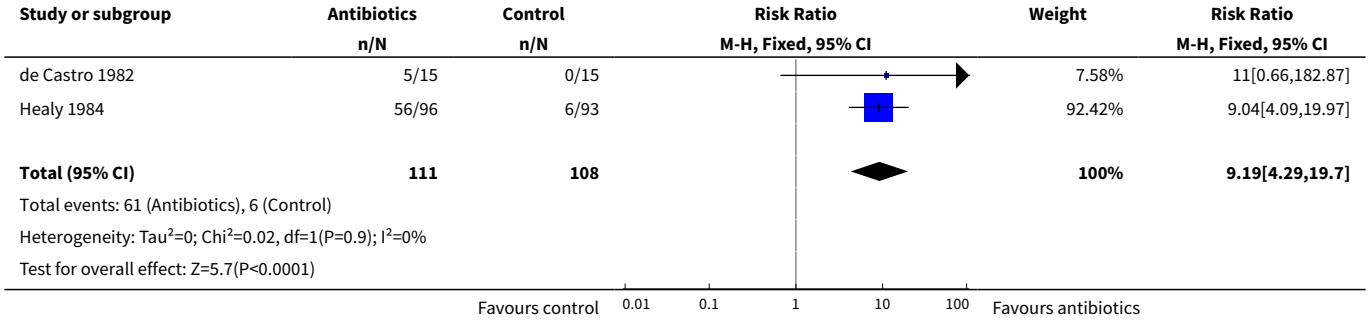


Analysis 2.5. Comparison 2 Sensitivity analysis - Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 5 Complete resolution of OME at end of treatment (10 to 14 days).

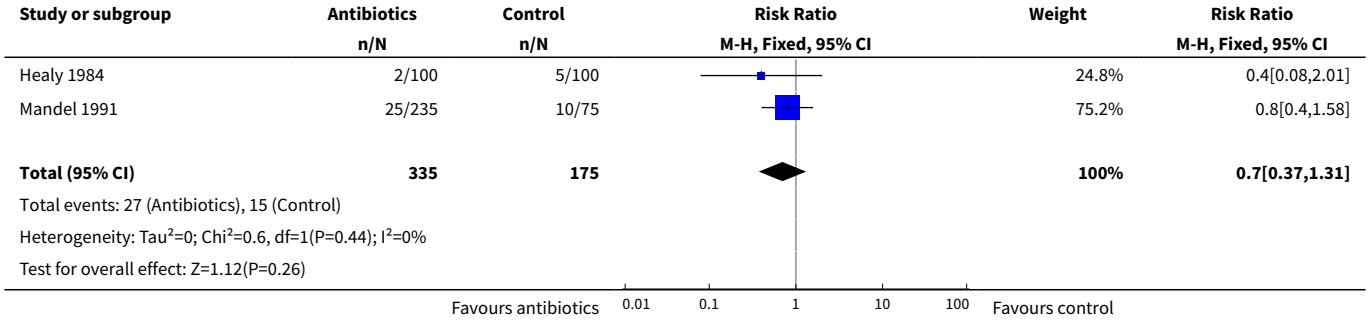
Study or subgroup	Antibiotics n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Duration of OME prior to study entry < 3 month					
Daly 1991	5/21	2/21		10.79%	2.5[0.54,11.48]
Mandel 1991	59/236	11/78		89.21%	1.77[0.98,3.2]
Subtotal (95% CI)	**257**	**99**		**100%**	**1.85[1.07,3.21]**
Total events: 64 (Antibiotics), 13 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=2.2(P=0.03)					
2.5.2 Duration of OME prior to study entry ≥ 3 months					



Analysis 2.6. Comparison 2 Sensitivity analysis - Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 6 Complete resolution of OME at end of treatment (4 weeks).



Analysis 2.7. Comparison 2 Sensitivity analysis - Antibiotics versus placebo, no treatment or therapy of unproven effectiveness, Outcome 7 AOM within 4 to 8 weeks.



ADDITIONAL TABLES

Table 1. Details of type and duration of antibiotic and control treatment used in the included trials

Type of antibiotic	N*	Treatment duration	N
Amoxicillin	6	10 to 14 days	15

Table 1. Details of type and duration of antibiotic and control treatment used in the included trials *(Continued)*

TMP-SMX	6	4 weeks	6
Amoxicillin/clavulanic acid	5	3 months	2
Cefaclor	3	6 months	2
Erythromycin-sulfisoxazole	2	—	—
Erythromycin	1	—	—
Sulfisoxazole	1	—	—
Azithromycin	1	—	—
Cefixime	1	—	—
Ceftibuten	1	—	—
Clarithromycin	1	—	—

* Numbers do not add up to 25 because some trials assessed the effect of multiple antibiotics.
TMP-SMX: trimethoprim-sulfamethoxazole

APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)
#1 MeSH descriptor Otitis Media with Effusion explode all trees #2 MeSH descriptor Ear, Middle explode all trees with qualifier: SE #3 glue NEXT ear OR otitis NEXT media NEAR effusion* OR middle NEXT ear NEAR effusion* OR nonsuppurative NEXT otitis OR non NEXT suppurative NEXT otitis #4 tympanitis OR serous NEXT otitis OR secretory NEXT otitis OR otitis NEXT serosa #5 mucoid NEAR otitis OR mucous NEAR otitis OR seromuco* NEAR otitis OR sero NEXT muco* NEAR otitis #6 mucoid NEAR middle NEXT ear OR mucous NEAR middle NEXT ear OR seromuc* NEAR middle NEXT ear #7 adhesive NEAR otitis OR exudative NEAR otitis #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #9 MeSH descriptor Anti-Bacterial Agents explode all trees #10 MeSH descriptor Antibiotic Prophylaxis explode all trees #11 MeSH descriptor Lactams explode all trees #12 MeSH descriptor Quinolones explode all trees #13 MeSH descriptor Macrolides explode all trees #14 antibiot* OR (anti NEXT biot*) OR antimicrobial* OR (anti NEXT microbial*) OR bacteriocid* OR antibacterial* OR (anti NEXT bacterial*)	("Otitis Media with Effusion"[Mesh]) OR ("Ear, Middle/secretion"[Mesh]) OR ("glue ear"[tiab] OR (otitis[tiab] AND media[tiab] AND effusion[tiab])) OR ((middle[ti] AND ear[ti] AND effusion*[ti]) OR "nonsuppurative otitis"[ti] OR "non suppurative otitis"[ti] OR tympanitis[ti] OR "serous otitis"[ti] OR "secretory otitis"[ti] OR "otitis serosa"[ti] OR (mucoid[ti] AND otitis[ti]) OR (mucous[ti] AND otitis[ti]) OR (seromuco*[ti] AND otitis[ti]) OR (sero[ti] AND muco*[ti] AND otitis[ti]) OR (mucoid[ti] AND middle[ti] AND ear[ti]) OR (mucous[ti] AND middle[ti] AND ear[ti]) OR (seromuc*[ti] AND middle[ti] AND ear[ti]) OR (adhesive[ti] AND otitis[ti]) OR (exudative[ti] AND otitis[ti]))) AND (macrolide*[tiab] OR erythromycin[tiab] OR erymax[tiab] OR erythrocin[tiab] OR erythroped[tiab] OR azithromycin[tiab] OR zithromax[tiab] OR clarithromycin[tiab] OR klaricid[tiab] OR telithromycin[tiab] OR sulfisoxazole[tiab] OR ketek[tiab] OR trimoxazole[tiab] OR septrin[tiab] OR trimethoprim[tiab] OR monotrim[tiab] OR trimopan[tiab] OR	1 exp *secretory otitis media/ 2 (glue and ear).tw. 3 (otitis and media and effusion).tw. 4 ((middle and ear and effusion*) or (nonsuppurative adj otitis) or (non adj suppurative adj otitis) or tympanitis or (serous adj otitis) or (secretory adj otitis) or (otitis adj serosa) or (mucoid and otitis) or (mucous and otitis) or (seromuco* and otitis) or (sero and muco* and otitis) or (mucoid and middle and ear) or (mucous and middle and ear) or (seromuc* and middle and ear) or (adhesive and otitis) or (exudative and otitis)).ti. 5 1 or 2 or 3 or 4 6 exp antibiotic agent/ 7 exp antibiotic agent/

(Continued)

#15 penicillin* OR amoxicillin OR ampicillin OR clavulanic acid OR amoxiclav OR augmentin OR ticarcillin OR timentin OR flucloxacillin OR fluampicil OR magnapen OR piperacillin OR tazocin
#16 cephalosporin* OR cefaclor OR distaclor OR cefadroxil OR baxan OR cefalexin OR ceporex OR keflex OR cefamandole OR kefadol OR cefazolin OR kefzol OR cefixime OR suprax OR cefotaxime OR claforan OR cefoxitin OR mefoxin OR cefpirome OR cefrom OR cefpodoxime OR orelox OR cefprozil OR cefzil OR cefradine OR velosel OR ceftazidime OR fortum OR kefadim OR ceftriaxone OR rocephin OR cefuroxime OR zinacef OR zinnat OR cefonicid OR aztreonam OR azactam OR imipenem OR cilastatin OR primaxin OR meropenem or meronem or tetracycline* or deteclo or demecleocyclin or ledermycin or doxycycline or vibramycin or minocycline or minocine or oxytetracycline or terramycin
#17 macrolide* OR erythromycin OR erymax OR erythrocin OR erythroped OR azithromycin OR zithromax OR clarithromycin OR klaricid OR telithromycin OR sulfisoxazole OR ketek OR trimoxazole OR septrin
#18 trimethoprim OR monotrim OR trimopan OR metronidazole OR flagyl OR metrolyl OR quinolone* OR ciprofloxacin OR ciproxin or phenoxymethylpenicillin OR sulfamethoxazole OR oxacillin OR cephalothin OR sulbactam OR ofloxacin OR clindamycin OR gentamycin OR vancomycin
#19 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 #8 AND #19

metronidazole[tiab] OR flagyl[tiab] OR metrolyl[tiab] OR quinolone*[tiab] OR ciprofloxacin[tiab] OR ciproxin[tiab] OR phenoxymethylpenicillin[tiab] OR sulfamethoxazole[tiab] OR oxacillin[tiab] OR cephalothin[tiab] OR sulbactam[tiab] OR ofloxacin[tiab] OR clindamycin[tiab] OR gentamycin[tiab] OR vancomycin)

8 (antibiot* or (anti and biot*) or antimicrobial* or (anti and microbial*) or bacteriocid* or antibacterial* or (anti and bacterial*) or penicillin* or amoxicillin or ampicillin or clavulanic or amoxiclav or augmentin or ticarcillin or timentin or flucloxacillin or fluampicil or magnapen or piperacillin or tazocin).tw.
9 (cephalosporin* or cefaclor or distaclor or cefadroxil or baxan or cefalexin or ceporex or keflex or cefamandole or kefadol or cefazolin or kefzol or cefixime or suprax or cefotaxime or claforan or cefoxitin or mefoxin or cefpirome or cefrom or cefpodoxime or orelox or cefprozil or cefzil or cefradine or velosel or ceftazidime or fortum or kefadim or ceftriaxone or rocephin or cefuroxime or zinacef or zinnat or cefonicid or aztreonam or azactam or imipenem or cilastatin or primaxin or meropenem or meronem or tetracycline* or deteclo or demecleocyclin or ledermycin or doxycycline or vibramycin or minocycline or minocine or oxytetracycline or terramycin).tw.
10 (macrolide* or erythromycin or erymax or erythrocin or erythroped or azithromycin or zithromax or clarithromycin or klaricid or telithromycin or sulfisoxazole or ketek or trimoxazole or septrin or trimethoprim or monotrim or trimopan or metronidazole or flagyl or metrolyl or quinolone* or ciprofloxacin or ciproxin or phenoxymethylpenicillin or sulfamethoxazole or oxacillin or cephalothin or sulbactam or ofloxacin or clindamycin or gentamycin or vancomycin or sulfisoxazole).tw.
11 7 or 8 or 9 or 10

(Continued)

		12 5 and 11
CINAHL (EBSCO)	**Web of Science (Web of Knowledge)**	**ICTRP**
#1 TS=((glue adj ear) OR (otitis AND media AND effusion)) #2 TI=((middle AND ear AND effusion*) OR (nonsuppurative adj otitis) OR (non adj suppurative adj otitis) OR tympanitis OR (serous adj otitis) OR (secretory adj otitis) OR (otitis adj serosa) OR (mucoid AND otitis) OR (mucous AND otitis) OR (seromuco* AND otitis) OR (sero AND muco* AND otitis) OR (mucoid AND middle AND ear) OR (mucous AND middle AND ear) OR (seromuc* AND middle AND ear) OR (adhesive AND otitis) OR (exudative AND otitis)) #3 TS=(antibiot* OR (anti AND biot*) OR antimicrobial* OR (anti AND microbial*) OR bacteriocid* OR antibacterial* OR (anti AND bacterial*) OR penicillin* OR amoxicillin OR ampicillin OR clavulanic OR amoxiclav OR augmentin OR ticarcillin OR timentin OR flucloxacillin OR fluampicil OR magnapen OR piperacillin OR tazocin) #4 TS=(cephalosporin* OR cefaclor OR distaclor OR cefadroxil OR baxan OR cefalexin OR ceporex OR keflex OR cefamandole OR kefadol OR cefazolin OR kefzol OR cefixime OR suprax OR cefotaxime OR claforan OR cefoxitin OR mefoxin OR cefpirome OR cefrom) #5 TS=(cefpodoxime OR orelox OR cefprozil OR cefzil OR cefradine OR velosel OR ceftazidime OR fortum OR kefadim OR ceftriaxone OR rocephin OR cefuroxime OR zinacef OR zinnat OR cefonicid OR aztreonam OR azactam OR imipenem OR cilastatin OR primaxin OR meropenem or meronem or tetracycline* or deteclo or demecleocyclin or ledermycin or doxycycline or vibramycin or minocycline or minocine or oxytetracycline or terramycin) #6 TS=(macrolide* OR erythromycin OR erymax OR erythrocin OR erythroped OR azithromycin OR zithromax OR clarithromycin OR klaricid OR telithromycin OR sulfisoxazole OR ketek OR trimoxazole OR septrin OR trimethoprim OR monotrim OR trimopan OR metronidazole OR flagyl OR metrolyl OR quinolone* OR ciprofloxacin OR ciproxin or phenoxymethylpenicillin OR sulfamethoxazole OR oxacillin OR cephalothin OR sulbactam OR ofloxacin OR clindamycin OR gentamycin OR vancomycin OR sulfisoxazole) #7 #2 OR #1 #8 #3 OR #4 OR #5 OR #6 #9 #7 AND #8	#1 TS=((glue adj ear) OR (otitis adj media adj effusion)) #2 TI=((middle AND ear AND effusion*) OR (nonsuppurative adj otitis) OR (non adj suppurative adj otitis) OR tympanitis OR (serous adj otitis) OR (secretory adj otitis) OR (otitis adj serosa) OR (mucoid AND otitis) OR (mucous AND otitis) OR (seromuco* AND otitis) OR (sero AND muco* AND otitis) OR (mucoid AND middle AND ear) OR (mucous AND middle AND ear) OR (seromuc* AND middle AND ear) OR (adhesive AND otitis) OR (exudative AND otitis)) #3 #1 OR #2 #4 TS=(antibiot* OR (anti AND biot*) OR antimicrobial* OR (anti AND microbial*) OR bacteriocid* OR antibacterial* OR (anti AND bacterial*) OR penicillin* OR amoxicillin OR ampicillin OR clavulanic OR amoxiclav OR augmentin OR ticarcillin OR timentin OR flucloxacillin OR fluampicil OR magnapen OR piperacillin OR tazocin) #5 TS=(cephalosporin* OR cefaclor OR distaclor OR cefadroxil OR baxan OR cefalexin OR ceporex OR keflex OR cefamandole OR kefadol OR cefazolin OR kefzol OR cefixime OR suprax OR cefotaxime OR claforan OR cefoxitin OR mefoxin OR cefpirome OR cefrom) #6 TS=(cefpodoxime OR orelox OR cefprozil OR cefzil OR cefradine OR velosel OR ceftazidime OR fortum OR kefadim OR ceftriaxone OR rocephin OR cefuroxime OR zinacef OR zinnat OR cefonicid OR aztreonam OR azactam OR imipenem OR cilastatin OR primaxin OR meropenem or meronem or tetracycline* or deteclo or demecleocyclin or ledermycin or doxycycline or vibramycin or minocycline or minocine or oxytetracycline or terramycin) #7 TS=(macrolide* OR erythromycin OR erymax OR erythrocin OR erythroped OR azithromycin OR zithromax OR clarithromycin OR klaricid OR telithromycin OR sulfisoxazole OR ketek OR trimoxazole OR septrin OR trimethoprim OR monotrim OR trimopan OR metronidazole OR flagyl OR metrolyl OR quinolone* OR ciprofloxacin OR ciproxin or phenoxymethylpenicillin OR sulfamethoxazole OR oxacillin OR cephalothin OR sulbactam OR ofloxacin OR clindamycin OR gentamycin OR vancomycin OR sulfisoxazole) #8 #7 OR #6 OR #5 OR #4 #9 #8 OR #3 #10 #8 AND #3	otitis AND media AND effusion OR glue AND ear OR middle AND ear AND effusion OR otitis AND secretory

WHAT'S NEW

Date	Event	Description
14 April 2016	New citation required but conclusions have not changed	In general, the results and conclusions regarding the benefits and harms of oral antibiotics for otitis media with effusion in children remain unchanged.
14 April 2016	New search has been performed	We updated the search on 14 April 2016. In the original version of our review 23 studies were included (van Zon 2012). In this 2016 update, we included one new study and excluded one study that was previously included on the basis that this was not a randomised controlled trial. We also included two trials that were previously excluded on the basis that they did not report on any outcomes of interest (according to new Cochrane standards), but these trials provided no relevant data for this review. This left 23 trials (3258 children) that reported on at least one of our outcomes of interest. We did not identify any ongoing trials. One new review author (Roderick Venekamp) joined the team to update this review.

CONTRIBUTIONS OF AUTHORS

Original version of the review (van Zon 2012):

Alice van Zon (AvZ): protocol development, selection of eligible studies, quality assessment of trials, data extraction, analyses and interpretation of data, and development of the final review.

Geert J van der Heijden (GJvdH): protocol development, analyses and interpretation of data, revision of the review and approval of the final content.

Thijs MA van Dongen (TMAvD): selection of eligible studies, quality assessment of trials and data extraction.

Martin J Burton (MJB): interpretation of data, revision of the review and approval of the final content.

Anne GM Schilder (AGMS): initiation of the review, protocol development, interpretation of data, revision of the review and approval of the final content.

2016 update of the review:

Roderick Paul Venekamp (RPV): selection of eligible studies, quality assessment of trials, data extraction, analyses and interpretation of data, and writing of the 2016 updated review

TMAvD: selection of eligible studies, quality assessment of trials, data extraction, interpretation of data, revision of the review and approval of the final content.

GJvdH, AvZ, MJB and AGMS: interpretation of data, revision of the review and approval of the final content.

DECLARATIONS OF INTEREST

AGMS has received an honorarium from GlaxoSmithKline for participating in educational activities and workshops related to pneumococcal vaccination and otitis media. She has received funds from GlaxoSmithKline for research on microbial pathogens in acute tympanostomy tube otorrhoea.

AGMS and MJB are Co-ordinating Editors of Cochrane ENT, but had no role in the editorial process for this review.

RPV is an Editor for the Cochrane Acute Respiratory Infections Group and Cochrane ENT, but had no role in the editorial process for this review.

TMAvD, AGMS and RPV were involved in research on microbial pathogens in acute tympanostomy tube otorrhoea, partly funded by GlaxoSmithKline.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

  Cochrane Review Incentive Award 2011 (original publication of review)
- National Institute for Health Research, UK.

  Infrastructure funding for Cochrane ENT

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Original version of the review (van Zon 2012 **):**

The following changes were made in the final version of the review:

Two co-authors, not mentioned in the protocol version, contributed to the review (TMAvD and MJB).

Types of participants

Although we planned to include only studies in which the clinical diagnosis of OME was made by a combination of otoscopy, tympanometry and/or audiometry, we decided to include studies using tympanometry alone or in combination with otoscopy.

Data synthesis

We planned to perform stratified analyses regarding the outcome complete resolution of OME. Due to thin data and large heterogeneity amongst the included studies, we could not present the results of these analyses.

2016 update of the review:

- A new review author (RPV) joined the team to update this review.
- In the original 2012 review, we included the following as a secondary outcome measure:

Partial or complete resolution of OME (partial or complete treatment success) at all possible time points defined as resolution of OME in the affected ear in children with unilateral OME at randomisation and resolution of OME in one or both ears in children with bilateral OME at randomisation; in either case, the diagnosis having been made by tympanometry alone or in combination with otoscopy.

We felt that partial improvement in the form of resolution of OME in one ear in a child with bilateral OME might be a clinical meaningful improvement. However, we found that this analysis did not contribute to the overall clinical implications of this review and made readability and interpretation more difficult. We therefore removed this outcome measure and the subsequent analyses based upon it.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Bacterial Infections [*drug therapy]; Hearing Loss [drug therapy] [prevention & control]; Otitis Media with Effusion [*drug therapy] [microbiology]; Randomized Controlled Trials as Topic; Time Factors; Treatment Outcome

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant