RevMan: review – intervention; 7673210803135753 79 (version 1.2.142)

Status: UNPUBLISHED DRAFT

Antibiotics for otitis media with effusion (OME) in children

Editors: Cochrane ENT Group

Contact Person: Samuel MacKeith (samuel.mackeith@ouh.nhs.uk)

ENT Department, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Caroline A Mulvaney[1]Kevin Galbraith[1]Katie E Webster[1]Mridul Rana[2]

Rachel Connolly[3]Tal Marom[4]Mat Daniel[5]Roderick P Venekamp[6]

Anne GM Schilder[7][8]Samuel MacKeith[9]

[1] Cochrane ENT, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK

[2] ENT Department, Frimley Health NHS Foundation Trust, Slough, UK

[3] National Institute for Health and Care Excellence, London, UK

[4] Department of Otolaryngology-Head and Neck Surgery, Samson Assuta Ashdod University Hospital, Ben Gurion University Faculty of Health Sciences, Ashdod, Israel

[5] Nottingham Children's Hospital, Nottingham, UK

[6] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

[7] evidENT, Ear Institute, University College London, London, UK

[8] NIHR UCLH Biomedical Research Centre, University College London, London, UK

[9] ENT Department, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

Citation

Mulvaney CA, Galbraith K, Webster KE, Rana M, Connolly R, Marom T, Daniel M, Venekamp RP, Schilder AGM, MacKeith S. Antibiotics for otitis media with effusion (OME) in children. Cochrane Database of Systematic Reviews TBD, Issue TBD. Art. No.: CD015254. DOI: 10.1002/14651858.CD015254.pub2.

Dates

Revision published: Issue TBD, TBD (TBD)

Version published (citation changed): Issue TBD, TBD (TBD)

Review first published: Issue TBD, TBD

Protocol first published: Issue 4, 2022

Abstract

Background

Otitis media with effusion (OME) is an accumulation of fluid in the middle ear cavity, common amongst young children. The fluid may cause hearing loss. When persistent, it may lead to developmental delay, social difficulty and poor quality of life. Management of OME includes watchful waiting, autoinflation, medical and surgical treatment. Antibiotics are sometimes used to treat any bacteria present in the effusion, or associated biofilms.

Objectives

To assess the efficacy (benefits and harms) of antibiotics for the treatment of otitis media with effusion in children.

Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Register; CENTRAL; Ovid MEDLINE; Ovid Embase; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished studies. The date of the search was 20 January 2023.

Selection criteria

We included randomised controlled trials and quasi-randomised trials in children aged 6 months to 12 years with unilateral or bilateral OME. We included studies that compared oral antibiotics with either placebo or no treatment.

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were determined following a multi-stakeholder prioritisation exercise and were: 1) hearing, 2) otitis media-specific quality of life and 3) anaphylaxis. Secondary outcomes were: 1) persistence of OME, 2) adverse effects, 3) receptive language skills, 4) speech development, 5) cognitive development, 6) psychosocial skills, 7) listening skills, 8) generic health-related quality of life, 9) parental stress, 10) vestibular function and 12) episodes of acute otitis media. We used GRADE to assess the certainty of evidence for each outcome.

Although we included all measures of hearing assessment, the proportion of children who returned to normal hearing was our preferred method to assess hearing, due to challenges in interpreting the results of mean hearing thresholds.

Main results

We identified 19 completed studies that met our inclusion criteria (2581 participants). They assessed a variety of antibiotics (including penicillins, cephalosporins, macrolides and trimethoprim), with most studies using a 10- to 14-day treatment course. Here we report our primary outcomes and main secondary outcome, at the longest reported follow-up time.

Antibiotics compared to placebo

We included 11 studies for this comparison, but no studies reported all of our outcomes of interest and limited meta-analysis was possible.

Hearing

One study found that more children returned to normal hearing by two months (resolution of the air-bone gap) after receiving antibiotics (Peto odds ratio (OR) 9.59, 95% confidence interval (CI) 3.51 to 26.18; 20/49 children who received antibiotics returned to normal hearing, compared to 0/37 who received placebo; 1 study; 86 participants; very low-certainty evidence).

Disease-specific quality of life

No studies assessed this outcome.

Presence/persistence of OME

At 6 to 12 months of follow-up, antibiotics may slightly reduce the number of children with persistent OME, but the confidence intervals were wide and the evidence is uncertain (risk ratio (RR) 0.89, 95% CI 0.68 to 1.17; 48% versus 54%; number needed to treat (NNT) 17; 2 studies; 324 participants; very low-certainty evidence).

Anaphylaxis

No studies provided specific data on anaphylaxis. Three of the included studies (448 children) did report adverse events in sufficient detail to assume that no anaphylactic reactions occurred (very low-certainty evidence).

Antibiotics compared to no treatment

We included eight studies for this comparison, but very limited meta-analysis was possible.

Hearing

One study found an increase in the proportion of children whose hearing returned to normal after 10 days of antibiotics (RR 4.70, 95% CI 1.96 to 11.22; 1 study; 91 participants; very low-certainty evidence). One further study found the mean difference in final hearing threshold at three months was -5.38 dB HL (95% CI -9.12 to -1.64; 1 study; 73 participants, low-certainty evidence).

Disease-specific quality of life

No studies assessed this outcome.

Presence/persistence of OME

Antibiotics may reduce the proportion of children who have persistent OME at up to three months of follow-up. Overall, the RR was 0.64 for those receiving antibiotics (95% CI 0.50 to 0.80, 6 studies; 542 participants, low-certainty evidence).

Anaphylaxis

No studies provided specific data on anaphylaxis. Two of the included studies (180 children) did report adverse events in sufficient detail to assume that no anaphylactic reactions occurred (very low-certainty evidence).

Authors' conclusions

The evidence for the use of antibiotics for OME is all of low or very low certainty. Although there may be a slight beneficial effect on the resolution of OME at up to three months, the impact on hearing is very uncertain. The impact of antibiotics in the longer term is also unclear. Few of the studies included in this review reported on potential harms from treatment. However, there are well-recognised adverse effects associated with the use of antibiotics, as well as concerns over antimicrobial resistance. These should be considered when weighing up the potential short-term benefits and harms of treatment in a condition with a high spontaneous resolution rate.

Plain language summary

Antibiotics for glue ear in children

Key messages

We are uncertain whether the use of antibiotics improves hearing for children with glue ear, due to a lack of robust evidence.

The use of antibiotics might slightly reduce the number of children who have glue ear at three months of follow-up. It is unclear whether this is a long-lasting effect, as few studies followed up children for more than three months.

The studies included in this review did not report serious harms from treatment with antibiotics. However, we know from other studies that antibiotics can cause unpleasant side effects, and occasionally cause severe allergic reactions.

What is OME?

Glue ear (or 'otitis media with effusion', OME) is a relatively common condition affecting young children. Fluid collects in the middle ear, which may cause hearing impairment. As a result of their poor hearing, children may be behind in their speech and may have difficulties at school.

How is OME treated?

Most of the time OME does not need any treatment and the symptoms will get better with time. In children with persistent OME, different treatments have been used, including medications or surgery (insertion of grommets (ventilation tubes), with or without adenoidectomy). Sometimes, bacteria are present in the fluid that collects in the middle ear. Antibiotics are sometimes used to try and get rid of these bacteria, and improve the symptoms of OME.

What did we want to find out?

We wanted to identify whether antibiotics are better than placebo (sham or dummy treatment), or no treatment, for children with OME.

We also wanted to see whether there are any unwanted effects associated with taking antibiotics for this condition.

What did we do?

We searched for studies that compared antibiotic treatment with either placebo or no treatment in children with OME. We compared and summarised the study results, and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We included 19 studies involving over 2500 children. Many different types of antibiotics were used and the duration of treatment varied a lot between the studies.

It is unclear whether antibiotics have any effect on hearing, as the evidence was not robust.

Antibiotics might slightly reduce the number of children who have OME after three months of follow-up. Only two studies looked at the number of children with OME after a longer follow-up time, so we are not certain whether this is a long-lasting effect, as OME may recur.

We do not know if treatment with antibiotics has any effect on quality of life, as none of the studies included in this review assessed this. We were also unable to find much evidence on the occurrence of anaphylaxis - a rare but very serious allergic reaction. None of the studies reported that any children suffered from anaphylaxis, but this may be was because no one had a reaction, or simply because the studies did not report this.

What are the limitations of the evidence?

As the evidence was uncertain, we cannot be sure if treatment with antibiotics gives any benefit for children with OME. As most of the studies were very short, we do not know if any effect of antibiotics would continue over longer time periods - even if OME appears to get better in the short term, it may recur.

How up-to-date is this evidence?

The evidence is up-to-date to January 2023.

Summary of findings

Summary of findings 1

Antibiotics compared to placebo for otitis media with effusion (OME) in children

Antibiotics compared to placebo for otitis media with effusion (OME) in children

Patient or population: children with otitis media with effusion (OME)
Setting: outpatient
Intervention: antibiotics
Comparison: placebo

Outcomes	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty of the evidence (GRADE)	What happens
		With placebo	With antibiotics	Difference		
Normal hearing (as complete improvement in air-bone gap in the worst ear) Follow-up: 2 months (short-term) № of participants: 86 (1 RCT)	Peto OR 9.59 (3.51 to 26.18)	Lower-risk population*			⊕⊖⊖⊖ Very low [1]	The evidence is very uncertain about the effect of antibiotics on return to normal hearing at 2 months, when compared to placebo.
		5.0%	33.5% (15.6 to 57.9)	28.5% more (10.6 more to 52.9 more)		
		Moderate-risk population*				
		11.0%	54.2% (30.3 to 76.4)	43.2% more (19.3 more to 65.4 more)		
		Higher-risk population*				
		15.0%	62.9% (38.2 to 82.2)	47.9% more (23.2 more to 67.2 more)		
Persistence of OME Follow-up: range 6 months to 12 months (medium-term) № of participants: 324 (2 RCTs)	RR 0.89 (0.68 to 1.17)	Study population			⊕⊖⊖⊖ Very low [2]	The evidence is very uncertain about the effect of antibiotics on persistence of OME at 6 to 12 months, when compared to placebo.
		54.0%	48.1% (36.7 to 63.2)	5.9% fewer (17.3 fewer to 9.2 more)		
Adverse event: anaphylaxis Follow-up: range 3 weeks to 12 months № of participants: 244 (3 RCTs)	Three trials that did not report the incidence of anaphylaxis directly did, however, provide sufficient information to reasonably assume there were no such cases. One trial reported that there were no unwanted side effects from the drug (antibiotic) itself(Thomsen 1989); one trial did not list anaphylaxis amongst adverse events that were reported as "probably or possibly related to active treatment" (Hemlin 1997); and one trial reported that "no infant was withdrawn as a result of direct adverse reaction due to medication" (Leach 2008).				⊕⊖⊖⊖ Very low [3]	The evidence is very uncertain about the risk of anaphylaxis.

*__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). Where there were zero events in the comparison group, the assumed risk in the comparison group was imputed from the same outcome comparing antibiotic with no treatment (Summary of findings table 2). This value was assumed to represent a 'moderate' control group event rate (CER), and values roughly 50% lower and higher are presented as 'lower' and 'higher' CERs respectively.

CI: confidence interval; **OR:** odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different

from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded by two levels for risk of performance detection and attrition bias. Downgraded by one level for imprecision as the optimal information size was not reached (< 300 events).

[2]Downgraded by one level for risk of bias, due to the potential for underestimating the prevalence of OME at six months. Participants with two normal examinations at < 6 months were not re-assessed, but were considered to have resolution of OME. Downgraded one level for inconsistency, as the studies showed opposite directions of effect. Downgraded by one level for indirectness, as a high risk population of children aged < 12 months contributed most of the weight in the analysis. Downgraded by one level for serious imprecision, as the optimal information size was not reached (< 300 events) and one decision threshold was crossed by the confidence interval (RR 0.80).

[3]Downgraded by three levels for extremely serious imprecision, as this was a narrative synthesis with zero events amongst 244 participants. We are unable to provide an estimate of the effect.

Summary of findings 2

Antibiotics compared to no treatment for otitis media with effusion (OME) in children

Antibiotics compared to no treatment for otitis media with effusion (OME) in children

Patient or population: children with otitis media with effusion (OME)
Setting: outpatient
Intervention: antibiotics
Comparison: no treatment

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without Antibiotic	With Antibiotics	Difference		
Return to normal hearing (10 days - very short-term) № of participants: 91 (1 RCT)	RR 4.70 (1.96 to 11.22)	11.1%	52.2% (21.8 to 100)	41.1% more (10.7 more to 113.6 more)	⊕⊖⊖⊖ Very low [1]	The evidence is very uncertain about the effect of antibiotics on return to normal hearing at 10 days, when compared with no treatment.
Final hearing threshold (3 months - short-term) № of participants: 73 (1 RCT)	—	The mean final hearing threshold was 14.1 dB	—	MD 5.38 dB lower (9.12 lower to 1.64 lower)	⊕⊕⊖⊖ Low [2]	The evidence suggests that antibiotics result in little to no difference in hearing threshold at 3 months when compared with no treatment.
Persistence of OME (up to 3 months) № of participants: 542 (6 RCTs)	RR 0.64 (0.50 to 0.80)	87.4%	55.9% (43.7 to 69.9)	31.5% fewer (from 43.7 fewer to 17.5 fewer)	⊕⊕⊖⊖ Low [3]	Antibiotics may reduce the proportion of children with persistent OME at up to 3 months when compared with no treatment.
Adverse event: anaphylaxis Follow-up: range 2 months to 3 months № of participants: 88 (2 RCTs)	Without referring directly to anaphylaxis, two studies reported that no subjects experienced adverse effects (Ardehali 2008; Marchisio 1998). It is unlikely, therefore, that any participants experienced anaphylaxis.				⊕⊖⊖⊖ Very low [4]	The evidence is very uncertain about the risk of anaphylaxis.

*__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; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded by two levels for risk of performance and detection bias. Downgraded by one level for serious imprecision as the optimal information size (OIS) was not reached (< 300 events).

[2]Downgraded by one level for a risk of performance bias. Downgraded by one level for serious imprecision as the OIS was not reached (< 400 participants).

[3]Downgraded by two levels for risk of performance and detection bias. Not downgraded for imprecision, as there was a common direction of effect, despite some inconsistency (I^2 = 72%).

[4]Downgraded by three levels for extremely serious imprecision, as this was a narrative synthesis with no events reported amongst only 88 children. No estimate of effect size could be calculated. We did not downgrade for risk of bias, as this is an objective outcome, unlikely to be influenced by performance bias.

Background

Description of the condition

Otitis media with effusion (OME) is a common condition in early childhood. The condition, also known as 'glue ear' and serous otitis media, is defined as "the presence of fluid in the middle ear without signs or symptoms of acute infection" (Rosenfeld 2016).

A key clinical feature of OME is hearing loss, due to decreased mobility of the tympanic membrane and consequent loss of sound conduction (Rosenfeld 2016). When hearing loss persists, this may affect speech and language development, and lead to behavioural problems in some children (NICE 2008). Other symptoms that may be attributable to OME include balance (vestibular) problems and ear discomfort (Rosenfeld 2016). When symptoms persist, they may lead to poor school performance and affect a child's daily activities, social interactions and emotions, possibly leading to a poorer quality of life for the child (Rosenfeld 2000).

It is thought that up to 80% of children have had OME by the age of four years, but a decline in prevalence is observed for children beyond six years of age (Williamson 2011). Most episodes of OME in children resolve spontaneously within three months, however approximately 35% of children will have more than one episode of OME and, furthermore, 5% to 10% of episodes will last for more than a year (Rosenfeld 2016). Children with OME following an episode of untreated AOM have a 59% rate of resolution by one month rising to 74% by three months, while children with newly diagnosed OME of unknown duration demonstrate a resolution rate of 28% by three months and up to 42% by six months (Rosenfeld 2003). The condition is more prevalent in children with Down syndrome or cleft palate (Flynn 2009; Maris 2014). Atopy has been considered a potential risk factor for OME in children (Kreiner-Møller 2012; Marseglia 2008; Zernotti 2017).

Diagnosis of OME is typically by clinical examination including (pneumatic) otoscopy and/or tympanometry in primary care. Following diagnosis, there will often be a period of active observation, for at least three months. During the observation period the care provider may offer a non-surgical intervention such as hearing aids or autoinflation. The National Institute for Health and Care Excellence (NICE) and the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) do not currently recommend the use of antibiotics, antihistamines, decongestants or corticosteroids for OME as there is insufficient evidence to suggest that they are effective treatments (NICE 2008; Rosenfeld 2016). If OME has not resolved within the three-month observation period, the child may be referred for further management/active intervention. This may include hearing aid

provision or review by an ENT surgeon for consideration for myringotomy, ventilation tubes insertion and/or adenoidectomy. The choice of active intervention varies considerably. Earlier active intervention may be considered for children at increased risk of developmental difficulties (see Rosenfeld 2016 for a list of 'at-risk' factors).

This Cochrane Review focusses on antibiotics as a treatment for OME in children. This review forms part of a suite of five reviews of OME treatment, which will address those interventions identified in a prioritisation exercise as being most important and in need of up-to-date Cochrane Reviews, namely ventilation tubes, adenoidectomy with or without ventilation tubes, autoinflation, topical and oral steroids, and antibiotics (Cochrane ENT 2020).

Description of the intervention

The rationale for using antibiotics is to treat the bacteria that are identified in the middle ear fluid of approximately one-third of children with OME (Park 2004; Poetker 2005), and/or bacterial biofilms that are present even more frequently (Daniel 2012). Studies of antibiotics of any type and duration will be included in this review.

How the intervention might work

A bacterial pathogen has been identified in the middle ear fluid of approximately a third of all children with OME (Poetker 2005), and bacterial biofilms have been implicated in the aetiology of OME (Daniel 2012; Seppanen 2020), thus treatment of the infection by antibiotics offers a promising non-surgical intervention. If antibiotics successfully eliminate the bacteria, this may more speedily resolve the problem of middle ear fluid and its sequelae observed in children with OME (Venekamp 2016). However, not all cases of OME are of bacterial origin and thus the potential benefits of antibiotics must be weighed against the adverse effects of antibiotics and possible risk of bacterial resistance (Venekamp 2016).

Why it is important to do this review

A Cochrane Review assessing the use of antibiotics to treat OME was published in 2016 (Venekamp 2016). The review excluded children with pre-existing or past ventilation tubes, cleft palate or Down syndrome and included 25 randomised controlled trials (RCTs). The Cochrane authors concluded that oral antibiotics are associated with an increased chance of complete resolution of OME at two to three months post-randomisation (moderate-quality evidence). However, there was a higher incidence of adverse effects associated with antibiotics, such as diarrhoea, vomiting or skin rash. The review authors found uncertain evidence for improvements in short-term hearing, and did not find evidence that children treated with antibiotics had fewer ventilation tube insertions. They found no data on outcomes such as speech, language and cognitive development, or quality of life.

A scoping search undertaken in 2020 identified three abstracts of studies of antibiotics for OME published since the Cochrane Review (Venekamp 2016), although these do not appear to be RCTs. A prioritisation exercise undertaken in 2020 identified a review of antibiotics for OME in children as a top priority (Cochrane ENT 2020). Given the potentially promising findings of the Cochrane Review and the recommendations by international guidelines against the use of antibiotics to treat OME in children, it is timely to update the evidence.

Objectives

To assess the effects (benefits and harms) of oral antibiotics for otitis media with effusion (OME) in children.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-randomised trials (where trials were designed as RCTs, but the sequence generation for allocation of treatment used methods such as alternative allocation, birth dates or alphabetical order). We included studies that randomised by participant or by cluster.

Types of participants

The population of interest is children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion. If a study included children aged younger than 6 months and older than 12 years, we only included the study if the majority of children fitted our inclusion criteria, or if the authors presented outcome data by age group. We included all children regardless of any comorbidity, such as Down syndrome or cleft palate. The clinical diagnosis of OME was confirmed by oto(micro)scopy or tympanometry, or both.

Types of interventions

Intervention

Antibiotics of all types and courses of duration.

Comparator

We were interested in the following two comparisons:

- oral antibiotics versus placebo;
- oral antibiotics versus no treatment.

If study participants received other treatments, for example intranasal steroids, oral steroids, mucolytics or decongestants, we included these studies if both arms received identical treatment.

We excluded studies in which one antibiotic was compared with another, or studies comparing one dose of an antibiotic to a different dose of the same antibiotic.

Types of outcome measures

We analysed the following outcomes in the review, but we did not use them as a basis for including or excluding studies. We assessed all outcomes at very short term (< 6 weeks for adverse events), short term (≤ 3 months), medium term (> 3 months to ≤ 1 year) and long term (> 1 year).

Primary outcomes

- Hearing:
    - Proportion of children whose hearing has returned to normal, with normal hearing defined as 20 dB HL or less (assessed using age-appropriate tests).
    - Hearing threshold.

It was anticipated that study data for these outcomes may be derived from a variety of assessment methods. To avoid loss of important evidence, we extracted all such data for analysis. However, we gave consideration to the appropriateness of pooling different types of data in meta-analysis. Our selection of primary outcomes was based principally upon clinical importance, but also permitted applicability across a variety of age-appropriate assessment methods and considered the types of outcome data that are most likely to be available. Accordingly, we regard the proportion of participants whose hearing has returned to normal as the most important measure of hearing impact. We considered medium- and long-term outcome data as the most clinically important.

- Disease-specific quality of life measured using a validated instrument, for example:

    - OM8-30 (Haggard 2003);
    - Otitis Media-6 (Rosenfeld 1997).
- Adverse events - anaphylactic reaction.

Secondary outcomes

- Presence/persistence of OME.
- Adverse events - measured by the number of participants affected.
    - Tympanic membrane changes, such as:
        - atrophy;
        - atelectasis or retraction;
        - persistent perforation;
        - myringosclerosis;
        - tympanosclerosis.
    - Patient-related, such as:
        - vomiting;
        - diarrhoea;
        - dry throat;
        - nasal stinging;
        - cough;
        - long-term hearing loss;
        - postsurgical haemorrhage;
        - pain.
- Receptive language skills, measured using a validated scale, for example:
    - Peabody Picture Vocabulary Test - Revised (Dunn 2007);
    - relevant domains of the Reynell Developmental Language Scales (Reynell 1985);
    - relevant domains of the Preschool Language Scale (PLS) (Zimmerman 1992);
    - relevant domains of the Sequenced Inventory of Communication (SCID) (Hedrick 1984).
- Speech development, or expressive language skills, measured using a validated scale, for example:
    - Schlichting test (Schlichting 2010);
    - Lexi list (Schlichting 2007);
    - relevant domains of the Reynell Developmental Language Scales (Reynell 1985);
    - relevant domains of the PLS (Zimmerman 1992);
    - relevant domains of the SCID (Hedrick 1984).
- Cognitive development, measured using a validated scale, for example:
    - Griffiths Mental Development Scales (Griffiths 1996);
    - McCarthy General Cognitive Index (McCarthy 1972);
    - Bayley Scales of Infant and Toddler Development (Bayley 2006).
- Psychosocial outcomes, measured using a validated scale, for example:
    - the Social Skills Scale of the Social Skills Rating System (Gresham 1990);

    - Child Behavior Checklist (Achenbach 2011);
    - Strengths and Difficulties Questionnaire (Goodman 1997);
    - Pediatric Symptom Checklist (Jellinek 1988).
- Listening skills, for example listening to stories and instructions effectively. Given that there are few validated scales to assess listening skills in children with OME, we will include any methods used by trialists.
- Generic health-related quality of life assessed using a validated instrument, for example:
    - EQ-5D (Rabin 2001);
    - TNO AZL Children's QoL (TACQOL) (Verrips 1998);
    - TNO AZL Pre-school children QoL (TAPQOL) (Fekkes 2000);
    - TNO AZL Infant Quality of Life (TAIQOL) (TNO 1997);
    - Infant Toddler Quality of Life Questionnaire (ITQOL) (Landgraf 1994);
    - Child Health Questionnaire (CHQ) (Landgraf 1996).
- Parental stress, measured using a validated scale, for example:
    - Parenting Stress Index (Abidin 1995).
- Vestibular function:
    - balance;
    - co-ordination.
- Number of doctor-diagnosed AOM episodes within a specified time frame.

These outcomes were identified as the most important in two studies that aimed to develop a core outcome set for children with OME (Bruce 2015; Liu 2020). As this review forms part of a suite of reviews of interventions for OME, not all outcomes are relevant for all reviews.

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. We contacted original authors for clarification and further data if trial reports were unclear, and we arranged translations of papers where necessary. The date of the search was 20 January 2023.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Register (searched via the Cochrane Register of Studies to 20 January 2023);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (searched via the Cochrane Register of Studies to 20 January 2023);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 20 January 2023);
- Ovid EMBASE (1974 to 20 January 2023);
- Web of Science, Web of Science (1945 to 20 January 2023);
- ClinicalTrials.gov, www.clinicaltrials.gov:
    - searched via the Cochrane Register of Studies to 20 January 2023;
    - searched via www.clinicaltrials.gov to 20 January 2023;

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), https://apps.who.int/trialsearch/:
    - searched via the Cochrane Register of Studies to 20 January 2023;
    - searched via https://apps.who.int/trialsearch/ to 20 January 2023.

The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. The search strategies were designed to identify all relevant studies for a suite of reviews on various interventions for otitis media with effusion. 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 Technical Supplement to Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1) (Lefebvre 2020). 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. The Information Specialist also ran non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

We did not perform a separate search for adverse effects. We considered adverse effects described in included studies only.

Data collection and analysis

Selection of studies

The Cochrane ENT Information Specialist used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components:

1. Known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as 'a RCT' or as 'not a RCT'.
2. The machine learning classifier (RCT model) (Wallace 2017), available in the Cochrane Register of Studies (CRS-Web), which assigns a probability of being a true RCT (from 0 to 100) to each citation. For citations that are assigned a probability score below the cut-point at a recall of 99% we will assume these to be non-RCTs. For those that score on or above the cut-point we will either manually dual screen these results or send them to Cochrane Crowd for screening.
3. Cochrane Crowd is Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. For more information about Screen4Me and the evaluations that have been done, please go to the Screen4Me website on the Cochrane Information Specialist's portal and see Marshall 2018; McDonald 2017; Noel-Storr 2018; Thomas 2017.

Two review authors (KG, CM) independently screened titles and abstracts retrieved by the search to identify potentially relevant studies. At least two review authors (of KG, CM, SM) then independently evaluated the full text of each potentially relevant study to determine whether it met the inclusion/exclusion criteria for this review. Any differences were resolved by discussion and consensus, with the involvement of a third author (KW) where necessary.

Screening eligible studies for trustworthiness

Two review authors (of KG, CM, MR, RV, KW) appraised all studies meeting our inclusion criteria for trustworthiness using a screening tool developed by Cochrane Pregnancy and Childbirth. This tool includes specified criteria to identify studies that are considered sufficiently trustworthy to be included in the review (see Appendix 2 and Figure 1). For any studies assessed as being potentially 'high risk', we attempted to contact the study

authors to obtain further information or address any concerns. We had planned to exclude these studies from the review if we were unable to contact the authors, or there was persisting uncertainty about the study. However, when using the trustworthiness tool, there were only four studies where we had no concerns (Leach 2008; Mandel 1987; Mandel 1991; van Balen 1996).

All the remaining studies had at least some concerns - although this was often due to a paucity of information, rather than a specific concern over trustworthiness:

- Balle 1990; Endo 1997; Ernston 1985; Hemlin 1997; Karlidag 2002; Manrique 1987; Marchisio 1998; Møller 1990; Podoshin 1990; Puhakka 1985; Sundberg 1984 and Thomsen 1989 all reported few (or no) baseline characteristics for the participants included in the study. We were therefore unable to assess whether there was excessive similarity between the randomised groups.
- Three studies recruited identical numbers of participants to each group, without a description of blocked randomisation (Ardehali 2008; Chen 2013; Healy 1984), and two studies did not clearly report the numbers allocated to each group (Møller 1990; Podoshin 1990).
- The number of participants lost to follow-up was known (or appeared) to be zero for four trials, without adequate explanation (Ardehali 2008; Endo 1997; Karlidag 2002; Puhakka 1985).
- Finally, we were unable to identify prospective trial registration for one recently published study (Chen 2013).

We were unsure whether this high level of studies with concerns reflected a genuine problem with the data from these studies, or whether the assessment tool was perhaps too sensitive. We note that this tool - and others used for the same purpose - has not yet been validated.

Consequently, we decided to include all studies in the main analyses of this review, but we did investigate the effect of excluding studies with concerns over trustworthiness on the overall results (see Sensitivity analysis).

Data extraction and management

At least two review authors (of KG, CM, MR, RV, KW) independently extracted outcome data from each study using a standardised data collection form. Where a study had more than one publication, we retrieved all publications to ensure complete extraction of data. Any discrepancies in the data extracted by the two authors were checked against the original reports, and differences were resolved through discussion and consensus, with recourse to a third author where necessary. If required, we contacted the study authors for clarification. We included key characteristics of the studies, such as the study design, setting, sample size, population and the methods for defining or collecting outcome data in the studies.

We extracted data on study findings according to treatment assignment, irrespective of whether study participants complied with treatment or received treatment to which they were randomised.

In addition to extracting pre-specified information about study characteristics and aspects of methodology relevant to risk of bias, we extracted the following summary statistics for each study and outcome:

- For continuous data: the mean values, standard deviation and number of patients for each treatment group at the different time points for outcome measurement. Where endpoint data were not available, we extracted the values for change-from-baseline data instead. If values for the individual treatment groups were not reported, where possible we extracted summary statistics (e.g. mean difference) from the studies.
- For binary data: we extracted information on the number of participants experiencing an event, and the number of participants assessed at that time point. If

values for the individual treatment groups were not reported, where possible we extracted summary statistics (e.g. risk ratio) from the studies.

- For ordinal scale data: we did not include any data from an ordinal scale in this review.

We pre-specified time points of interest for the outcomes in this review. Where studies reported data at multiple time points, we took the longest available follow-up point within each of the specific time frames. For example, if a study reported an outcome at 4 months, 8 months and 12 months of follow-up, then the 12-month data are included for the time point > 3 months to ≤ 1 year.

Assessment of risk of bias in included studies

Two authors (of KG, CM, MR, RV, KW) undertook assessment of the risk of bias of the included studies independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We used the Cochrane risk of bias tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the study and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

We summarised dichotomous data - such as presence of OME - as risk ratios (RR) and 95% confidence intervals (CI), and we summarised continuous data as a mean difference (MD) and 95% CI. For the outcomes presented in the summary of findings tables, we also provide both the relative and absolute measures of effect.

Unit of analysis issues

For this review we anticipated that the unit of analysis would be the child. However, some studies reported findings by ear, and therefore we have used both the child and ear as the unit of analysis.

All studies randomised participants to antibiotics or no treatment/placebo at the level of the child - as this is an intervention that affects both ears. Some studies in this review included children with bilateral OME - either exclusively (Endo 1997; Møller 1990), or as a proportion of included participants (Balle 1990; Ernston 1985; Hemlin 1997; Manrique 1987; Sundberg 1984; Thomsen 1989). This gave rise to a number of issues regarding the unit of analysis, as some studies reported outcomes (particularly the persistence of OME) for each ear.

We considered that outcomes for ears within the same individual were likely to be correlated - for example, if a child had resolution of OME in one ear, they may be more likely to experience resolution in the contralateral ear. Ears of the same individual are not independent. Standard meta-analysis techniques assume that all data are independent. Therefore, inclusion of the raw data (for the number of ears) is likely to overestimate the precision of any effect, and result in an excessively narrow confidence interval.

To account for this correlation, we used the suggested methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011), which are more commonly employed in the analysis of cluster-randomised trials. We treated individuals who contributed two ears to the analysis (all of those with bilateral disease) as a 'cluster' of two data points. We then attempted to account for the correlation in these clusters, by

assuming a certain correlation between ears of the same individual. We could not identify a figure for this correlation in the published literature, so we used an estimated correlation of 0.5 in the main analysis, but conducted sensitivity analyses using correlations of 0 and 1, to test the limits of this assumption. We then reduced the effective size of the trials by the 'design effect' - which accounts for correlation between ears, and the average cluster size (which would be 2 for trials where all children had bilateral disease, and less than 2 if trials included a mixture of children with bilateral and unilateral disease).

Dealing with missing data

We attempted to contact study authors by email where data on an outcome of interest to the review were not reported, but the methods described in the paper suggested that the outcome was assessed. We did the same if not all data required for meta-analysis were reported. If standard deviation data were not available, we approximated these using the standard estimation methods from P values, standard errors or 95% CIs (if these are reported), as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the included studies for potential differences between them in the types of participants recruited, interventions or controls used, and the outcomes measured. We assessed statistical heterogeneity by considering both the I^2 statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance (with values over 50% suggesting substantial heterogeneity) and the P value from the Chi^2 test (Higgins 2021).

Assessment of reporting biases

We assessed reporting bias as within-study outcome reporting bias and between-study publication bias.

Outcome reporting bias (within-study reporting bias)

We assessed within-study reporting bias by comparing the outcomes reported in the published report against the study protocol or trial registry, whenever this could be obtained. If the protocol or trial registry entry was not available, we compared the outcomes reported to those listed in the methods section. If results are mentioned but not reported adequately in a way that allows analysis (e.g. the report only mentions whether the results were statistically significant or not), bias in a meta-analysis is likely to occur. We then sought further information from the study authors. If no further information could be found, we noted this as being a 'high' risk of bias when the risk of bias tool is used. If there was insufficient information to judge the risk of bias we noted this as an 'unclear' risk of bias (Handbook 2011).

Publication bias (between-study reporting bias)

We planned to produce a funnel plot to explore possible publication biases, if we were able to pool 10 or more studies in a single analysis. However, this was not possible, as too few studies were included in the meta-analyses.

Data synthesis

Where two or more studies reported the same outcome we performed a meta-analysis using Review Manager 5 (RevMan 2014). We report pooled effect measures for dichotomous outcomes as a risk ratio (RR) using the Mantel-Haenszel methods. For continuous outcomes measured using the same scales we report the mean difference (MD). We used a random-effects model.

Where it was not possible to pool the findings from studies in a meta-analysis, we have presented the results of each study and provide a narrative synthesis of findings.

Subgroup analysis and investigation of heterogeneity

We proposed the following subgroup analyses if sufficient data were available in study reports:

- children with mild hearing loss versus moderate or worse;
- children with allergy versus those without (using the trialists' own definition);
- children aged up to four years versus children aged four years and over;
- children with previous ventilation tubes versus those without ventilation tubes;
- children with cleft palate versus children without;
- children with Down syndrome versus children without.

However, we did not find any data suitable for conducting these subgroup analyses. No studies provided subgroup data for children with different features (for example, for those with mild hearing loss, compared to those with moderate or worse hearing loss). Many of the trials did not provide sufficient background information (for example on hearing level) for us to conduct subgroup analysis at the level of the individual study. Where data were provided, trials often recruited a mixed population that encompassed all subgroups (for example, most trials recruited children aged 1 to 12 years, not specifically children aged < 4 years, or ≥ 4 years).

Sensitivity analysis

All pre-specified sensitivity analyses are reported in Table 1.

According to our protocol, we carried out sensitivity analyses to assess whether the results of a fixed-effect model were notably different to those from a random-effects model.

We also planned to conduct a sensitivity analysis to exclude studies at high risk of bias (with four or more domains rated as high risk, using the risk of bias tool). This applied to a single study (Ernston 1985).

Where possible, we also carried out sensitivity analyses to assess the impact of excluding studies that had any concerns when using the Trustworthiness Screening tool.

Two studies reported hearing data separately for right and left ears. We pooled these data for analysis, and made adjustments to account for the correlation between ears of the same individual. We were unable to identify a published correlation coefficient, therefore for the main analysis we assumed correlation of 0.5 between ears of the same individual, but tested this assumption using correlation coefficients of 0.3 and 0.7 in a sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

Two independent authors (KG, CM) used the GRADE approach to rate the overall certainty of evidence using GRADEpro GDT (https://gradepro.org/). The certainty of evidence reflects the extent to which we are confident that an estimate of effect is correct, and we applied this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high certainty of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low certainty implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high certainty. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. 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.

When assessing imprecision, we used a minimally important difference of a risk ratio (or odds ratio) of 0.8 or 1.25 for dichotomous outcomes. For most continuous data we considered a minimally important difference to be half of the standard deviation for the control/comparator group. The exception to this was hearing thresholds, where a difference of 10 dB HL was used as the minimally important difference.

We have included a summary of findings table, constructed according to the recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), for the following comparisons:

- oral antibiotics versus placebo;
- oral antibiotics versus no treatment.

We prioritised the following four outcomes for the summary of findings tables:

- hearing;
- disease-specific quality of life;
- presence/persistence of OME;
- adverse events - anaphylactic reaction.

Results

Description of studies

Results of the search

The searches (January 2023 and September 2021) retrieved a total of 7441 records. This reduced to 4157 after the removal of duplicates. The Cochrane ENT Information Specialist sent all 4157 records to the Screen4Me workflow. The Screen4Me workflow identified 68 records as having previously been assessed: 50 had been rejected as not RCTs and 34 had been assessed as possible RCTs. The RCT classifier rejected an additional 1514 records as not RCTs (with 99% sensitivity). The Cochrane Crowd assessed the remaining 2443 references, rejecting 1313 as not RCTs and identifying 1130 as possible RCTs. Following this process, the Screen4Me workflow had rejected 2877 records and identified 1280 possible RCTs for title and abstract screening.

	Possible RCTs	Rejected
Known assessments	34	50
RCT classifier	2559	1514
Cochrane Crowd	1130	1313
Total	1280	2877

We identified 76 additional duplicates. We screened the titles and abstracts of the remaining 1204 records. We discarded 886 records and assessed 318 full-text records. We subsequently discarded an additional 240 records and identified an additional five duplicates.

We excluded 49 records (linked to 41 studies) with reasons recorded in the review (see Excluded studies).

We included 19 studies (23 records) where results were available (Ardehali 2008; Balle 1990; Chen 2013; Endo 1997; Ernston 1985; Healy 1984; Hemlin 1997; Karlidag 2002; Leach 2008; Mandel 1987; Mandel 1991; Manrique 1987; Marchisio 1998; Møller 1990; Podoshin 1990; Puhakka 1985; Sundberg 1984; Thomsen 1989; van Balen 1996).

We identified two studies that remain in awaiting assessment because we did not have enough information to determine eligibility (Koay 1998; Tawfik 2002).

A flow chart of study retrieval and selection is provided in Figure 2.

Included studies

A full description of each included study is given in Characteristics of included studies, and a summary of the main features of all studies is shown in Table 2.

Study design

All the included studies were described as randomised controlled trials.

Participants

Most of the studies recruited children aged from approximately 2 to 12 years, with bilateral or unilateral OME. One study included participants of mixed ages, but we were only able to use the data for children aged < 2 years (as older children received a different intervention; Endo 1997).

Many, but not all, studies required participants to have a diagnosis of OME that had persisted for at least three months (Ardehali 2008; Balle 1990; Ernston 1985; Hemlin 1997; Manrique 1987; Marchisio 1998; Møller 1990; Sundberg 1984; Thomsen 1989; van Balen 1996). One study required the persistence of OME for at least six weeks (Healy 1984), and another for two months (Podoshin 1990). A single study specifically recruited individuals with short duration of symptoms (< 3 months; Chen 2013), whilst the remainder did not specify the duration of OME.

Few studies provided information on the extent of hearing impairment at baseline.

Interventions and comparisons

Comparison 1: antibiotics versus placebo

We identified 11 studies for this comparison (Balle 1990; Endo 1997; Hemlin 1997; Leach 2008; Mandel 1987; Mandel 1991; Møller 1990; Podoshin 1990; Puhakka 1985; Thomsen 1989; van Balen 1996). However, Balle 1990 does not provide data for any outcomes of interest to this review.

A number of different antibiotics were used, including:

- Penicillins
    - Amoxicillin (Leach 2008; Mandel 1987; Mandel 1991; Podoshin 1990).
    - Co-amoxiclav (Balle 1990; Thomsen 1989; van Balen 1996).
- 2nd or 3rd generation cephalosporins
    - Cefaclor (Mandel 1991).
    - Cefixime (Hemlin 1997).
    - Ceftibuten (Marchisio 1998).
- Macrolides
    - Erythromycin (Møller 1990).
    - Erythromycin and sulfisoxazole (Mandel 1991).
- Trimethoprim and sulfamethoxazole (Endo 1997) or trimethoprim and sulfadizine (Puhakka 1985).

Most studies provided antibiotic treatment for 10 to 14 days, although some required a longer course (28 to 30 days: Balle 1990; Endo 1997; Thomsen 1989) and one used treatment for 24 weeks (Leach 2008). Three studies assessed outcomes as soon as the antibiotics were stopped (Endo 1997; Leach 2008; van Balen 1996). Four studies assessed outcomes approximately two weeks after stopping antibiotics (Hemlin 1997; Mandel 1987; Mandel 1991; Møller 1990), and the remaining four studies had a delay of approximately six to eight weeks before assessing outcomes (Marchisio 1998; Podoshin 1990; Puhakka 1985; Thomsen 1989).

Comparison 2: antibiotics versus no treatment

We identified eight studies for this comparison (Ardehali 2008; Chen 2013; Ernston 1985; Healy 1984; Karlidag 2002; Manrique 1987; Marchisio 1998; Sundberg 1984). However, Sundberg 1984 does not provide data for any outcomes of interest to this review.

A number of different antibiotics were used, including:

- Penicillins
    - Amoxicillin (Manrique 1987).
    - Co-amoxiclav (Ardehali 2008).
    - Ampicillin and sulbactam (Karlidag 2002).
- 2nd or 3rd generation cephalosporins
    - Cefaclor (Ernston 1985).
- Macrolides
    - Erythromycin (Sundberg 1984).
    - Clarithromycin (Chen 2013).
- Trimethoprim and sulfamethoxazole (Healy 1984).

The duration of treatment varied from a minimum of 8 or 10 days (Ernston 1985; Manrique 1987; Sundberg 1984) to a maximum of three months (Ardehali 2008). Follow-up was typically at the end of the treatment (immediately after antibiotics were discontinued), except for Chen 2013 (5 to 12 weeks of treatment, follow-up at 12 weeks) and Manrique 1987 (eight days of treatment, follow-up at three months).

Outcomes

Hearing

Return to normal hearing

As with other reviews in this suite, few studies reported our preferred outcome measure for hearing - the proportion of children in whom hearing returns to normal. This outcome was only measured by two studies. Podoshin 1990 reported the proportion of children in whom there was complete resolution of the air-bone gap in the worst affected ear, after two months of follow-up. Ernston 1985 reported the proportion of children in whom "hearing thresholds returned to normal", but did not provide a definition of normal hearing.

Final hearing thresholds or change in hearing threshold

Two studies assessed speech reception thresholds (Mandel 1987; Mandel 1991); one of these also assessed speech awareness thresholds for younger children (Mandel 1987). One study reported the mean air-bone gap after three months of follow-up (Chen 2013).

Disease-specific quality of life

We did not identify any studies that assessed disease-specific quality of life.

Anaphylaxis

None of the studies included in this review specifically reported on the occurrence of anaphylaxis. However, five studies did provide some information which suggested that no anaphylactic reactions had occurred (Ardehali 2008; Hemlin 1997; Leach 2008; Marchisio 1998; Thomsen 1989).

Persistence of OME

We noted that there was some variation in how the outcome 'presence or persistence of OME' was assessed and reported. Most studies reported on clearance or resolution of OME - i.e. the number of participants with no evidence of OME in either ear at follow-up. Many studies included participants with both bilateral and unilateral disease.

Consequently, for those with bilateral disease, this would only include children in whom both ears had resolved.

For the majority of studies we were therefore able to identify the proportion of participants in each in whom *at least one ear* had persistent OME at the follow-up time - both ears were assessed in every participant. However, some studies reported this outcome slightly differently:

- Two studies only assessed the ear(s) that had been affected at the start of the trial (Healy 1984; Marchisio 1998). Both ears were assessed for those with bilateral disease, but for those with unilateral disease only one ear was checked at follow-up - the ear affected by OME at the start of the study.
- One study only classed OME as persistent if any ear affected at baseline was still affected at follow-up (Hemlin 1997). For those with bilateral disease, if one ear had resolved at follow-up then the child was not considered to have "persistent OME".
- One study assessed only one ear in each participant: for those with bilateral disease, the "worst affected ear" was assessed at follow-up (Podoshin 1990).
- Some studies assessed and reported the outcome (presence of OME) at the level of the individual ear, rather than at the level of the participant. Children with bilateral disease therefore contributed two data points to the outcome measure. We are aware that the outcomes for ears within the same individual are likely to be strongly correlated, and these data are clustered. We therefore adjusted these data according to the methods in the *Cochrane Handbook for Systematic Reviews of Interventions*, using an estimated intra-cluster correlation coefficient of 0.5. However, we also conducted a sensitivity analysis to assess the impact of this adjustment, using an ICC of zero (no correlation between the ears of a given individual) and one (complete correlation between the ears of a given individual).

The underlying approach in all the studies was to assess the difference in persistence of OME, albeit with slightly different methods of measuring this effect. We therefore considered that it was reasonable to pool the data in a meta-analysis. However, we also undertook a subgroup analysis to identify whether there may be differences in the effect estimates depending on which method of outcome assessment was used.

Adverse events

Adverse events were inconsistently reported across the studies. Data were frequently presented for only one group - those who received the intervention. It was not clear whether this was because no events occurred in the placebo arm, or whether adverse events were not assessed in this group.

Number of doctor-diagnosed episodes of acute otitis media

This outcome was only assessed by three studies (Healy 1984; Mandel 1987; Mandel 1991), and was reported as the proportion of participants who experienced at least one episode of acute otitis media during a four-week follow-up period.

We did not identify any data for our other outcomes of interest, including expressive and receptive language skills, cognitive development, psychosocial skills, listening skills, generic health-related quality of life, parental stress and vestibular function.

Excluded studies

We excluded 41 studies (linked to 49 records) from this review. The main reason for exclusion of each study is listed below:

Nineteen articles were not randomised controlled trials (de Castro 1982; Eiden 1997; Fujita 1994; Gasper 2003; Gibson 1996; Hozawa 2001; Iino 1989; Iino 2001; Kobayashi 2001; Kuriyama 1980; Leonetti 1988; Paradise 1997; Parlea 2012; Persico 1978; Shubich 1996; Smales 1992; Stenstrom 2005; van Balen 1997; Zocconi 1994)

Twelve articles considered an incorrect population, enroling participants who did not have OME, including:

- children with acute otitis media (Perrin 1974);
- children with a persistent effusion after a recent episode of acute otitis media (Corwin 1986; Giebink 1990; Schloss 1988);
- children with recurrent episodes of acute otitis media (Ferrara 2005; Gaskins 1982; Principi 1989; Roark 1997; Schwartz 1982; Schwartz 1982a; Tracy 1995; Varsano 1985).

Six articles used an intervention other than antibiotics (Berman 1990; Bernard 1991; Choung 2008; Daly 1991; Rohail 2006; Velepic 2011).

Three studies compared the use of antibiotics to a different, active intervention (not to placebo or no treatment), including:

- different doses of the same antibiotic (Donaldson 1990);
- a decongestant (Marks 1981);
- a different antibiotic (Yin 2002).

Yeldandi 2001 did use a relevant comparator. However, both groups received co-interventions, and the nature and frequency of these was not balanced across the groups. This rendered the comparison inaccurate, therefore we excluded this study.

Risk of bias in included studies

See Figure 3 for a summary for the risk of bias across all included studies, and Figure 4 for details of the risk of bias for individual studies.

Allocation

We rated the risk of selection bias as unclear for almost all the studies included in this review. This was due to insufficient detail describing the methods for random allocation to the study groups, and/or a lack of detail regarding methods used to conceal allocation. Only four studies provided a description of adequate randomisation methods (Ardehali 2008; Healy 1984; Leach 2008; van Balen 1996). Only one of these studies also described appropriate methods to conceal allocation (Leach 2008).

Blinding

The assessment of performance and detection bias varied across the different studies.

We rated a number of studies at high risk of performance bias, as participants would have been aware if they were receiving the active intervention or were in the control group. This included all of the studies for the comparison 'antibiotics versus no treatment' (Ardehali 2008; Chen 2013; Ernston 1985; Healy 1984; Karlidag 2002; Manrique 1987; Marchisio 1998; Sundberg 1984). We rated one further study at high risk of performance bias, as we had concerns over the adequacy of blinding, despite the use of placebo (Podoshin 1990). We rated a number of studies as at unclear risk of performance bias - although participants appeared to be blinded to group allocation, it was not clear whether this also extended to study personnel (Balle 1990; Mandel 1987; Puhakka 1985; Thomsen 1989). We assessed five studies as having a low risk of performance bias, due to blinding of participants and study personnel (Hemlin 1997; Leach 2008; Mandel 1991; Møller 1990; van Balen 1996).

Only seven studies indicated that outcome data were collected by blinded assessors, or the outcomes were sufficiently objective that blinding was considered unlikely to impact on the results (Ardehali 2008; Balle 1990; Leach 2008; Mandel 1991; Marchisio 1998; Sundberg 1984; van Balen 1996). We rated five studies at high risk of detection bias, as outcome assessors were aware of group allocation (Endo 1997; Ernston 1985; Healy 1984; Karlidag 2002; Mandel 1987; Puhakka 1985), and we rated a number

of studies at unclear risk for this domain, due to a lack of information on blinding (Chen 2013; Hemlin 1997; Manrique 1987; Møller 1990; Podoshin 1990; Thomsen 1989).

Incomplete outcome data

Most of the studies had complete outcome data for most or all randomised participants, and we therefore considered them at low risk of bias for this domain (Ardehali 2008; Balle 1990; Chen 2013; Ernston 1985; Healy 1984; Hemlin 1997; Karlidag 2002; Leach 2008; Mandel 1987; Mandel 1991; Marchisio 1998; Møller 1990; Puhakka 1985; Sundberg 1984; Thomsen 1989; van Balen 1996).

Endo 1997 and Manrique 1987 did not provide details on loss to follow-up, therefore it was unclear whether there was a risk of bias for this domain. We noted very substantial dropout in the placebo group for the study by Podoshin 1990, leading to imbalance in the groups and the potential for bias.

Selective reporting

We rated almost all of the included studies at unclear risk of selective reporting bias, as we were unable to identify a published protocol for the studies and could therefore not compare the reported results to the intended analysis plan. We had specific concerns for three of the included studies, which we rated at high risk of selective reporting. The study by Balle 1990 included a narrative report of improvement in OME, but did not provide any data to support this claim. Data included in the study by Mandel 1987 were subsequently reported in a second paper (Cantekin 1991), which identified a different rate of 'cure' for OME, suggesting that there may be a risk of reporting bias. Finally, Møller 1990 assessed hearing outcomes, but presented very limited data, which precluded comparison across the two groups.

Other potential sources of bias

We considered that an additional source of bias for many studies was the short duration of follow-up (three months or less, sometimes as short as 10 days). This would likely be insufficient to expect natural resolution of OME for those who received no treatment or placebo. Consequently there is a risk that any treatment effect seen in favour of antibiotics may be overestimated.

Effects of interventions

Antibiotics compared to placebo

We identified 11 studies for this comparison (Balle 1990; Endo 1997; Hemlin 1997; Leach 2008; Mandel 1987; Mandel 1991; Møller 1990; Podoshin 1990; Puhakka 1985; Thomsen 1989; van Balen 1996). However, Balle 1990 did not provide data for any outcomes of interest to this review.

Return to normal hearing

Short-term follow-up

A single study considered the number of participants in whom hearing returned to normal after two months of follow-up. This was reported as the proportion of children in whom the air-bone gap completely resolved over the follow-up period. The Peto odds ratio for complete resolution of the air-bone gap was 9.59 for those receiving antibiotics compared to placebo (95% CI 3.51 to 26.18; 41% versus 0%; 1 study; 86 participants; Analysis 1.1; very low-certainty evidence).

Hearing threshold

Short-term follow-up

This was assessed by two studies at four weeks, using the speech reception threshold. The mean difference was -2.58 dB HL in favour of antibiotics (95% CI -4.52 to -0.65; 2

studies; 499 participants; I^2 0%; Analysis 1.2; low-certainty evidence). One study presented data from both ears separately for this analysis. We therefore pooled the data, assuming a correlation between ears of 0.5. However, varying this correlation coefficient made very little difference to the overall effect estimates (Analysis 1.3; Analysis 1.4).

One study also presented data on speech awareness thresholds, for those children aged under two years, or in whom hearing could not be assessed in other ways. The results were very similar, with a mean difference in hearing level of -2.14 dB HL (95% CI -5.10 to 0.82; 1 study; 102 participants; Analysis 1.5; very low-certainty evidence).

Presence or persistence of OME

Short-term follow-up

Nine studies assessed the presence of OME at up to three months follow-up. The risk ratio for the persistence of OME in those who received antibiotics was 0.88 (95% CI 0.78 to 1.00; 66% versus 76%; 9 studies; 1375 participants; I^2 = 69%; Analysis 1.6; low-certainty evidence).

We conducted some sensitivity analyses for this result. One study also reported the number of participants with acute otitis (in whom persistence of OME would be difficult to assess). Assuming that these participants also had persistent OME made little difference to the overall result (RR 0.87, 95% CI 0.79 to 0.96, Analysis 1.7). Using different correlation coefficients between ears of the same individual also had almost no impact on the overall results (Analysis 1.8; Analysis 1.9).

Medium-term follow-up

The remaining two studies assessed the presence of OME at 6 to 12 months of follow-up. The risk ratio for persistence in those receiving antibiotics was 0.89 (95% CI 0.68 to 1.17; 48% versus 54%; 2 studies; 324 participants; I^2 = 32%; Analysis 1.10; very low-certainty evidence).

Again, one study also reported the number of children with acute otitis media without perforation, in whom a diagnosis of persistent OME would have been difficult to assess. Inclusion of these participants in the analysis made very slight difference to the overall effect estimate (RR 0.93, 95% CI 0.69 to 1.25; Analysis 1.11).

Adverse events

Adverse events were inconsistently reported across the studies. Data were frequently presented for only one group - those who received the intervention. It was not clear whether this was because no events occurred in the placebo arm, or whether adverse events were not assessed in this group. We have therefore provided a narrative summary of the adverse events that were reported in Table 3.

Two studies indicated that no adverse events occurred:

- Møller 1990 reported that "no adverse events were reported".
- Thomsen 1989 reported that "no unwanted side effects from the drug" were experienced.

Endo 1997, Podoshin 1990 and Puhakka 1985 did not report on adverse events. It is not clear whether this is because none occurred, or simply because they were not assessed and reported.

Number of doctor-diagnosed episodes of acute otitis media

Short-term follow-up (up to three months)

Two studies provided information on the number of participants who experienced at least one episode of acute otitis media over four weeks of follow-up. The risk ratio for acute otitis media was 0.68 for those receiving antibiotics (95% CI 0.42 to 1.10; 9% versus 13%; 2 studies; 615 participants; I^2 = 0%; Analysis 1.14; very low-certainty evidence).

Antibiotics compared to no treatment

Eight studies were included in this comparison (Ardehali 2008 Chen 2013; Ernston 1985; Healy 1984; Karlidag 2002; Manrique 1987; Marchisio 1998; Sundberg 1984). However, very limited data were available for our outcomes of interest.

Hearing

Return to normal hearing

Very short-term follow-up (< 6 weeks)

A single study assessed the proportion of children whose hearing had "returned to normal thresholds" after 10 days of antibiotic treatment. No definition of normal hearing was provided. The risk ratio was 4.70 in favour of antibiotics (95% CI 1.96 to 11.22; 52% versus 11%; 1 study; 91 participants; Analysis 2.1; very low-certainty evidence).

This outcome was not assessed at later time points.

Final hearing threshold

Short-term follow-up (up to three months)

Again, this outcome was assessed by a single study. The mean final hearing threshold after three months of follow-up was -5.38 dB HL lower (better) for those who received antibiotics (95% CI -9.12 to -1.64; 1 study; 73 participants; Analysis 2.2; low-certainty evidence).

This outcome was not assessed at any other time points.

Presence/persistence of OME

Short-term follow-up (up to three months)

Five studies provided data at this time point. Overall, the risk ratio for persistence of OME at up to three months was 0.64 for those receiving antibiotics (95% CI 0.50 to 0.80; 56% versus 87%; 6 studies; 542 participants; I^2 = 72%; Analysis 2.3; low-certainty evidence). As some data were adjusted to account for potential correlation between ears of the same individual, we conducted a sensitivity analysis to ensure that this did not affect the results. However, the overall effect estimates were similar when using different assumed correlation between the ears of the same individual (Analysis 2.4; Analysis 2.5).

No data are available for later time points.

Adverse events

We were unable to carry out any meta-analysis of adverse events, as these were inconsistently reported across the studies. Data from Chen 2013 are presented in Table 3 - this was the only study to report any adverse effects.

Two studies indicated that no adverse events occurred:

- Ardehali 2008 stated that "No subjects experienced complications during or after the study".
- Marchisio 1998 stated "No medication side effects were reported in any subject".

Five studies did not report on adverse events (Ernston 1985; Healy 1984; Manrique 1987; Karlidag 2002; Sundberg 1984). It is not clear whether this is because none occurred, or simply because they were not assessed and reported.

Number of doctor-diagnosed episodes of acute otitis media

Short-term follow-up (up to three months)

One study assessed this outcome. The proportion of children who experienced one or more episodes of acute otitis media during four weeks of follow-up was lower in the group who received antibiotics, but the confidence intervals were very wide, and the absolute

effect was small (RR 0.40, 95% CI 0.08 to 2.01; 2% versus 5%; 1 study; 196 participants; Analysis 2.6; very low-certainty evidence).

Discussion

Summary of main results

Antibiotics compared to placebo

One study provided very low-certainty evidence of an increase in the proportion of children with normal hearing at two months following antibiotic treatment. Two studies indicated that there may be a small difference in mean final hearing thresholds between those who received antibiotics or placebo, after four weeks of follow-up. However, we have some concerns regarding the use of mean hearing thresholds to assess hearing in this condition (see below).

Persistence of OME after three months of follow-up may be reduced for those who received antibiotics, compared to placebo. A similar effect size was seen after 6 to 12 months of follow-up, but the confidence intervals were very wide and the evidence at this later time point was very uncertain.

The evidence on anaphylaxis was very uncertain, as few studies reported specifically on this outcome. However, antibiotics probably increase the risk of gastrointestinal disturbance, and may increase the risk of vomiting, abdominal pain and itching or rash. The evidence was very uncertain for other adverse effects (including diarrhoea and sedation or irritability).

The effect of antibiotics compared to placebo on episodes of acute otitis media was very uncertain.

Antibiotics compared to no treatment

Similar effects were seen when antibiotics were compared to no treatment. A single study indicated that there may be improvement in the number of children whose hearing returns to normal levels after using antibiotics, but the follow-up was extremely short (10 days), and the evidence was very uncertain. One other study considered final hearing thresholds after three months of follow-up, and found that there may be a small mean difference between those who received and did not receive antibiotics.

Antibiotics may reduce the proportion of children who have persistent OME after up to three months of follow-up. It is very uncertain whether the use of antibiotics has an impact on the number of episodes of acute otitis media during three months of follow-up. The evidence on adverse effects was also very uncertain. We did not identify any evidence on quality of life or developmental outcomes.

Overall completeness and applicability of evidence

Many of the studies included in this review specifically enrolled children who had symptoms of OME for at least three months. Therefore, we do not know whether this treatment may have similar effects in children with a shorter duration of disease. However, this is likely to be the appropriate population, as many practitioners would recommend a period of watchful waiting (to see if the symptoms of OME resolve) before considering any treatment.

A wide range of antibiotics were included across the studies in this review. The duration of treatment was also extremely varied, ranging from a 10-day course of antibiotics up to six months of continuous treatment. We did not have sufficient data to determine if the efficacy (and harms) of different antibiotics or treatment strategies varied.

In keeping with other reviews in this suite, we noted that few studies reported our preferred outcome measure for hearing - the number of children who returned to normal hearing. We have concerns that assessment of hearing using the mean difference in final

hearing threshold (or mean change in hearing threshold) may not be the most appropriate way to assess hearing. OME has a high spontaneous resolution rate. Consequently, we would anticipate that the change in hearing threshold for most children will be similar across the groups, as many children will improve with or without treatment. Therefore, even if a subset of children had substantial benefit from the intervention, the overall mean difference between the two groups would appear to be small. When assessed using the mean difference, the marked benefit seen in a subgroup of participants is 'diluted' by the children who get better regardless of treatment. Therefore, an apparently small mean difference between the two groups may actually be consistent with a substantial change in the number of children in whom hearing returns to normal.

Most of the studies included in this review assessed outcomes at the end of the treatment period. However, it is not clear whether any effects seen immediately after discontinuation of antibiotics will persist in the longer term. Importantly, we did not assess whether the use of antibiotics has any impact on the need for further medical treatment, or the requirement for surgery in children with OME.

Quality of the evidence

We considered the certainty of all the evidence to be low or very low. Many of the studies had significant concerns or lack of clarity regarding the risk of bias. The majority of studies failed to give sufficient information on their randomisation and allocation concealment, therefore we had concerns over the possibility of differences in confounding variables between the two groups. We also had concerns about some studies regarding the potential for performance or detection bias, as participants, study personnel and outcome assessors were not always blinded to the group allocation.

Although we included 19 studies, many considered only a few of our pre-specified outcomes of interest. Outcomes were also reported at a variety of time points, precluding meaningful meta-analysis. Consequently, the number of participants included in many of the analyses was small, leading to wide confidence intervals and imprecision in the estimated effects.

Potential biases in the review process

We have attempted to minimise the potential for bias during the review process by adhering to the *Cochrane Handbook for Systematic Reviews of Interventions* throughout the conduct of this review (Higgins 2021). We conducted comprehensive searches, and ensured that study selection, data extraction and GRADE assessment were carried out by at least two independent authors, to ensure reproducibility of findings.

Agreements and disagreements with other studies or reviews

The previous Cochrane Review on this topic came to similar conclusions - that antibiotics may increase the resolution of OME, but the impact on hearing was uncertain, and they can be associated with adverse effects (Venekamp 2016). It should be noted that the previous review also included a number of trials that compared antibiotics to medical interventions (including antihistamines, decongestants, mucolytics and intranasal corticosteroids).

Authors' conclusions

Implications for practice

The use of antibiotics may slightly reduce the proportion of children with persistent otitis media with effusion (OME) at up to three months of follow-up. However, the impact of antibiotics on hearing is very uncertain. Although adverse effects were poorly reported in the studies included in this review, it is well recognised that antibiotics may be associated with the potential for harm.

In addition, consideration should be given to antibiotic stewardship - particularly where benefits from treatment are uncertain.

Implications for research

This review forms part of a suite of five reviews that consider interventions for OME (Galbraith 2022; MacKeith 2022a; MacKeith 2022b; Mulvaney 2022a; Mulvaney 2022b). Here we present implications for research in this field, which are shared across the suite of reviews:

1. As OME is a fluctuating condition with high rates of resolution and recurrence, and a highly variable impact on children, clinical trials (and, in particular, randomised controlled trials) may not be the research design of choice. Instead, evidence may be better obtained from surgical or clinical registries (for example, see Schmalbach 2021) or prospective cohort studies, with the use of 'big data'. These data sets may also be used to help identify subgroups of children who are at greater risk of persistent disease or long-term consequences of OME. A clearer understanding of possible subgroups of children is needed to better target interventions to those who need them most, whilst avoiding over-treatment for those in whom spontaneous resolution is anticipated.

2. Adverse effects of interventions are important and should always be assessed. However, randomised controlled trials are also not the best method to consider these, especially when events are rare. Observational studies with longer follow-up and larger numbers of participants are needed to provide more robust evidence on the frequency of side effects.

3. It is encouraging that a core outcome set has been developed in this field (Bruce 2015; Liu 2020). Guidance on *how* to measure the different outcomes would also be helpful for future research.

4. Comparison of mean hearing thresholds is widely used in research to assess the impact of different interventions on hearing. However, this outcome measure risks underestimating the potential impact of interventions on hearing. Small changes in mean hearing thresholds may be consistent with a substantial improvement in the number of children whose hearing returns to normal - particularly in a condition with a high spontaneous resolution rate. We would encourage researchers to assess hearing with the proportion of children in whom hearing returns to normal, in preference to mean hearing thresholds.

Acknowledgements

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.

The authors are grateful to Anne Littlewood, Information Specialist with Cochrane Oral Health, for providing peer review comments on the draft search methods. *[To be updated after peer review/sign-off]*

We are also grateful to Dr Richard Rosenfeld for providing editorial sign-off of this protocol.

We are grateful to the 20 Cochrane Crowd screeners for screening 2443 records to identify 1130 possible RCTs, and reject 1313 references as not RCTs. We are particularly grateful to Bernardo Costa, Stefanie Rosumeck, Nikolaos Sideris, Susanna Wisniewski, Anna Resolver, Lai Ogunsola, Shammas Mohammed, Sarah Moore, Brian Duncan, Mohammad Aloulou, Ana-Marija Ljubenković, Vighnesh D, Ahlam Jamal Alhemedi, Neetu Bhadra, Amin Sharifan, Abu Emmil Qawarizmi Bin Abu Sofian, Helen Ramsay, Dinah Amoah, Maike Scherhans and Natalya Clark for screening more than 200 records each.

Editorial and peer reviewer contributions

[To be completed after peer review/sign-off] Cochrane ENT supported the authors in the development of this review.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): [NAME, AFFILIATION];
- Managing Editor (selected peer reviewers, collated peer reviewer comments, provided editorial guidance to authors, edited the article): [NAME, AFFILIATION];
- Copy Editor (copy editing and production): [NAME, AFFILIATION];
- Peer reviewers (provided comments and recommended an editorial decision): [NAME, AFFILIATION] (clinical/content review)*, [NAME, AFFILIATION] (consumer review), [NAME, AFFILIATION] (methods review), [NAME, AFFILIATION] (search review). [NUMBER] of additional peer reviewers provided [CLINICAL/CONTENT/CONSUMER/METHODS/SEARCH] peer review, but chose not to be publicly acknowledged.

Data and analyses

Comparison 1

Antibiotic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Normal hearing (as complete improvement in air-bone gap in worst ear): short-term	1	86	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.59 [3.51, 26.18]
1.2 Hearing threshold: speech reception threshold (short-term). Correction of variance assuming correlation coefficient of 0.5	2	499	Mean Difference (IV, Random, 95% CI)	-2.58 [-4.52, -0.65]
1.3 Sensitivity analysis: speech reception threshold: assuming correlation coefficient of 0.3	2	499	Mean Difference (IV, Random, 95% CI)	-2.58 [-4.38, -0.78]
1.4 Sensitivity analysis: speech reception threshold: assuming correlation coefficient of 0.7	2	499	Mean Difference (IV, Random, 95% CI)	-2.58 [-4.64, -0.53]
1.5 Hearing threshold: speech awareness threshold (short-term)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.6 Persistence of OME (short-term)	9	1375	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.6.1 Persistence defined as effusion in one ear or both	7	1208	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.06]
1.6.2 Persistence defined as effusion both ears if bilateral at baseline, and in one/both ears if unilateral	1	81	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 0.99]
1.6.3 Persistence defined as effusion in the worst ear	1	86	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.58, 0.84]
1.7 Sensitivity analysis: persistence (short-term) including cases of acute otitis (Mandel 1987)	9	1456	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.79, 0.96]
1.7.1 Persistence defined as effusion in one ear or both	8	1289	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.01]
1.7.2 Persistence defined as effusion in both ears (if bilateral at baseline) and in one or both ears (if unilateral)	1	81	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 0.99]
1.7.3 Persistence defined as effusion in the worst ear	1	86	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.58, 0.84]
1.8 Sensitivity analysis: persistence (short-term) assuming ICC of 1.0 [complete correlation between ears] (Puhakka 1985)	9	1445	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.97]
1.8.1 Persistence defined as effusion in one ear or both	8	1278	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.02]
1.8.2 Persistence defined as effusion in both ears (if bilateral at baseline) and in one or both ears (if unilateral)	1	81	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 0.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.3 Persistence defined as effusion in the worst ear	1	86	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.58, 0.84]
1.9 Sensitivity analysis: persistence (short-term) assuming ICC of zero [no correlation between ears] (Puhakka 1985)	9	1473	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.79, 0.98]
1.9.1 Persistence defined as effusion in one ear or both	8	1306	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.03]
1.9.2 Persistence defined as effusion in both ears (if bilateral at baseline) and in one or both ears (if unilateral)	1	81	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 0.99]
1.9.3 Persistence defined as effusion in the worst ear	1	86	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.58, 0.84]
1.10 Persistence of OME (medium-term)	2	324	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.68, 1.17]
1.10.1 Persistence defined as 'OME' in one or both affected ears	1	103	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.73, 1.53]
1.10.2 Persistence defined as effusion in affected ear	1	221	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.61, 1.04]
1.11 Sensitivity analysis: persistence of OME (medium-term); defined as 'OME' or 'AOM without perforation' (Leach 2008)	2	324	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.69, 1.25]
1.11.1 Persistence defined as 'OME or AOM without perforation' in one or both affected ears	1	103	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.33]
1.11.2 Persistence defined as	1	221	Risk Ratio (M-H,	0.80 [0.61, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
effusion in affected ear			Random, 95% CI)		
1.12 Adverse event: eardrum perforation	1	103	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.18, 1.01]	
1.13 Adverse event: 'gastrointestinal'	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only	
1.14 Episodes of acute otitis media	2	615	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.42, 1.10]	

Comparison 2

Antibiotic versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Hearing returned to normal (very short-term)	1	91	Risk Ratio (M-H, Random, 95% CI)	4.70 [1.96, 11.22]
2.2 Final hearing threshold (short-term)	1	73	Mean Difference (IV, Random, 95% CI)	-5.38 [-9.12, -1.64]
2.3 Persistence of OME (short-term)	6	542	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.50, 0.80]
2.3.1 Analysis by child: persistence in any ear	2	151	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.48, 0.75]
2.3.2 Analysis by child: persistence in any affected ear	2	300	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.34, 1.03]
2.3.3 Analysis by ear. Adjusted for non-independence, assuming ICC of 0.5	2	91	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.64, 0.98]
2.4 Sensitivity analysis 1: persistence of OME (short-term). ICC = zero	6	580	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.50, 0.80]
2.4.1 Analysis by child: persistence in any ear	2	151	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.48, 0.75]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size	
2.4.2 Analysis by child: persistence in any affected ear	2	300	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.34, 1.03]	
2.4.3 Analysis by ear. Adjusted for non-independence, assuming ICC of 0	2	129	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.65, 0.94]	
2.5 Sensitivity analysis 2: persistence of OME (short-term). ICC = 1.0	6	523	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.50, 0.79]	
2.5.1 Analysis by child: persistence in any ear	2	151	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.48, 0.75]	
2.5.2 Analysis by child: persistence in any affected ear	2	300	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.34, 1.03]	
2.5.3 Analysis by ear. Adjusted for non-independence, assuming ICC of 1	2	72	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.59, 0.99]	
2.6 Episodes of acute otitis media (short-term)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only	

History

Protocol first published: Issue 4, 2022

Contributions of authors

Caroline A Mulvaney: drafted the protocol. Screened the search results and selected studies, conducted data extraction, carried out statistical analyses and GRADE assessment. Drafted the text of the review.

Kevin Galbraith: drafted the protocol. Screened the search results and selected studies, conducted data extraction, carried out statistical analyses and GRADE assessment. Drafted the text of the review.

Katie Webster: screened the search results and selected studies, conducted data extraction and carried out statistical analyses. Drafted the text of the review.

Mridul Rana: conducted data extraction and reviewed and edited the text of the review.

Rachel Connolly: conducted data extraction and reviewed and edited the text of the review.

Tal Marom: reviewed the protocol. Reviewed the analyses and reviewed and edited the text of the review.

Mat Daniel: reviewed the protocol. Reviewed the analyses and reviewed and edited the text of the review.

Roderick P Venekamp: co-wrote and edited the protocol. Reviewed the analyses and reviewed and edited the text of the review.

Anne GM Schilder: co-wrote and edited the protocol. Reviewed the analyses and reviewed and edited the text of the review.

Samuel MacKeith: drafted the protocol. Screened the search results and selected studies. Provided clinical guidance throughout the review process. Reviewed the analyses and reviewed and edited the text of the review.

Declarations of interest

Caroline A Mulvaney: none known.

Kevin Galbraith: none known.

Katie Webster: none known.

Mridul Rana:

Rachel Connolly:

Tal Marom: none known.

Mat Daniel: has a financial interest in Aventamed, a company that produces a ventilation tube insertion device.

Roderick P Venekamp: is an Editor for Cochrane Acute Respiratory Infections and Cochrane ENT, but had no role in the editorial process for this review.

Anne GM Schilder: Professor Anne Schilder was joint Co-ordinating Editor of Cochrane ENT until April 2020, but had no role in the editorial process for this review. Her evidENT team at the UCL Ear Institute is supported by the National Institute of Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC), with research projects being supported by the NIHR, Wellcome Trust, RNiD, ENT UK and industry. She is the National Specialty Lead for the NIHR Clinical Research Network ENT and Surgical Specialty Lead for ENT for the Royal College of Surgeons of England's Clinical Research Initiative. In her role as director of the NIHR UCLH BRC Deafness and Hearing Problems Theme, she advises CRO, biotech and pharma companies in the hearing field on clinical trial design and delivery.

Samuel MacKeith: treats patients with OME in his NHS and private practice and is Assistant Co-ordinating Editor of Cochrane ENT but has not been involved in the editorial process for this review.

Sources of support

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK
  Infrastructure funding for Cochrane ENT

Differences between protocol and review

In our protocol we planned to use the Trustworthiness Tool developed by the Cochrane Pregnancy and Childbirth Group to determine which studies would be included in the main analyses (Mulvaney 2022b). As described in the text, we used this tool to assess the studies, but did not use it to determine whether a study should be included in the main analysis.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Ardehali 2008

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial with 3 months of treatment and follow-up An additional group received anti-reflux medication. Data for this group were not extracted, as the intervention was not of relevance to this review.

Participants	**Setting:**
	Conducted in Iran. No further details provided.
	Sample size:
	• **Number randomised:** 90 participants total (60 relevant to this review)
	• **Number completed:** 90 participants total (60 relevant to this review)
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ Antibiotics group: mean 5.8 years (SD 0.3)
	  ◦ No treatment group: mean 5.1 years (SD 0.5)
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 14 males
	  ▪ 16 females
	  ◦ No treatment group:
	  ▪ 15 males
	  ▪ 15 females
	Inclusion criteria:
	Aged 2 to 12 years. Children with chronic otitis media with effusion which lasted 3 months or more. Refractory to 3 periods of antibacterial treatment. Confirmed by physical examination and type B tympanogram in at least 1 ear without clinical signs and signs of active infection.
	Exclusion criteria:
	• Down syndrome
	• Cleft palate
	• Neurodevelopmental delay
	• Genetic or congenital palate
	• Craniofacial malformations
	• Previous VT or adenoidectomy
	• Immunodeficiency
	• Cholesteatoma
	• Sensorineural hearing loss
	• Other medical conditions (e.g. renal, liver or cardiac illnesses)

Interventions	**Antibiotic group** Co-amoxiclav 40 mg/kg/day in 3 divided doses, max 750 mg/day

	Comparator No treatment

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ Favourable response was considered as complete resolution of effusion clinically and type A or more than -200 peak in tympanometry at 3 months
	• **Other adverse effects**
	  ◦ No numeric data are reported; a narrative summary of adverse events was provided
	Other outcomes reported in the study:
	No other results assessed at 2-week follow-up

Funding sources	Not reported
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retractions or expressions of concern were identified • Trial registration is not applicable as this study was published prior to 2010 • Limited baseline characteristics were reported, but we had no concerns over the data that were available • No loss to follow-up was reported and it is unclear why this was • No implausible results were reported • Equal numbers were randomised to each group and there is no report of blocked randomisation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quotes: “In a prospective randomized clinical trial study…” “The patients were randomly allocated to receive…” "...according to a computer-generated randomization schedule" Comment: computer-generated randomisation process.
Allocation concealment (selection bias)	Unclear risk	Comment: no information is provided regarding concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants were not blinded to their intervention; no placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “by two unique independent ENT surgeons blinded to subject group assignment.” Comment: outcome assessors were blinded to the interventions received by participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: full follow-up is reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registration is available for assessment.
Other bias	Low risk	Comment: no other concerns were noted.

Balle 1990

Study characteristics	
Methods	Parallel-group, double-blind randomised controlled trial with 4 weeks of treatment and a total of 12 months of follow-up

Participants	**Setting:**
	Study conducted in Denmark. No details regarding recruitment.
	Sample size:
	• **Number randomised:** 264 participants (131 to antibiotics, 133 to placebo)
	• **Number completed:** 223 participants (109 antibiotics, 112 placebo)
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ mean 4.4 years for whole cohort (no standard deviation reported)
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 63 boys (48%): 68 girls (52%)
	  ◦ Placebo group:
	  ▪ 74 boys (56%): 68 girls (44%)
	Inclusion criteria:
	At least 3 months of type C2 or B tympanometry curves uni- or bilaterally, and not allergic to penicillin
	Exclusion criteria:
	None reported

Interventions	**Antibiotic group:** 4 weeks treatment with amoxicillin and clavulanate potassium. Concentration not stated. Children aged 1 to 5 had 5 mL 3 times daily, children aged 6 to 10 had 7.5 mL 3 times daily. **Comparator:** Placebo was used, but no details on the nature of this were provided
Outcomes	No data are reported for any of the outcomes included in this review The only outcome described is the specific type of bacteria cultured from the nasopharynx
Funding sources	Quote: “We thank Astra Medical company for supplying the antibiotic and their kind support.” Pharmaceutical company funding
Declarations of interest	No declaration is made
Notes	**Research integrity checklist:** • No retraction notices or expressions of concern were identified • Trial registration is not applicable, as this study was published before 2010 • Very few baseline characteristics were reported, therefore we are unable to assess whether there was excessive similarity between the groups • Plausible loss to follow-up was reported • No implausible results were identified • Unequal numbers of participants were randomised to each group

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information is provided on the randomisation process.
Allocation concealment (selection bias)	Unclear risk	No information is provided on any methods used to conceal allocation.

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study states that this trial was "double blind" but there is no information on how blinding of study personnel was achieved.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	For the outcomes in this paper, outcome measurement is unlikely to be influenced by the (possible) lack of blinding for study personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Relatively few dropouts across the trial, and balanced between groups. Likely insufficient to cause bias in the reported results.
Selective reporting (reporting bias)	High risk	No protocol is available. Authors allude to an improvement in OME during the initial treatment phase, but do not report any data to support this claim.
Other bias	Low risk	No other concerns were identified.

Chen 2013

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial with 8 to 12 weeks of treatment and follow-up

Participants	**Setting:**
	Single-centre, conducted in a University ENT Department in China between June 2009 and March 2011
	Sample size:
	• **Number randomised:** 84 participants
	• **Number completed:** 73 participants
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ Antibiotics group: mean 67.7 months (SD 22.3)
	  ◦ No treatment group: mean 67.8 months (SD 23.1)
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 22 males
	  ▪ 14 females
	  ◦ No treatment group:
	  ▪ 20 males
	  ▪ 17 females
	• **Duration of disease**
	  ◦ Antibiotics group: 10.2 days (SD 6.58)
	  ◦ No treatment group: 11.1 days (SD 6.45)
	• **Hearing thresholds**
	  ◦ Antibiotics group: mean 10.2 dB (SD 6.83)
	  ◦ No treatment group: mean 30.6 dB (SD 7.82)
	Inclusion criteria:
	Aged 3 to 14 years. Otitis media with effusion less than 3 months. Aural fullness, hearing loss or tinnitus; integrity, invagination or fluid level of tympanic membrane; type B or C2 tympanogram
	Exclusion criteria:
	• Suppurative otitis media
	• Tympanic membrane perforation
	• Adenoid hypertrophy
	• Tumour
	• Severe systemic diseases
	• Allergy or intolerance to macrolides

Interventions	**Antibiotic group (n = 42 randomised, n = 36 completed)** Clarithromycin 15 mg/kg/day in 2 divided doses for 1 week, followed by low-dose clarithromycin (5 to 8 mg/kg/day) in 4 divided doses until the tympanogram was type A. The low-dose antibiotic was continued for 1 week after the effusion resolved, then stopped. The entire course was less than 12 weeks duration (range 5 to 12 weeks, mean 9.91 (SD 2.41) weeks). Two children in this group received azithromycin instead **Comparator (n = 42 randomised, n = 37 completed)** No treatment **Background interventions administered to all participants** Both groups received a topical glucocorticoid nasal spray for 12 weeks **Treatment administered before entry into the trial** All children appear to have undergone tympanocentesis at the start of the trial for study of bacterial colonisation in the ear

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing: mean (SD) final hearing threshold (dB)**
	  ◦ Measure by air-bone gap at 12 weeks
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME**
	  ◦ Data are reported but cannot be used - it is unclear how this outcome was assessed. Data are reported as a percentage. It is unclear whether the denominator should be the number of children, or the number of ears assessed. Attempts to back-calculate the raw data (number with persistence/total number) from the reported percentages did not result in an integer value.
	• **Episodes of acute otitis media**
	  ◦ No numeric data are reported; a narrative summary was provided
	• **Other adverse effects**
	  ◦ Proportion of children with vomiting
	  ◦ A narrative summary of other adverse events was provided
	Other outcomes reported in the study:
	Detection of bacterial biofilm in the middle ear

Funding sources	The study was supported by grants from National Basic Research Program of China (2011CB504502), National Natural Science fund of China (30973306) and Key Nature Fund of Guangdong Province (8251008901000016)
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retractions or expressions of concern were identified • No registered protocol was identified • Baseline characteristics were not excessively similar between the groups • Plausible loss to follow-up occurred • No implausible results were noted • Equal numbers were randomised to each group and there is no report of blocked randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "involved subjects were randomly divided into two subgroups" Comment: no information on sequence generation.

Allocation concealment (selection bias)	Unclear risk	Comment: no information is provided regarding methods used to conceal allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: this was an open-label study and participants were aware of their group allocation. No placebo was used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: there is no information to describe whether outcome assessors were blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: there are few dropouts and the numbers are relatively balanced between the 2 groups. This is probably insufficient to change the direction of effect seen in the study.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registration is available with which to compare the reported outcomes.
Other bias	Low risk	Comment: no other concerns identified.

Endo 1997

Study characteristics	
Methods	Three-arm, parallel-group, randomised controlled trial with 8 month follow-up
Participants	**Setting:** Study conducted in Brazil. No further details provided. **Sample size:** • Total number: 148 participants Unclear whether this is the number randomised or the number completed. • Number relevant to the review (antibiotics versus placebo): 26 participants **Participant (baseline) characteristics:** • **Age:** ◦ Range 9 months to 11 years. ◦ Only data from participants less than 2 years used, as the others received another intervention (antibiotics versus steroids) • **Gender** ◦ Not reported **Inclusion criteria:** Children with bilateral secretory otitis media. Diagnostic criteria, based on 3 parameters: clinical picture; otoscopy; and pure tone audiometry and/or tympanometry **Exclusion criteria:** not reported
Interventions	**Antibiotic group** Sulfamethoxazole-trimethoprim 20 mg/kg/day in a single night-time dose for 30 days **Placebo group** No information is provided on nature of the placebo
Outcomes	**Primary outcomes relevant to this review:** • **Hearing** ◦ Not reported • **Disease-specific quality of life** ◦ Not reported • **Adverse event** ◦ Not reported **Secondary outcomes relevant to this review:** • Presence/persistence of OME: proportion of children with persistence of OME

	◦ Assessed by clinical picture, otoscopy and PTA/tympanometry at 4 weeks. Defined as: ▪ partial improvement: some improvement but without total regression; ▪ unchanged: still changes in one of the parameters.
Funding sources	Not reported
Declarations of interest	None reported
Notes	Children over 2 years of age received antibiotics AND prednisolone, therefore we can only use the data for those aged ≤ 2 years in analysis **Research integrity checklist** • No retractions or expressions of concern were identified • This trial was published prior to 2010, therefore trial registration was not required • No baseline characteristics ware reported, therefore we are unable to assess them for similarities • Loss to follow-up was unclear, but may be zero • No implausible results were reported • Different numbers were randomised to each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “with 40 children being randomly chosen to enter the placebo group and 108 receiving clinical treatment”. Comment: no information is provided regarding the process for randomisation.
Allocation concealment (selection bias)	Unclear risk	Comment: no details are reported on methods used to conceal allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: participants were blinded as they received either active drug or placebo. There was no report, however, regarding whether personnel were blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: it was not reported whether outcome assessments were carried out blind to treatment assignment. A lack of blinding could affect the interpretation of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no details are provided regarding loss to follow-up. It is unclear whether the authors are reporting full follow-up, or whether they simply do not report details of those who failed to return for follow-up, as the total number randomised to each intervention is not reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available with which to compare the reported outcomes.
Other bias	High risk	Comment: very limited information on how the outcome 'resolution' of OME was assessed. Follow-up is inadequate to allow appropriate comparison of antibiotics and no intervention. Outcomes reported at this stage may be more likely to favour the active intervention, as insufficient time has elapsed to allow for spontaneous resolution.

Ernston 1985

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial with 10 days of treatment and follow-up
Participants	**Setting:** Single-centre, conducted in a hospital setting in Sweden. Study dates not reported. **Sample size:** • **Number randomised:** 91 participants • **Number completed:** 91 participants

	Participant (baseline) characteristics:
	• **Age:**
	  ◦ Antibiotics group: mean 4.8 years (SD 2.4)
	  ◦ Watchful waiting group: mean 4.6 years (SD 2.6)
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 28 males
	  ▪ 18 females
	  ◦ Watchful waiting group:
	  ▪ 17 males
	  ▪ 28 females
	Inclusion criteria:
	Aged less than 12 years. OME in one or both ears, diagnosed by otomicroscopy, showing fluid behind an intact ear drum and tympanometry disclosing a type “B” curve.
	Unhealed at several examinations during a more than 3-month period
	Exclusion criteria:
	• Children with cleft palate
	• Children with upper respiratory tract infection during the period of observation (at least 3 months before the trial)
	• Children who had received antibiotics during the preceding 4 weeks

Interventions	**Antibiotic group (n = 46 randomised, n = 46 completed)** Cefaclor 20 mg/kg twice daily for 10 days **Watchful waiting (n = 45 randomised, n = 45 completed)** Remained untreated awaiting surgery **Treatment administered before entry into the trial** At least 3 months of watchful waiting

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ Defined as participants who had not healed. Healed participants had normal middle ear status on otomicroscopy and a type A or C1 curve on tympanometry and a normal threshold of hearing at 10 days.
	Other outcomes reported in the study:
	Data are reported for long-term relapse after treatment, but this is only available for children who initially ‘healed’, as other children received myringotomy +/- VT insertion

Funding sources	Not reported
Declarations of interest	Not reported
Notes	**Research integrity checklist** • No retractions or expressions of concern were identified • This trial was published prior to 2010, therefore trial registration was not required • Limited baseline characteristics ware reported, therefore we are unable to assess them for similarities

	• Loss to follow-up was zero, but this is plausible (all participants were awaiting surgery, and follow-up was only for 10 days) • No implausible results were reported • Different numbers were randomised to each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: “The children were randomly divided into two groups”. Comment: no information about random sequence generation. However, we note an unusual discrepancy in the gender balance between the 2 groups, with 28 boys and 18 girls in one group, and 28 girls and 17 boys in the other group. This seems unlikely to have occurred by chance alone, therefore may suggest a problem with randomisation.
Allocation concealment (selection bias)	Unclear risk	Comment: no information is provided regarding any methods used to conceal allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no placebo was used, this was an open-label trial therefore participants were aware of their group allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: there is no statement to suggest that outcome assessors were blinded. As no placebo was used we presume that this was an open trial, and outcome assessors were aware of group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: full follow-up is reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available for comparison.
Other bias	High risk	Comment: follow-up is inadequate to allow appropriate comparison of antibiotics and no intervention. Outcomes reported at this stage may be more likely to favour the active intervention, as insufficient time has elapsed to allow for spontaneous resolution.

Healy 1984

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial with 4 weeks of treatment and follow-up

Participants	**Setting:**
	Single-centre, conducted in a university hospital in Boston, USA between September 1981 and August 1982
	Sample size:
	• **Number randomised:** 200 participants
	• **Number completed:** 189 participants
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ 2 to 5 years
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 63 males
	  ▪ 37 females
	  ◦ Watchful waiting group:
	  ▪ 58 males
	  ▪ 42 females
	Inclusion criteria:

	Aged 2 to 5 years with otitis media with effusion, present for more than 6 weeks. Defined as a positive pneumatic otoscopic exam and/or type B, C1 or C2 tympanogram. **Exclusion criteria:** • Prior history of tonsillectomy, adenoidectomy and or VT insertion • Middle ear abnormalities such as adhesive otitis media, tympanic membrane perforation or cholesteatoma • Facial anomalies or congenital syndromes, i.e. Down syndrome • Upper respiratory tract infection in previous 4 weeks • Systemic illness, e.g. cystic fibrosis • Acute suppurative otitis media • Sinusitis • Strong family history of allergy • Received medical therapy for middle ear effusion within the previous 4 weeks including sympathomimetic amines, antihistamines or antibiotics
Interventions	**Antibiotic group (n = 100 randomised, n = 96 completed)** Trimethoprim-sulfamethoxazole (8 mg and 40 mg/kg/day respectively) in 2 divided doses. Administered in liquid preparation for 4 weeks. **No treatment group (n = 100 randomised, n = 93 completed)** Observation

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Episodes of acute otitis media: mean (SD) number of episodes**
	  ◦ Proportion of participants developing at least 1 episode of acute otitis media within 4 weeks

Funding sources	Not reported
Declarations of interest	Not reported
Notes	**Research integrity checklist** • No retractions or expressions of concern were identified • This trial was published prior to 2010, therefore trial registration was not required • Limited baseline characteristics were reported, but we do not have concerns over the data available • Plausible loss to follow-up was reported • No implausible results were reported • Equal numbers were randomised to each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The author would simply call a disinterested person who would pull a previously randomly arranged card which would show the word either 'control' or 'antibiotic'". Comment: simple drawing of lots - adequate method for random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: no information on whether or how group allocation was concealed.

Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants and study personnel were aware of group allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: outcome assessors were aware of group allocation. Tympanometry and otoscopy were used for outcome assessment, and there may be some subjectivity in interpretation of these results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: limited number of dropouts, insufficient to cause a risk of bias in the results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registration is available for comparison.
Other bias	High risk	Comment: follow-up is inadequate to allow appropriate comparison of antibiotics and no intervention. Outcomes reported at this stage may be more likely to favour the active intervention, as insufficient time has elapsed to allow for spontaneous resolution.

Hemlin 1997

Study characteristics	
Methods	Three-arm, double-blind, parallel-group, randomised controlled trial with 10 days of treatment and 12 to 21 days follow-up For this review, we compared those who received antibiotics (alone), to those with no treatment. Data on steroids are relevant for a separate review in this suite (Mulvaney 2022a).

Participants	**Setting:**
	
	Single-centre, conducted in a hospital ENT department in Sweden. No study dates reported.
	
	Sample size:
	
	• **Number randomised:** 142 participants
	• **Number completed:** 140 participants
	
	Participant (baseline) characteristics:
	
	• **Age:**
	  ◦ Antibiotics group: mean 63 months
	  ◦ Steroids and antibiotics group: mean 67 months
	  ◦ Placebo group: mean 63 months
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 37 males
	  ▪ 24 females
	  ◦ Steroids and antibiotics group:
	  ▪ 36 males
	  ▪ 23 females
	  ◦ Placebo group:
	  ▪ 14 males
	  ▪ 6 females
	• **Number of doctor-diagnosed AOM episodes within a specified time frame**
	  ◦ Number of AOM episodes within 12 months of study, using patient history
	
	Inclusion criteria:
	
	Aged 2 to 12 years. Unilateral or bilateral secretory otitis media of at least 3 months duration, confirmed by otomicroscopy and tympanometry. Immobile and pale eardrum on otomicroscopy and a type B tympanogram in at least one of the ears.
	
	Exclusion criteria:
	
	• Severe underlying disease

	• Immunologic deficiency • Cleft palate • Known or suspected allergy to penicillin or cephalosporins • Antibiotic treatment within the preceding 4 weeks • Previous inclusion in the study
Interventions	**Antibiotics group (n = 61 completed)** Liquid suspension of cefixime 20 mg/mL, given at a dose of 8 mg/kg per day in 2 divided doses for 10 days **Steroids and antibiotics group (n = 59 completed)** Received antibiotic as above, plus 6 mg betamethasone tablets given in a single dose on the morning of day 10 **Placebo group (n = 20 completed)** Placebo suspension and tablets of similar appearance

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Anaphylaxis (presumed)
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children/ears with persistence of OME**
	  ◦ Measured using otomicroscopy and tympanometry. Defined as any child who did not have a normal middle ear status – pale eardrum with normal mobility and type A tympanogram or type C with a peak of more than -300 decapascals
	• **Other adverse effects**
	  ◦ Proportion of children with vomiting
	  ◦ Proportion of children with diarrhoea
	Other outcomes reported in the study:
	Some longer-term outcomes reported, but only for those who were healed at early follow-up

Funding sources	Not reported
Declarations of interest	Not reported
Notes	**Research integrity checklist** • No retractions or expressions of concern were identified • This trial was published prior to 2010, therefore trial registration was not required • Limited baseline characteristics were reported, but we do not have concerns over the available data • Loss to follow-up was plausible, given the short duration of total follow-up • No implausible results were reported • A balanced allocation process was used for randomisation, to ensure a 3:3:1 ratio for the groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Treatment with cefixime or cefixime plus betamethasone or placebo was allocated at random with a ratio of 3:3:1." Comment: no information on generation of random sequence.
Allocation concealment	Unclear risk	Comment: no information was provided regarding how allocation was concealed.

(selection bias)		
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The drugs were dispensed double-blind by a double-dummy technique" Comment: participants and study personnel were blinded to group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information regarding whether outcome assessors were blinded. Tympanometry and otomicroscopy were both used in assessment of the outcome, and may involve some subjectivity.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: for the data used in this review, dropout was low and unlikely to affect the results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registration was available to compare.
Other bias	High risk	Comment: follow-up is inadequate to allow appropriate comparison of antibiotics and no intervention. Outcomes reported at this stage may be more likely to favour the active intervention, as insufficient time has elapsed to allow for spontaneous resolution.

Karlidag 2002

Study characteristics	
Methods	Unblinded, parallel-group randomised controlled trial with 8 weeks of treatment and follow-up For this review, we compared those who received antibiotics (alone) to those with no treatment. Data on steroids are relevant for a separate review in this suite (Mulvaney 2022a).

Participants	**Setting:**
	Single-centre, conducted in Turkey between January and December 2001
	Sample size:
	• **Number randomised:** 62 participants
	• **Number completed:** 62 participants
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ Antibiotics group: mean 5.8 years (SD 2.47)
	  ◦ Steroids and antibiotics group: mean 6.57 years (SD 3.17)
	  ◦ Watchful waiting group: mean 4.58 years (SD 2.30)
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 13 males
	  ▪ 7 females
	  ◦ Steroids and antibiotics group:
	  ▪ 14 males
	  ▪ 6 females
	  ◦ Watchful waiting group:
	  ▪ 11 males
	  ▪ 11 females
	Inclusion criteria:
	Aged 2 to 12 years. Diagnosed with otitis media with effusion based on:
	• History: hearing loss, feeling of fullness in the ear, watching TV with a loud volume, apathy, comprehension and speech impairment
	• Otoscopy: grey, dull or light pink eardrum with thickening, retraction or increased vascularity
	• Rinne negativity on tuning fork test
	• Conductive hearing loss
	• Type B or C tympanogram

	Exclusion criteria: • Previous insertion of ventilation tubes • Allergy to ampicillin/sulbactam • Antibiotic or nasal spray use in the past 2 weeks • Immune disorders or systemic illnesses
Interventions	**Antibiotic group (n = 20 randomised, n = 20 completed)** Ampicillin/sulbactam 25 mg/kg/day, administered in 2 divided doses, orally for 8 weeks **Steroids and antibiotics group (n = 20 randomised, n = 20 completed)** Antibiotic as above, plus budesonide intranasal spray, 200 µg/day administered in 2 divided doses for 8 weeks **No treatment group (n = 22 randomised, n = 22 completed)** Active monitoring
Outcomes	**Primary outcomes relevant to this review:** • **Hearing** ◦ Not reported • **Disease-specific quality of life** ◦ Not reported • **Adverse event** ◦ Not reported **Secondary outcomes relevant to this review:** • **Presence/persistence of otitis media: proportion of ears with persistence of OME** ◦ At 8 weeks
Funding sources	None reported
Declarations of interest	Not reported
Notes	**Research integrity checklist** • No retractions or expressions of concerns were identified • Prospective trial registration was not applicable, as this study was published before 2010 • Limited information on baseline characteristics was presented, but no concerns were identified from the reported data • Full follow-up was reported, with no reasons given • No implausible results were noted • Different numbers were recruited to each group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: participants were "randomly allocated" into 3 groups. No information on sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: no details were provided on any methods used to conceal allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants were aware of their treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an unblinded trial. We presume that the outcome assessors were also aware of treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: full follow-up is reported.

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available with which to compare the reported outcomes.
Other bias	High risk	Comment: follow-up is inadequate to allow appropriate comparison of antibiotics and no intervention. Outcomes reported at this stage may be more likely to favour the active intervention, as insufficient time has elapsed to allow for spontaneous resolution.

Leach 2008

Study characteristics	
Methods	Two-arm, double-blind, parallel-group, randomised controlled trial with 24 weeks of treatment and follow-up

Participants	**Setting:**
	Three Aboriginal communities in tropical northern Australia, recruitment between 1996 and 2001
	Sample size:
	• **Number randomised:** 103 participants
	• **Number completed:** 103 participants
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ Antibiotics group: mean 4.2 months
	  ◦ Placebo group: mean 3.2 months
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 24 males
	  ▪ 28 females
	  ◦ Placebo group:
	  ▪ 30 males
	  ▪ 21 females
	Inclusion criteria:
	Aboriginal infants aged less than 12 months - enrolled as soon as possible after birth. OME diagnosed with:
	• Video pneumatic otoscopy and tympanometry were used to assess ear status
	• Fluid behind an intact tympanic membrane, reduced mobility on pneumatic otoscopy
	• Type B tympanogram, with or without mild bulging, and in the absence of signs or symptoms of an acute infection
	Exclusion criteria:
	• Prematurity (born < 34 weeks)
	• Chronic infection requiring prophylactic antibiotics
	• Craniofacial abnormalities or immunodeficiency syndromes

Interventions	**Antibiotic group (n = 52 randomised, n = 51 completed)** Amoxicillin 50 mg/kg/day in 2 divided doses. Administered for 24 weeks, or until bilateral normal middle ear status was detected at 2 consecutive monthly examinations (i.e. success). Mean duration of treatment 5.7 months. **Placebo group (n = 52 randomised, n = 51 completed)** Placebo of equivalent volume. Mean duration of treatment 5.2 months.

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**

	◦ Not reported. Authors state “No infant was withdrawn as a result of direct adverse reaction due to medication.” **Secondary outcomes relevant to this review:** • **Presence/persistence of OME: proportion of children with persistence of OME** ◦ Measured at 24 weeks **Other outcomes reported in the study:** • Nasopharyngeal swab analysis for carriage of pathogens • Number of children with perforation • Number of children with normal ears at 2 successive monthly visits • Number of children with normal ears at follow-up (but not at 2 successive visits)
Funding sources	The NHMRC and the Menzies School of Health Research
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retractions or expressions of concern were identified • This trial was registered retrospectively with clinicaltrials.gov (but prospective registration was not required, as published prior to 2010) • Baseline characteristics were not excessively similar • Loss to follow-up was plausible • No implausible results were reported • Blocked randomisation was used to allocate similar numbers to each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer generated random number series was stratified by age at randomization (less than 6 months versus greater than 6 months) and allocation was randomized within blocks of 7 subjects”; “Participants were consecutively allocated a random number according to the sequence provided by the systems manager.” Comment: computerised randomisation method.
Allocation concealment (selection bias)	Low risk	Quote: “The use and size of block randomization was concealed from investigators until data collection was completed” Comment: adequate attempts to conceal allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “Placebo was designed, manufactured and packaged by Institute of Drug Technology, Melbourne. Bottles were provided by the manufacturers of amoxicillin. Original amoxicillin labels were removed before applying the study label. Senior staff at the community clinics had access to the allocation via a locked box containing stapled double envelopes. Clinic staff were not involved in data collection. The biostatistician was provided with the codes and the allocation to either ‘A’ or ‘B’, but was unaware of whether ‘A’ or ‘B’ was amoxicillin or placebo.” Comment: participants and study personnel were unaware of group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Placebo was designed, manufactured and packaged by Institute of Drug Technology, Melbourne. Bottles were provided by the manufacturers of amoxicillin. Original amoxicillin labels were removed before applying the study label. Senior staff at the community clinics had access to the allocation via a locked box containing stapled double envelopes. Clinic staff were not involved in data collection. The biostatistician was provided with the codes and the allocation to either ‘A’ or ‘B’, but was unaware of whether ‘A’ or ‘B’ was amoxicillin or placebo.” “Allocation to placebo or amoxicillin, and the use and size of block randomization was concealed from investigators until data collection was completed. “ Comment: outcome assessors were blinded to treatment allocation.
Incomplete outcome data	Low risk	Comment: limited dropout (2 in antibiotics group and 7 in the placebo group). This is unlikely to substantially impact on the results.

(attrition bias) All outcomes		
Selective reporting (reporting bias)	Unclear risk	Comment: a trial registration was identified for this study, although we note that this was retrospectively registered, after completion of the study. Therefore, we are unable to compare the reported outcomes with the pre-specified analysis plan.
Other bias	High risk	Comment: during follow-up, children with 2 consecutive normal examinations were discharged, and did not continue follow-up for the full 6 months. Outcome data at 6 months may therefore underestimate the occurrence of OME - as children may have relapsed during the follow-up period, but investigators would have been unaware of this.

Mandel 1987

Study characteristics	
Methods	Three-arm, double-blind, parallel-group, randomised controlled trial with 2 weeks of treatment, and main follow-up at 2 and 4 weeks. Additional follow-up for up to 3 months. One study arm received antibiotics plus antihistamine – data were not included in this extraction, as they are not of relevance to this review.

Participants	**Setting:**
	Single-centre, conducted in an outpatient setting at the Children's Hospital of Pittsburgh between July 1981 and October 1984
	Sample size:
	• **Number randomised:** 518 participants
	• **Number completed:** 488 participants
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ Antibiotics and placebo group:
	  ▪ 7 to 23 months: 53/155 (34.2%)
	  ▪ 2 to 5 years: 73/155 (47.1%)
	  ▪ 6 to 12 years: 29/155 (18.7%)
	  ◦ Placebo group:
	  ▪ 7 to 23 months: 48/150 (32%)
	  ▪ 2 to 5 years: 74/150 (49.3%)
	  ▪ 6 to 12 years: 28/150 (18.7%)
	• **Gender:**
	  ◦ Antibiotics and placebo group:
	  ▪ 63.8% males
	  ▪ 36.2% females
	  ◦ Placebo group:
	  ▪ 64.1% males
	  ▪ 35.9% females
	• **Duration of disease**
	  ◦ Antibiotics and placebo group:
	  ▪ < 4 weeks: 15.6%
	  ▪ 4 to 8 weeks: 15.6%
	  ▪ > 8 weeks: 33.8%
	  ▪ Unknown: 35%
	  ◦ Placebo group:
	  ▪ < 4 weeks: 15.4%
	  ▪ 4 to 8 weeks: 18.0%
	  ▪ > 8 weeks: 34.6%
	  ▪ Unknown: 34%
	• **Hearing thresholds: speech reception thresholds**

	◦ Antibiotics and placebo group: ▪ Right ear: mean 18.42 (SD 10.95), n = 98 ▪ Left ear: mean 20.00 (SD 10.10), n = 97 ◦ Placebo group: ▪ Right ear: mean 20.60 (SD 11.40), n = 91 ▪ Left ear: mean 20.17 (SD 11.84), n = 91 • **Other measure of hearing status: maximum threshold in either ear for pure tone average or speech awareness (db/HL)** ◦ Antibiotics and placebo group: ▪ 0 to 10: 13/155 (8.4%) ▪ 11 to 20: 46/155 (29.7%) ▪ 21 to 30: 49/155 (31.6%) ▪ 31 to 40: 26/155 (16.8%) ▪ > 40: 10/155 (6.4%) ▪ Not measured: 11/155 (7.1%) ◦ Placebo group: ▪ 0 to 10: 9/150 (6%) ▪ 11 to 20: 43/150 (28.7%) ▪ 21 to 30: 48/150 (32%) ▪ 31 to 40: 34/150 (22.7%) ▪ > 40: 8/150 (5.3%) ▪ Not measured: 8/150 (5.3%) **Inclusion criteria:** Diagnosis of otitis media with effusion. Based on a decision tree algorithm, combining findings of a validated otoscopist with results of tympanometry and middle ear muscle reflex testing (Cantekin 1983). If tympanometry or middle ear muscle reflex testing could not be used then otoscopy alone was used. **Exclusion criteria:** • Congenital craniofacial malformation • Systemic illness • Previous tonsillectomy, adenoidectomy or insertion of VT • Structural middle ear abnormalities • Hearing loss not attributable to middle ear effusion • Severe upper airway obstruction • Acute otitis media • Acute or chronic sinusitis • Treatment with sympathomimetic amines or antihistamines during the previous 30 days • Hypersensitivity to any form of penicillin
Interventions	**Antibiotic and placebo group (n = 168 randomised, n = 155 completed)** Liquid suspension of amoxicillin, 40 mg/kg per day in 3 divided doses, and a placebo of similar appearance and taste to decongestant-antihistamine **Placebo group (n = 172 randomised, n = 150 completed)** Two placebos similar in appearance and taste to amoxicillin and decongestant-antihistamine respectively, and containing the same inert ingredients There was another intervention group, antibiotics plus antihistamines; these data were not used in this review **Background interventions administered to all participants** If an acute symptomatic episode (i.e. one accompanied by fever, otalgia, or both) occurred, an antimicrobial agent other than amoxicillin (e.g. cefaclor or erythromycin-sulfisoxazole) was administered for 10 days concurrently with the originally assigned decongestant-antihistamine or its placebo.
Outcomes	**Primary outcomes relevant to this review:**

	• **Hearing: mean (SD) final hearing threshold (dB) per child**
	  ◦ Speech reception thresholds (baseline and 4 weeks)
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ Assessed by tympanometry and tympanogram type 1, 2, 3, 4, 6, 9 or 10 at 4 weeks
	• **Episodes of acute otitis media: proportion exceeding a specified cut-off value for number of episodes of AOM**
	  ◦ Number of children with an acute otitis media at 4 weeks
	• **Other adverse effects**
	  ◦ Mild sedation/and or irritability at 2 and 4 weeks
	  ◦ Diarrhoea at 2 and 4 weeks
	  ◦ Rash at 2 and 4 weeks
	Other outcomes reported in the study:
	• Some data also available at 2 weeks
	• Additional follow-up at 12 weeks but only for participants in whom no effusion was detected at 4 weeks, therefore only for a subset of the RCT participants
	• Assessment of correlation between features of disease and outcome

Funding sources	Funding from a national grant. Methods state that study drugs were “supplied by” Beecham Laboratories, but it is unclear whether this was a funding source for the trial, or simply where the medication was obtained
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retractions or expressions of concern were identified • This trial was published prior to 2010, therefore trial registration was not required • Baseline characteristics are not excessively similar between the groups • Plausible loss to follow-up was reported • No implausible results were reported • Different numbers were randomised to each group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: “Subjects were then grouped according to age (7 to 23 months, 2 to 5 years, or 6 to 12 years), duration of otitis media with effusion (less than four weeks, four to eight weeks, more than eight weeks, or unknown), and whether an antimicrobial agent had been administered during the preceding two months for the otitis media present at entry. The stratification scheme thus resulted in 24 subgroups. Within each subgroup, subjects were randomly assigned in a double-blind fashion (in blocks of three) to one of the following three groups…” Comment: actual method of randomisation is not stated.
Allocation concealment (selection bias)	Unclear risk	Comment: there is no information regarding how or whether allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: authors report that participants were blinded. Unclear whether study personnel were all blinded to group allocations, and some study visits were conducted separately (and prior) to outcome assessment.

Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: “Ninety-two percent of the observations were made by one of us (E.M.M.), who was blinded to the subjects’ treatment groups.” “At 4 weeks, coherence [between tympanometry and otoscopy findings] for the placebo-treated group was 88%, which was significantly higher than coherence values for the two antibiotic-treated groups (P= .012). Although the observers were blinded to treatment assignments, some unknown factors such as reported side effects or conversations with parents might have induced clues about the assignment, thus influencing the observer.” Comment: although blinding was reported, concerns have been raised over the adequacy of blinding, due to differences in outcome data between the intervention and comparator arms. Therefore, we considered that this trial may be at risk of detection bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 6% loss to follow-up, balanced across groups (from data in Cantekin 1991). Unlikely to significantly affect results.
Selective reporting (reporting bias)	High risk	Comment: no protocol available to assess. Cantekin 1991 reports a different cure rate using the same data as Mandel 1987, raising concerns that data were selectively reported.
Other bias	High risk	Comment: potential detection bias through a very short period of follow-up and through the use of a diagnostic algorithm that relied mainly on otoscopic rather than more objective tympanometric measurements.

Mandel 1991

Study characteristics	
Methods	Four-arm, double-blind, parallel-group, randomised controlled trial with 2 weeks of treatment and 4 weeks of follow-up
Participants	**Setting:** Conducted in the USA between July 1984 and December 1987 **Sample size:** • **Number randomised:** 331 participants • **Number completed:** 310 participants **Participant (baseline) characteristics:** • **Age:** ◦ Erythromycin-sulfisoxazole group: ▪ 7 to 23 months: n = 25 (29.8%) ▪ 2 to 5 years: n = 47 (56.0%) ▪ 6 to 12 years: n = 12 (14.3%) ◦ Cefaclor group: ▪ 7 to 23 months: n = 22 (26.5%) ▪ 2 to 5 years: n = 46 (55.4%) ▪ 6 to 12 years: n = 15 (18.1%) ◦ Amoxicillin group: ▪ 7 to 23 months: n = 19 (22.9%) ▪ 2 to 5 years: n = 52 (62.7%) ▪ 6 to 12 years n = 12 (14.5%) ◦ Placebo group: ▪ 7 to 23 months: n = 17 (21%) ▪ 2 to 5 years: n = 43 (53.1%) ▪ 6 to 12 years: n = 21 (25.9%) • **Gender:** ◦ Erythromycin-sulfisoxazole group: ▪ 44 (52.4%) males ▪ 40 (47.6%) females ◦ Cefaclor group:

        - 52 (62.7%) males
        - 31 (37.3%) females
    - Amoxicillin group:
        - 45 (54.2%) males
        - 38 (45.8%) females
    - Placebo group:
        - 45 (55.6%) males
        - 36 (44.4%) females
- **Duration of disease**
    - Erythromycin-sulfisoxazole group:
        - < 4 weeks: n = 15 (17.9%)
        - 4 to 8 weeks: n = 10 (11.9%)
        - > 8 weeks: n = 28 (33.3%)
        - Unknown: n = 31 (36.9%)
    - Cefaclor group:
        - < 4 weeks: n = 14 (16.9%)
        - 4 to 8 weeks: n = 11 (13.3%)
        - > 8 weeks: n = 28 (33.7%)
        - Unknown: n = 30 (36.1%)
    - Amoxicillin group:
        - < 4 weeks: n = 15 (18.1%)
        - 4 to 8 weeks: n = 10 (12%)
        - > 8 weeks: n = 27 (32.5%)
        - Unknown: n = 31 (37.4%)
    - Placebo group
        - < 4 weeks: n = 13 (16.0%)
        - 4 to 8 weeks: n = 10 (12.4%)
        - > 8 weeks: n = 28 (34.6%)
        - Unknown: n = 30 (37%)
- **Hearing speech reception thresholds**
    - Erythromycin-sulfisoxazole group:
        - Right ear: mean 19.2 dB (SD 10.6)
        - Left ear: mean 20.2 dB (SD 10.4)
    - Cefaclor group:
        - Right ear: mean 21.7 dB (SD 12.1)
        - Left ear: mean 20.1 dB (SD 10.4)
    - Amoxicillin group:
        - Right ear: mean 20.3 dB (SD 9.7)
        - Left ear: mean 19.2 dB (SD 10.0)
    - Placebo group:
        - Right ear: mean 22.1 dB (SD 10.3)
        - Left ear: mean 20.6 dB (SD 12.4)

Inclusion criteria:

Aged 7 months to 12 years. Otitis media with effusion and no symptoms of AOM (e.g. otalgia or fever). Based on a decision tree algorithm, combining findings of a validated otoscopist with results of tympanometry and middle ear muscle reflex testing (Cantekin 1983). If tympanometry or middle ear muscle reflex testing could not be used then otoscopy alone was used.

Exclusion criteria:

- Hypersensitivity to erythromycin, sulfonamides or cephalosporins
- Congenital craniofacial malformation

	• Systemic illness • Previous tonsillectomy, adenoidectomy or insertion of VT • Structural middle ear abnormalities • Hearing loss not attributable to middle ear effusion • Severe upper airway obstruction • Acute otitis media • Acute or chronic sinusitis • Treatment with sympathomimetic amines or antihistamines during the previous 30 days • Hypersensitivity to any form of penicillin
Interventions	**Erythromycin-sulfisoxazole group (n = 84 randomised)** 50 mg/kg/day erythromycin and 150 mg/kg/day sulfisoxazole in 4 divided doses for 2 weeks **Cefaclor group (n = 83 randomised)** 40 mg/kg/day in 3 divided doses for 2 weeks **Amoxicillin group (n = 83 randomised)** 40 mg/kg/day in 3 divided doses for 2 weeks **Placebo group (n = 81 randomised)** Three placebos were prepared, colour matched to the different drugs. Participants in this group received one of the 3 placebos.

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing: proportion of ears with hearing returned to normal**
	  ◦ Speech recognition thresholds at 4 weeks
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ Presence of effusion, based on algorithm described above, at 4 weeks
	• **Episodes of acute otitis media: proportion exceeding a specified cut-off value of AOM**
	  ◦ Measured at 2 and 4 weeks
	• **Other adverse effects**
	  ◦ No numeric data are reported; a narrative summary of adverse events was provided
	Other outcomes reported in the study:
	No other results assessed at 2-week follow-up

Funding sources	NIH, Eli Lilly (pharmaceutical funding) and Ross Laboratories (industry funded, in part)
Declarations of interest	Not reported
Notes	**Research integrity checklist:** • No retraction notices or expressions of concern were identified • Prospective trial registration was not required (published prior to 2010) • Baseline characteristics of the groups were not excessively similar • Plausible loss to follow-up is described • No implausible results were reported • Stratified, blocked randomisation was used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Quote: “Within each subgroup, subjects were randomly assigned, in blocks of four…” Comment: no information on generation of random sequence.
Allocation concealment (selection bias)	Unclear risk	Comment: no information is provided regarding whether or how allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “The medication assigned was unknown to the study physician and to the parent” Comment: placebo was used to maintain blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “The medication assigned was unknown to the study physician and to the parent” Comment: outcomes were assessed by blinded physicians.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: few dropouts, which we consider insufficient to introduce significant bias in the results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registration is available with which to compare the reported outcomes.
Other bias	High risk	Comment: follow-up is inadequate to allow appropriate comparison of antibiotics and no intervention. Outcomes reported at this stage may be more likely to favour the active intervention, as insufficient time has elapsed to allow for spontaneous resolution.

Manrique 1987

Study characteristics	
Methods	Four-arm, parallel-group, randomised controlled trial with 3 months of treatment and follow-up Note: data were only extracted for the 2 groups that provided a relevant comparison for this review. Additional groups received either no treatment, or antibiotics plus topical nasal antiseptic/decongestant.
Participants	**Setting:** Conducted in Spain **Sample size:** • **Number randomised:** 59 participants • **Number completed:** 59 participants **Participant (baseline) characteristics:** • **Age:** between 8 months and 13 years • **Gender:** 37 males: 22 female • **Number with bilateral disease:** 45 children **Inclusion criteria:** Children with unilateral or bilateral OME for at least 3 months **Exclusion criteria:** None stated
Interventions	**Antibiotic group:** Amoxicillin 50 mg/kg/day for 8 days (n = 31 ears) **Comparator:** No treatment (n = 21 ears) **Background interventions given to all participants:** Participants in both groups received a daily dose of a decongestant syrup (chlorhydrate ambroxol, dose-dependent on age) for the duration of the trial

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported

	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ Assessed with otoscopy, tympanometry and audiometry at 3 months. Unclear what criteria were used to consider OME to be "resolved" or "not resolved"
	Other outcomes reported in the study:
	No other outcomes were assessed

Funding sources	None reported
Declarations of interest	No declaration is made
Notes	**Research integrity checklist:** • No retraction notices or expressions of concern were identified • Trial registration was not applicable, as this study was published prior to 2010 • Baseline characteristics for each group are not reported, so we are unable to determine whether there is excessive similarity • Loss to follow-up was not reported • No implausible results were noted • The groups included different numbers of participants (ears)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	No report of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo was used for the amoxicillin, therefore we presume that participants were aware of their treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no report of whether blinding was used.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition was reported.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Unclear risk	From the translation, the trial does not appear to be reported in great detail. Therefore, we are unable to assess additional risks of bias.

Marchisio 1998

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial with 2 weeks of treatment and 8 weeks of follow-up
Participants	**Setting:** Multicentre study conducted in 11 primary schools in Italy, during the winter months (October to January), from 1993 to 1995 **Sample size:** • **Number randomised:** 120 participants • **Number completed:** 111 participants **Participant (baseline) characteristics:**

	• **Age:**
	  ◦ Not reported
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 31 (59.6%) males
	  ▪ 21 (40.4%) females
	  ◦ No treatment group:
	  ▪ 33 (55.9%) males
	  ▪ 26 (44.1%) females
	
	Inclusion criteria:
	Aged 5 to 7 years. Children attending the first year of primary school diagnosed with otitis media with effusion, which persisted for at least 3 months. Diagnosed with otoscopy and tympanometry. OME was defined as asymptomatic middle ear effusion, demonstrated by an abnormal appearance of the tympanic membrane, diffusely opaque, with impaired mobility or presence of air-fluid levels associated with a flat, type B tympanometric curve.
	Exclusion criteria:
	• Craniofacial abnormalities
	• Serious underlying disease
	• Major congenital malformation
	• Acute URTI including acute otitis media
	• High risk of sensorineural hearing loss
	• Chronic suppurative otitis media
	• Perforation of tympanic membrane
	• Previous ear surgery
	• Hypersensitivity to a beta-lactam drug
	• Antibiotic therapy in the previous month
	• Concomitant URTI that would preclude evaluation of response to study medication

Interventions	**Antibiotic group (n = 58 randomised, n = 52 completed)** Ceftibuten 9 mg/kg/day in one daily dose for 14 days **Comparator (n = 62 randomised, n = 59 completed)** Nasal saline drops (no information on duration or frequency of use)

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ Assessed at 8 weeks
	• **Other adverse effects**
	  ◦ No numeric data are reported; a narrative summary of adverse events was provided

Funding sources	Work was supported in part by Recordati SpA, Italy, which supplied Ceftibuten Isocef
Declarations of interest	None reported
Notes	**Research integrity checklist:** • No retraction notices or expressions of concern were identified

	• Prospective trial registration was not required (published prior to 2010) • Limited baseline characteristics are presented, but the available data were not excessively similar • Plausible loss to follow-up is described • No implausible results were reported • Different numbers of participants were randomised to each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “One hundred and twenty children were randomised” Comment: no information on random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Comment: no information is provided on how or whether allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: participants were aware of their allocated intervention.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Investigators were blinded to treatment assignments and patients and parents were asked not to discuss medications or duration of treatment with investigators” Comment: outcome assessors were blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: relatively few dropouts, probably insufficient to introduce bias in the results.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available with which to compare the reported outcomes.
Other bias	High risk	Comment: follow-up is inadequate to allow appropriate comparison of antibiotics and no intervention. Outcomes reported at this stage may be more likely to favour the active intervention, as insufficient time has elapsed to allow for spontaneous resolution.

Møller 1990

Study characteristics	
Methods	Two-arm, double-blind, parallel-group randomised controlled trial with 14 days of treatment and 1 month of follow-up

Participants	**Setting:**
	Single-centre, conducted in an outpatient setting in a hospital in Norway. Study dates not reported.
	Sample size:
	• **Number randomised:** 147 participants
	• **Number completed:** 141 participants
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ 1 to 15 years
	  ◦ Median age 5 years
	• **Gender:**
	  ◦ 83 males
	  ◦ 64 females
	Inclusion criteria:
	• Bilateral OME lasting over 3 months
	• No recent acute otitis media (within last 3 months)
	• No obstructive adenoid tissue

	• All patients were candidates for ventilation tubes Diagnosed by otomicroscopy, tympanometry and pure tone hearing tests **Exclusion criteria:** • Cleft palate • Congenital anomaly
Interventions	**Antibiotic group (n = 69 completed)** Erythromycin 50 mg/kg/day in 2 divided doses for 14 days **Placebo group (n = 72 completed)** Placebo treatment

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ Assessed at 1 month
	Other outcomes reported in the study:
	Pure tone hearing tests were performed, but not fully reported, and only reported according to ears with OME and ears without. No comparison of hearing in groups with and without antibiotics.

Funding sources	Not reported
Declarations of interest	None reported
Notes	**Research integrity checklist:** • No retraction notices or expressions of concern were identified • Prospective trial registration was not required (published prior to 2010) • No baseline characteristics were reported, therefore we are unable to assess whether there are excessive similarities • Plausible loss to follow-up is described • No implausible results were reported • The number allocated to each group is not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information is provided regarding randomisation.
Allocation concealment (selection bias)	Unclear risk	Comment: no information is provided regarding whether or how allocation was concealed.
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…” Comment: participants were blinded to their allocated intervention. As the only interaction with study personnel (prior to outcome assessment) was at the point of treatment allocation, we also consider the study personnel to have been blind to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information is provided regarding whether outcome assessors were blinded to treatment allocation.

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: relatively low dropout rate, likely insufficient to introduce bias in the results.
Selective reporting (reporting bias)	High risk	Comment: no protocol is available with which to compare the reported outcomes. Limited data are reported on hearing tests, precluding comparison of the 2 groups, despite this outcome being assessed and recorded.
Other bias	High risk	Comment: follow-up is inadequate to allow appropriate comparison of antibiotics and no intervention. Outcomes reported at this stage may be more likely to favour the active intervention, as insufficient time has elapsed to allow for spontaneous resolution.

Podoshin 1990

Study characteristics	
Methods	Three-arm, double-blind, parallel-group, randomised controlled trial with 2 weeks of treatment and 2 months follow-up

Participants	**Setting:**
	Single-centre, conducted in an ENT department in Israel between September 1987 and December 1988
	Sample size:
	• **Number randomised:** 150 participants
	• **Number completed:** 136 participants
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ Antibiotics plus placebo group:
	  ▪ Mean 7.3 years
	  ▪ Range 4 to 8 years
	  ◦ Antibiotics plus steroid group
	  ▪ Mean 6.5 years
	  ▪ Range 3 to 7 years
	  ◦ Placebo group:
	  ▪ Mean 6.7 years
	  ▪ Range 3 to 7 years
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 27 males
	  ▪ 22 females
	  ◦ Antibiotics plus steroids
	  ▪ 25 males
	  ▪ 25 females
	  ◦ Placebo group:
	  ▪ 20 males
	  ▪ 17 females
	Inclusion criteria:
	Aged greater than 4 years. OME of at least 2 month duration, who had received no previous treatment for OME. Diagnosis made by pneumo-otoscopy using a Welch Allyn halogen illuminated otoscope plus presence of a flat tympanogram (type B).
	Exclusion criteria:
	• Recurrent acute otitis media
	• Cleft palate
	• Hypertrophic adenoids
	• Children with signs of fluid lines, air bubbles or yellow fluid, indicating an already resolving effusion

Interventions	**Antibiotic plus placebo group (n = 49 completed)** Amoxicillin 50 mg/kg/day plus placebo **Antibiotics plus steroids group (n = 50 completed)** As above plus 1 mg/kg prednisolone, reduced by 5 mg every 2 days, therefore tapering course for a total of 14 days. Tablets of prednisolone were pulverised and placed in unmarked gelatin capsules. **Placebo group (n = 37 completed)** Two placebos of lactose powder placed in capsules that were identical to those containing the pulverised prednisolone

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing: proportion of children with hearing returned to normal**
	  ◦ Closure of air-bone gap in worst affected ear at 2 months
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ Tympanometry: anything other than type A at 2 months (performed only on the ear with the worst air-bone gap)

Funding sources	Not reported
Declarations of interest	None reported
Notes	**Research integrity checklist:** • No retraction notices or expressions of concern were identified • Prospective trial registration was not required (published prior to 2010) • Limited baseline characteristics were described, therefore we are unable to assess whether the groups were excessively similar • Plausible loss to follow-up is described • No implausible results were reported • The number allocated to each group is unclear, although may have been identical

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: “They were treated randomly by our directions.” Comment: no further information about generation of a random sequence.
Allocation concealment (selection bias)	Unclear risk	Comment: no information is provided regarding how or whether allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants stated to be blinded. However, no placebo seems to have been used for the antibiotic (only for the prednisolone). The attrition rate was much higher (13%) in the placebo-only group compared with either the antibiotic and placebo group (2%) or the prednisolone and placebo group (0%). This raises the possibility that participants may have been aware that they were not taking any active treatment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information is provided regarding whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: substantial dropout in the placebo group, which may be sufficient to introduce bias in the results.

Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available with which to compare the reported outcomes.
Other bias	High risk	Comment: follow-up is inadequate to allow appropriate comparison of antibiotics and no intervention. Outcomes reported at this stage may be more likely to favour the active intervention, as insufficient time has elapsed to allow for spontaneous resolution.

Puhakka 1985

Study characteristics	
Methods	Three-arm, parallel-group, randomised controlled trial with 6 or 10 days of treatment and 8 weeks of follow-up

Participants	**Setting:**
	Single-centre, conducted in an ENT department in a hospital in Finland. Study dates not reported.
	Sample size:
	• **Number randomised:** 75 participants (122 ears)
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ Mean 4 years and 10 months
	  ◦ Range 7 months to 11 years
	• **Gender**
	  ◦ Not reported
	Inclusion criteria:
	Children suffering from otitis media with effusion. Diagnosed by examination and if necessary otomicroscopy.
	Exclusion criteria:
	Acute otitis media within the preceding 3 months

Interventions	**Antibiotic group (n = 22 children (35 ears) randomised)** 6 mg trimethoprim and 18.5 mg sulfadiazine/kg/day in 2 divided doses for 10 days plus placebo **Antibiotics and steroids group (n = 29 children (47 ears) randomised)** As above plus 1 mg/kg/day of oral prednisolone, divided into 3 doses and given as a decreasing dose for 6 days **Comparator: (n = 24 children (40 ears) randomised)** Two placebo tablets **Background interventions administered to all participants** Myringotomy was conducted on all affected ears at the first visit

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of ears with persistence of OME**
	  ◦ Number of ears cured at 8 weeks
	Other outcomes reported in the study:
	Bacterial cultures of middle ear fluid

Funding sources	Not reported
Declarations of interest	None reported

Notes	**Research integrity checklist:** • No retraction notices or expressions of concern were identified • Prospective trial registration was not required (published prior to 2010) • Limited baseline characteristics of the groups were reported, therefore we are not able to assess them for similarity • No loss to follow-up was reported and no reasons are given for this • No implausible results were reported • Different numbers of participants were allocated to each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Children were randomly allocate *(sic)* to three therapy groups” Comment: no information about the sequence generation process to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: no information regarding whether or how allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: this is described as a double-blind study, but it is not clear who was blinded. It is possible that participants were blinded, but that study personnel were aware of group allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: “Follow-up examinations were always carried out by the ENT specialist who had examined the child initially”. Comment: there is no description of outcome assessors being blinded to group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available for comparison.
Other bias	High risk	Comment: randomisation occurred at the level of the child, but results are reported at the level of the individual ear. No description of correlation between ears, and we cannot determine whether an individual child had cure in both ears or only one ear.

Sundberg 1984

Study characteristics

Methods	Two-arm, parallel-group randomised controlled trial

Participants	**Setting:**
	Single-centre study from Sweden
	Sample size:
	• **Number randomised:** 75 participants
	• **Number completed:** 75 participants
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ Only given for whole cohort: 1.5 to 11 years of age
	• **Gender:**
	  ◦ Not reported
	Inclusion criteria:
	Children aged from 1.5 to 11 years with unilateral or bilateral OME for at least 3 months. OME was diagnosed in the presence of a non-purulent effusion behind an intact tympanic membrane on otomicroscopy, and the presence of a type "B" curve at tympanometry.
	All children were awaiting surgery (myringotomy) for OME
	Exclusion criteria:

	None reported
Interventions	**Antibiotics:** Erythromycin ethylsuccinate 20 to 30 mg/kg twice daily for 10 days **Control group:** No treatment
Outcomes	No data are reported for any of the outcomes included in this review The only outcome described is the specific type of bacteria cultured from the nasopharynx
Funding sources	No funding was reported
Declarations of interest	No declaration was made
Notes	**Research integrity checklist:** • No retraction notices or expressions of concern were identified • Trial registration is not applicable, as this study was published before 2010 • Very few baseline characteristics were reported, therefore we are unable to assess whether there was excessive similarity between the groups • No loss to follow-up was reported. However, children were awaiting surgery therefore this is plausible. • No implausible results were identified • Unequal numbers of participants were randomised to each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "At this stage every second consecutive child in the care of each otologist separately was allotted [*sic*] to the test group". Comment: quasi-randomisation.
Allocation concealment (selection bias)	High risk	Quote: "At this stage every second consecutive child in the care of each otologist separately was allotted [*sic*] to the test group". Comment: allocation was entirely predictable, due to alternate allocation to each group.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no placebo was used. Participants would have been aware of group allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: for the outcomes included in this study (identification of nasopharyngeal pathogens), risk of detection bias is likely to be low, despite the lack of blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: full follow-up is reported.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was identified.
Other bias	Low risk	Comment: no other concerns were identified.

Thomsen 1989

Study characteristics	
Methods	Two-arm, double-blind, parallel-group, randomised controlled trial with 1 month of treatment and 12 months of follow-up
Participants	**Setting:** Single-centre, conducted in a hospital in Denmark between June 1984 and June 1986 **Sample size:** • **Number randomised:** 264 participants • **Number completed:** 221 participants **Participant (baseline) characteristics:** • **Age:** ◦ Not reported

	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 63 males
	  ▪ 68 females
	  ◦ Placebo group
	  ▪ 74 males
	  ▪ 59 females
	Inclusion criteria:
	At least 3 months of unilateral or bilateral otitis media with effusion. Type C2 or B tympanometry curves.
	Exclusion criteria:
	Allergy to penicillin

Interventions	**Antibiotic group (n = 131 randomised, n = 109 completed)** Amoxicillin and clavulanate potassium with 125 mg amoxicillin and 31.25 mg clavulanate potassium per 5 mL. Dose 5 mL 3 times daily (if aged 1 to 5) or 7.5 mL 3 times daily (if aged 6 to 10). Administered for 1 month. **Placebo group (n = 133 randomised, n = 111 completed)** No further details provided **Background interventions administered to all participants** In patients with bilateral disease, a ventilation tube was inserted in the right ear, and the left ear was included in the study

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ Type B or C2 tympanogram at 3 months
	  ◦ Time with abnormal tympanogram by age
	• **Other adverse effects**
	  ◦ Proportion of children who dropped out due to diarrhoea
	Other outcomes reported in the study:
	• Time until first normal tympanogram
	• Subgroups according to unilateral or bilateral disease, and in relation to age
	• Association with seasonality

Funding sources	Not reported
Declarations of interest	None reported
Notes	**Research integrity checklist:** • No retraction notices or expressions of concern were identified • Prospective trial registration was not required (published prior to 2010) • Very limited baseline characteristics are presented, therefore we cannot assess for excessive similarities • Plausible loss to follow-up is described • No implausible results were reported • Different numbers were randomised to each group
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “a double-blind, randomized, placebo controlled clinical trial…” Comment: no further details on methods used for randomisation.
Allocation concealment (selection bias)	Unclear risk	Comment: no details are provided regarding whether or how allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: stated to be double-blind and placebo used. Participants were presumably blinded to intervention, but unclear if this extends to study personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information on whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: limited dropout, balanced across groups, and insufficient to introduce bias in the results. Some concern that dropout may have been related to intervention (9 in placebo had concomitant infection, compared to 3 in intervention group), but not a large number of participants.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol or trial registration is available with which to compare the reported outcomes.
Other bias	Low risk	Comment: no other concerns identified.

van Balen 1996

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial with 2 weeks of treatment and follow-up

Participants	**Setting:**
	Conducted in a general practice setting in the Netherlands between December 1992 and August 1994
	Sample size:
	• **Number randomised:** 162 participants
	• **Number completed:** 153 participants
	Participant (baseline) characteristics:
	• **Age:**
	  ◦ Antibiotics group:
	  ▪ 28% aged under 3 years (n = 23 participants)
	  ▪ 72% aged 3 to 6 years (n = 59 participants)
	  ◦ Placebo group:
	  ▪ 25% aged under 3 years (n = 20 participants)
	  ▪ 75% aged 3 to 6 years (n = 60 participants)
	• **Gender:**
	  ◦ Antibiotics group:
	  ▪ 36 (44%) male
	  ▪ 44 (56%) female
	  ◦ Placebo group:
	  ▪ 33 (41%) male
	  ▪ 49 (59%) female
	• **Other measure of hearing status**
	  ◦ Number with hearing loss
	• **Receptive language**
	  ◦ Language/speech problem
	Inclusion criteria:

	Children with bilateral otitis media with effusion for at least 3 months. Presence of fluid in the middle ear cavity behind an intact tympanic membrane, based on tympanometry findings by the GP with type B or C2 curves **Exclusion criteria:** • Antimicrobial therapy within 4 weeks preceding the trial • Penicillin allergy • Compromised immunity • Referral to an ENT surgeon at the time of inclusion • Craniofacial abnormalities • Down's syndrome • Cystic fibrosis
Interventions	**Antibiotic group (n = 82 randomised, n = 79 completed)** Suspension of co-amoxiclav 20 mg/kg/day amoxicillin plus 5 mg/kg/day clavulanic acid in 3 divided doses for 14 days **Placebo group (n = 80 randomised, n = 74 completed)** Placebo suspension with same colour and taste **Treatment administered before entry into the trial** Watchful waiting for 3 months to ensure OME persistence **Background interventions administered to all participants** One drop of oxymetazoline 0.25% (decongestant) 3 times daily

Outcomes	**Primary outcomes relevant to this review:**
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse event**
	  ◦ Not reported
	Secondary outcomes relevant to this review:
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ Number of children with bilateral OME on tympanometry at 2 weeks
	  ◦ Number of children with unilateral or bilateral OME on tympanometry at 2 weeks
	• **Other adverse effects**
	  ◦ Proportion of children with gastrointestinal side effects
	Other outcomes reported in the study:
	• Association between persistence of OME and other features, e.g. presence of URTI, daycare etc.
	• Prescription of antimicrobials at follow-up

Funding sources	Study drug and placebo were supplied by SmithKline Beecham
Declarations of interest	None reported
Notes	**Research integrity checklist:** • No retraction notices or expressions of concern were identified • Prospective trial registration was not required (published prior to 2010) • Baseline characteristics of the groups were not excessively similar • Plausible loss to follow-up is described • No implausible results were reported • Different numbers were randomised to each group
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The suspensions were dispensed to participating general practitioners in a double-blind fashion with computerised four-block randomisation" Comment: adequate method of randomisation reported.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information on allocation concealment to make a judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “The study groups were randomised to treatment with a suspension of co-amoxiclav, at a daily dose of 20 mg/kg amoxicillin with 5 mg/kg clavulanate potassium, or a placebo suspension with the same colour and taste”. “The suspensions were dispensed to participating general practitioners in a double-blind fashion with computerised four-block randomisation. Throughout the study, doctor and patient remained blinded.” Comment: adequate methods to ensure blinding of participants and study personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “All tympanograms were also classified by a second well-trained general practitioner (FvB). In cases of disagreement between the study doctor and FvB, a team of experts was consulted.” “Throughout the study, doctor and patient remained blinded.” Comment: outcome assessors were blinded to intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 9 of 162 children did not return for follow-up (5%).
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol is available with which to compare the reported outcomes.
Other bias	High risk	Comment: follow-up is inadequate to allow appropriate comparison of antibiotics and no intervention. Outcomes reported at this stage may be more likely to favour the active intervention, as insufficient time has elapsed to allow for spontaneous resolution.

ENT: ear, nose and throat; NIH: National Institutes of Health; OME: otitis media with effusion; PTA: pure tone average; SD: standard deviation; URTI: upper respiratory tract infection; VT: ventilation tube

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Berman 1990	INTERVENTION: treatment with steroids and is relevant for another review in this suite (Mulvaney 2022a)
Bernard 1991	INTERVENTION: treatment with ventilation tubes and is relevant for another review in this suite (MacKeith 2022b)
Choung 2008	INTERVENTION: treatment with steroids, and is relevant for another review in this suite (Mulvaney 2022a)
Corwin 1986	POPULATION: participants were children who had a persistent effusion, 1 month after an isolated episode of acute otitis media, not children with OME
Daly 1991	INTERVENTION: participants received a combined intervention of antibiotics and steroids
de Castro 1982	ALLOCATION: not randomised
Donaldson 1990	COMPARATOR: both groups received different doses of the same antibiotic
Eiden 1997	STUDY DESIGN: commentary article, not an RCT
Ferrara 2005	PARTICIPANTS: had recurrent acute otitis media not OME
Fujita 1994	ALLOCATION: not randomised
Gaskins 1982	PARTICIPANTS: wrong patient population (children with recurrent acute otitis media)
Gasper 2003	STUDY DESIGN: narrative review, not an RCT
Gibson 1996	ALLOCATION: not randomised
Giebink 1990	PARTICIPANTS: children with effusion after an episode of acute otitis media, not OME
Hozawa 2001	ALLOCATION: not randomised

Study	Reason for exclusion
Iino 1989	ALLOCATION: not randomised
Iino 2001	ALLOCATION: not randomised
Kobayashi 2001	ALLOCATION: not randomised
Kuriyama 1980	ALLOCATION: not randomised
Leonetti 1988	STUDY DESIGN: commentary article, not an RCT
Marks 1981	COMPARATOR: antibiotics are compared to a decongestant preparation containing brompheniramine maleate, dextromethorphan and phenylephrine
Paradise 1997	ALLOCATION: not randomised
Parlea 2012	ALLOCATION: not randomised
Perrin 1974	PARTICIPANTS: had acute otitis media, not OME
Persico 1978	ALLOCATION: not randomised
Principi 1989	PARTICIPANTS: wrong patient population
Roark 1997	PARTICIPANTS: wrong patient population
Rohail 2006	INTERVENTION: a variety of different interventions were used in this trial, including some antibiotics, decongestants, steroids and antihistamines
Schloss 1988	PARTICIPANTS: effusion persisting after acute otitis media, not OME
Schwartz 1982	PARTICIPANTS: had recurrent acute otitis media, not OME
Schwartz 1982a	PARTICIPANTS: had recurrent acute otitis media, not OME
Shubich 1996	ALLOCATION: not randomised
Smales 1992	ALLOCATION: not randomised
Stenstrom 2005	ALLOCATION: not randomised
Tracy 1995	PARTICIPANTS: had recurrent acute otitis media, not OME
van Balen 1997	STUDY DESIGN: commentary article, not an RCT
Varsano 1985	PARTICIPANTS: had recurrent acute otitis media, not OME
Velepic 2011	INTERVENTION: treatment with ventilation tubes and is relevant for another review in this suite (MacKeith 2022b)
Yeldandi 2001	COMPARISON: co-interventions were not identical across the 2 study arms
Yin 2002	COMPARISON: wrong comparator
Zocconi 1994	ALLOCATION: not randomised

OME: otitis media with effusion; RCT: randomised controlled trial

Characteristics of studies awaiting classification [ordered by study ID]

Koay 1998

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	Unable to obtain full text

Tawfik 2002

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	Unable to obtain full text

Appendices

Appendix 1. Search strategies

The search strategies were designed to identify all relevant studies for a suite of reviews on various interventions for otitis media with effusion.

CENTRAL (CRS)	Cochrane ENT Register (CRS)	MEDLINE (Ovid)
1 MESH DESCRIPTOR Otitis Media with Effusion EXPLODE ALL AND CENTRAL:TARGET 2 ("otitis media" adj6 effusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 3 (OME):TI,TO AND CENTRAL:TARGET 4 (Secretory otitis media):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 5 (Serous otitis media):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 6 (Middle-ear effusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 7 (glue ear):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 8 (middle-ear perfusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 9 MESH DESCRIPTOR Otitis Media AND CENTRAL:TARGET 10 (otitis media):TI,TO AND CENTRAL:TARGET 11 #9 OR #10 AND CENTRAL:TARGET 12 (((effusion or Recurrent or persistent or serous or secretory or perfusion) adj3 otitis)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 13 #11 AND #12 AND CENTRAL:TARGET 14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #13 AND CENTRAL:TARGET	1 MESH DESCRIPTOR Otitis Media EXPLODE ALL AND INREGISTER 2 ("otitis media" OR OME OR "glue ear" OR middle-ear effusion OR middle-ear perfusion):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 3 #1 OR #2 4 (effusion or Recurrent or persistent or serous or secretory or perfusion):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 5 #3 AND #4	1 exp Otitis Media with Effus 2 ("otitis media" adj6 effusion 3 OME.ti. 4 Secretory otitis media.ab,ti 5 Serous otitis media.ab,ti. 6 Middle-ear effusion.ab,ti. 7 Glue ear.ab,ti. 8 middle-ear perfusion.ab,ti. 9 Otitis Media/ 10 otitis media.ti. 11 9 or 10 12 ((effusion or Recurrent or or serous or secretory or per adj3 otitis).ab,ti. 13 11 and 12 14 1 or 2 or 3 or 4 or 5 or 6 o 13 15 randomized controlled tria 16 controlled clinical trial.pt. 17 randomized.ab. 18 placebo.ab. 19 drug therapy.fs. 20 randomly.ab. 21 trial.ab. 22 groups.ab. 23 15 or 16 or 17 or 18 or 19 21 or 22 24 exp animals/ not humans 25 23 not 24 26 14 and 25
Embase (Ovid)	**Web of Science (Web of knowledge)**	**Trial registries (CR**
1 exp secretory otitis media/ 2 ("otitis media" adj6 effusion).ab,ti. 3 OME.ti. 4 Secretory otitis media.ab,ti. 5 Serous otitis media.ab,ti. 6 Middle-ear effusion.ab,ti. 7 glue ear.ab,ti. 8 middle-ear perfusion.ab,ti. 9 otitis media/ 10 otitis media.ti. 11 9 or 10	11 #10 AND #9 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 10 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 9 TS=(randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple)))	1 ("otitis media" OR OME OR ear" OR middle-ear effusion middle-ear perfusion):AB,EH,KW,KY,MC AND CENTRAL:TARGET 2 (effusion or Recurrent or p serous or secretory or perfusion):AB,EH,KW,KY,MC AND CENTRAL:TARGET 3 #1 AND #2 4 http*:SO AND CENTRAL:T 5 (NCT0* or ACTRN* or Chi DRKS* or EUCTR* or eudra

12 ((effusion or Recurrent or persistent or serous or secretory or perfusion) adj3 otitis).ab,ti. 13 11 and 12 14 1 or 2 or 4 or 5 or 6 or 7 or 8 or 13 15 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw. 16 (control* adj group*).tw. 17 (trial* and (control* or comparative)).tw. 18 ((blind* or mask*) and (single or double or triple or treble)).tw. 19 (treatment adj arm*).tw. 20 (control* adj group*).tw. 21 (phase adj (III or three)).tw. 22 (versus or vs).tw. 23 rct.tw. 24 crossover procedure/ 25 double blind procedure/ 26 single blind procedure/ 27 randomization/ 28 placebo/ 29 exp clinical trial/ 30 parallel design/ 31 Latin square design/ 32 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 33 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/ 34 exp human/ 35 33 not 34 36 32 not 35 37 14 and 36	Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 8 (TI=(otitis media)) AND TS= ((effusion or Recurrent or persistent or serous or secretory or perfusion) NEAR/3 otitis) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 7 TOPIC: ((middle-ear perfusion)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 6 TOPIC: ((glue ear)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 5 TOPIC: ((Middle-ear effusion)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 4 TOPIC: ((Serous otitis media)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 3 TOPIC: ((Secretory otitis media)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 2 TITLE: (OME) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 1 TOPIC: ("otitis media" NEAR/6 effusion) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years	IRCT* or ISRCTN* or JapicC JPRN* or NTR0* or NTR1* o NTR3* or NTR4* or NTR5* o NTR7* or NTR8* or NTR9* o or UMIN0*):AU AND CENTRAL:TARGET 6 #4 OR #5 7 #3 AND #6
ClinicalTrials.gov	**ICTRP**	
(EXPAND[Concept] "otitis media" OR EXPAND[Concept] "glue ear" OR middle-ear) AND (effusion OR Recurrent OR persistent OR serous OR secretory OR perfusion) | Interventional Studies	(otitis media AND effusion) OR glue ear OR middle-ear effusion OR middle-ear perfusion	

Appendix 2. Tool for screening eligible studies for scientific integrity/trustworthiness

This screening tool has been developed by Cochrane Pregnancy and Childbirth. It includes a set of predefined criteria to select studies that, based on available information, are deemed to be sufficiently trustworthy to be included in the analysis.

Criteria questions	**Assessment**		**Comments and concerns**
	High risk	**Low risk**	
Research governance			
	Yes	No	

Are there any retraction notices or expressions of concern listed on the Retraction Watch Database relating to this study?			
Was the study prospectively registered (for those studies published after 2010) If not, was there a plausible reason?	No	Yes	
When requested, did the trial authors provide/share the protocol and/or ethics approval letter?	No	Yes	
Did the trial authors engage in communication with the Cochrane Review authors within the agreed timelines?	No	Yes	
Did the trial authors provide IPD data upon request? If not, was there a plausible reason?	No	Yes	
Baseline characteristics			
Is the study free from characteristics of the study participants that appear too similar? (e.g. distribution of the mean (SD) excessively narrow or excessively wide, as noted by Carlisle 2017)	No	Yes	
Feasibility			
Is the study free from characteristics that could be implausible? (e.g. large numbers of women with a rare condition (such as severe cholestasis in pregnancy) recruited within 12 months)	No	Yes	
In cases with (close to) zero losses to follow-up, is there a plausible explanation?	No	Yes	
Results			
Is the study free from results that could be implausible? (e.g. massive risk reduction for main outcomes with small sample size)?	No	Yes	
Do the numbers randomised to each group suggest that adequate randomisation methods were used (e.g. is the study free from issues such as unexpectedly even numbers of women 'randomised' including a mismatch between the numbers and the methods, if the authors say 'no blocking was used' but still end up with equal numbers, or if the authors say they used 'blocks of 4' but the final numbers differ by 6)?	No	Yes	
For abstracts only:			
Have the study authors confirmed in writing that the data to be included in the review have come from the final analysis and will not change?	No	Yes	

References

References to studies included in this review

Ardehali 2008 {published data only}

Mohammadi Ardehali M, Mahdizade Seraj J, Kiani Asiabar M, Adibi H. The possible role of gastroesophageal reflux disease in children suffering from chronic otitis media with effusion. Acta Medica Iranica 2008;46(1):33-7. [CENTRAL: CN-00708224] 1511305 [EMBASE: 351792703]

Balle 1990 {published data only}

Balle VH, Stangerup SE, Sederberg-Olsen J, Thomsen J, Vejlsgaard R. Amoxicillin/clavulanate treatment in secretory otitis media. Bacteriological findings in the nasopharynx. Acta Oto-laryngologica 1990;110(3-4):274-8. [CENTRAL: CN-00071274] 1006215 [PMID: 2239218]

Chen 2013 {published data only}

Chen K, Wu X, Jiang G, Du J, Jiang H. Low dose macrolide administration for long term is effective for otitis media with effusion in children. Auris, Nasus, Larynx 2013;40(1):46-50. [CENTRAL: CN-00880075] 1653896 [PMID: 22673738]

Endo 1997 {published data only}

Endo LH, Antunes AB, Vidolin C, Bilecki MM, Magalhaes KVB. Secretory media otitis: clinical treatment vs placebo [Otite media secretora: tratamento clinco versus placebo]. Revista Brasileira de Otorrinolaringologia 1997;63(2):116-9. [CENTRAL: CN-00316174] 1195554

Ernston 1985 {published data only}

Ernstson S, Anari M. Cefaclor in the treatment of otitis media with effusion. Acta Oto-laryngologica. Supplementum 1985;424:17-21. [CENTRAL: CN-00040675] 975731 [PMID: 3865493]

Healy 1984 {published data only}

Healy GB. Antimicrobial therapy of chronic otitis media with effusion. International Journal of Pediatric Otorhinolaryngology 1984;8(1):13-7. [CENTRAL: CN-00036115] 971176 [PMID: 6389394]

Hemlin 1997 {published data only}

Hemlin C, Carenfelt C, Papatziamos G. Single dose of betamethasone in combined medical treatment of secretory otitis media. Annals of Otology, Rhinology, and Laryngology 1997;106(5):359-63. [CENTRAL: CN-00139646] 1074207 [PMID: 9153098]

Papatziamos G, Hemlin C, Carenfelt C. A placebo-controlled study of cefixime and the combination of cefixime and betamethasone in children with secretory otitis-media. Recent Advances in Otitis Media 1994:747-9.

Karlidag 2002 {published data only}

Karlidag T, Kaygusuz I, Gok U, Yalcin S, Keles E, Ozturk L. The efficacy of combining antibiotic treatment with topical intranasal steroid administration in the treatment of chronic otitis media with effusion [Efuzyonlu otitis media tedavisinde antibiyotik ile birlikte intranazal steroid kullaniminin etkinligi]. Kulak Burun Bogaz Ihtisas Dergisi: KBB [Journal of Ear, Nose, and Throat] 2002;9(4):257-62. [CENTRAL: CN-00411239] 1270903 [PMID: 12422079]

Leach 2008 {published data only}

[CTG: NCT00539149]

Leach AJ, Morris PS, Mathews JD, Hayhurst B, Koops H, Melder A, et al. Compared to placebo, long-term antibiotics resolve otitis media with effusion (OME) and prevent acute otitis media with perforation (AOMwiP) in a high-risk population: a randomized controlled trial. BMC Pediatrics 2008;8:23. [CENTRAL: CN-00639992] 1454828 [EMBASE: 2008359321] [PMID: 18513453]

NCT00539149. Long-term antibiotics for treatment and prevention of otitis media in aborignal children [Amoxycillin versus placebo for resolution of otitis media with effusion and prevention of acute otitis media with perforation in aboriginal infants: a randomised controlled trial]. https://clinicaltrials.gov/show/NCT00539149 (first received 4 October 2007). [CENTRAL: CN-00652606] 1465946

Mandel 1987 {published data only}

Cantekin EI, McGuire TW, Griffith TL. Antimicrobial therapy for otitis media with effusion ('secretory' otitis media). JAMA 1991;266(23):3309-17. [CENTRAL: CN-00079882] 1014726 [PMID: 1683673]

Mandel EM, Rockette HE, Bluestone CD, Paradise JL, Nozza RJ. Efficacy of amoxicillin with and without decongestant-antihistamine for otitis media with effusion in children. Results of a double-blind, randomized trial. New England Journal of Medicine 1987;316(8):432-7. [CENTRAL: CN-00046384] 981437 [PMID: 2880294]

Mandel 1991 {published data only}

Mandel EM, Rockette HE, Paradise JL, Bluestone CD, Nozza RJ. Comparative efficacy of erythromycin-sulfisoxazole, cefaclor, amoxicillin or placebo for otitis media with effusion in children. Pediatric Infectious Disease Journal 1991;10(12):899-906. [CENTRAL: CN-00080817] 1015645 [PMID: 1766705]

Manrique 1987 {published data only}

Manrique MJ, Hernández J, Huarte A, Rivera R, García-Tapia R. Treatment of secretory otitis media with Ambroxol [Tratamiento de la otitis serosa con Ambroxol]. Acta Pediatrica Española 1987;45(1):17-20.

Marchisio 1998 {published data only}

Marchisio P, Principi N, Passali D, Salpietro DC, Boschi G, Chetrì G, et al. Epidemiology and treatment of otitis media with effusion in children in the first year of primary school. Acta Oto-Laryngologica 1998;118(4):557-62. [CENTRAL: CN-00154484] 1085418 [EMBASE: 1998254893] [PMID: 9726683]

Møller 1990 {published data only}

Moller P, Dingsor G. Otitis media with effusion: can erythromycin reduce the need for ventilating tubes? Journal of Laryngology and Otology 1990;104(3):200-2. [CENTRAL: CN-00067688] 1002714 [PMID: 2341774]

Podoshin 1990 {published data only}

Podoshin L, Fradis M, Ben-David Y, Faraggi D. The efficacy of oral steroids in the treatment of persistent otitis media with effusion. Archives of Otolaryngology--head & Neck Surgery 1990;116(12):1404-6. [CENTRAL: CN-00071613] 1006551 [PMID: 2248740]

Puhakka 1985 {published data only}

Puhakka H, Haapaniemi J, Tuohimaa P, Ruuskanen O, Eskola J. Peroral prednisolone in the treatment of middle-ear effusion in children: a double-blind study. Auris, Nasus, Larynx 1985;12 Suppl 1:S268-71. [CENTRAL: CN-00043250] 978305 [EMBASE: 16731329] [PMID: 3915207]

Sundberg 1984 {published data only}

Sundberg L, Cederberg A, Eden T, Ernstson S. The effect of erythromycin on the nasopharyngeal pathogens in children with secretory otitis media. Acta Oto-Laryngologica 1984;97(3-4):379-83.

Thomsen 1989 {published data only}

Thomsen J, Sederberg-Olsen J, Balle V, Vejlsgaard R, Stangerup SE, Bondesson G. Antibiotic treatment of children with secretory otitis media. A randomized, double-blind, placebo-controlled study. Archives of Otolaryngology--Head & Neck Surgery 1989;115(4):447-51. [CENTRAL: CN-00058572] 993615 [PMID: 2647105]

Thomsen J, Sederberg-Olsen J, Stangerup SE, Balle V, Vejlsgaard R. Long-term antibiotic treatment of children with secretory otitis media: a double-blind placebo-controlled study. Acta Oto-Laryngologica. Supplementum 1988;449(Suppl):49-50. [CENTRAL: CN-00056944] 991987 [PMID: 3059752]

van Balen 1996 {published data only}

van Balen FA, de Melker RA, Touw-Otten FW. Double-blind randomised trial of co-amoxiclav versus placebo for persistent otitis media with effusion in general practice. Lancet 1996;348(9029):713-6. [CENTRAL: CN-00129985] 1064577 [EMBASE: 1996280110] [PMID: 8806290]

References to studies excluded from this review

Berman 1990 {published data only}

Berman S, Grose K, Nuss R, Huber-Navin C, Roark R, Gabbard SA, et al. Management of chronic middle ear effusion with prednisone combined with trimethoprim-sulfamethoxazole. Pediatric Infectious Disease Journal 1990;9(8):533-8. [CENTRAL: CN-00071176] 1006118 [PMID: 2235167]

Bernard 1991 {published data only}

Bernard PA, Stenstrom RJ, Feldman W, Durieux-Smith A. Randomized, controlled trial comparing long-term sulfonamide therapy to ventilation tubes for otitis media with effusion. Pediatrics 1991;88(2):215-22. [CENTRAL: CN-00077175] 1012090 [PMID: 1861917]

Feldman W, Bernard P, Smith A, Stenstrom R. Sulfonamide prophylaxis vs ventilation tubes in hearing-loss due to recurrent otitis-media with effusion (Rome) - preliminary-results of a randomized controlled trial. Clinical and Investigative Medicine [Medecine Clinique et Experimentale] 1987;(4):A33. [CENTRAL: CN-02494379] 6720430

Feldman W, Bernard P, Smith A, Stenstrom R. Sulfonamide prophylaxis vs ventilation tubes in hearing-loss due to recurrent otitis-media with effusion - preliminary-results of a randomized controlled trial. American Journal of Diseases of Children 1987;(4):389-9. [CENTRAL: CN-02494378] 6720424

Feldman W, Bernard P, Smith A, Stenstrom R. Ventilation tubes vs sulfonamide prophylaxis for recurrent acute otitis-media or serious otitis-media - follow-up on a randomized, controlled trial. American Journal of Diseases of Children (first received 1988);(4):407-7. [CENTRAL: CN-02494377] 6720408

Choung 2008 {published data only}

Choung YH, Shin YR, Choi SJ, Park K, Park HY, Lee JB, et al. Management for the children with otitis media with effusion in the tertiary hospital. Clinical and Experimental Otorhinolaryngology 2008;1(4):201-5. [CENTRAL: CN-00671567] 1478067

Corwin 1986 {published data only}

Corwin MJ, Weiner LB, Daniels D. Efficacy of oral antibiotics for the treatment of persistent otitis media with effusion. International Journal of Pediatric Otorhinolaryngology 1986;11(2):109-12. [CENTRAL: CN-00044237] 979292 [PMID: 3488978]

Corwin MJ, Weiner LB, Daniels DA, Daniels DA. Effects of oral antibiotics on the outcome of serous otitis media. Pediatric Research 1982;16:238A. [CENTRAL: CN-00449256] 1302425

Daly 1991 {published data only}

Daly K, Giebink GS, Batalden PB, Anderson RS, Le CT, Lindgren B, et al. Resolution of otitis media with effusion with the use of a stepped treatment regimen of trimethoprim-sulfamethoxazole and prednisone. Pediatric Infectious Disease Journal 1991;10(7):500-6. [CENTRAL: CN-00077629] 1012544 [PMID: 1876465]

Daly K, Giebink GS, Lindgren B, Anderson RS. Controlled clinical trial for prevention of chronic otitis media with effusion. In: Lim DJ, Bluestone CD, Klein JO, editors(s). Recent Advances on Otitis Media: Proceedings of the 4th International Symposium; 1987 Jun 1-4; Toronto (ON). 1987:247-50. [CENTRAL: CN-00452502] 1304944

de Castro 1982 {published data only}

de Castro FJ, Jaeger RW, Martin L, Temeck JW, Tournour B. Serous otitis media. A double-blind trial with sulfisoxazole. Missouri Medicine 1982;79(9):629-30. [CENTRAL: CN-00029746] 964811 [EMBASE: 13245698] [PMID: 6757712]

Donaldson 1990 {published data only}

Donaldson JD, Martin GF, Maltby CC, Seywerd EB. The efficacy of pulse-dosed antibiotic therapy in the management of persistent otitis media with effusion. Journal of Otolaryngology 1990;19(3):175-8. [CENTRAL: CN-00068309] 1003330 [PMID: 2192073]

Eiden 1997 {published data only}

Eiden P. Antibiotic therapy for otitis media infection with effusion in children can make surgery unnecessary. Deutsche Apotheker Zeitung 1997;137(8):41-2. 3565119

Ferrara 2005 {published data only}

Ferrara S, Sammartano D, Ferrara P. Long-term management of recurrent otitis media with effusion in children. In: XVIII IFOS World Congress; 2005 Jun 25-30; Rome (Italy). 2005. [CENTRAL: CN-00526409] 1368400

Fujita 1994 {published data only}

Fujita A, Kurata K, Takahashi H, Takagita S. Clinical efficacy of clarithromycin treatment of refractory otitis media with effusion. Practica Otologica 1994;87(9):1287-91. 3565121

Gaskins 1982 {published data only}

Gaskins JD, Holt RJ, Kyong CU, Weart CW, Ward J. Chemoprophylaxis of recurrent otitis media using trimethoprim/sulfamethoxazole. Drug Intelligence & Clinical Pharmacy 1982;16(5):387-90. [CENTRAL: CN-00028043] 963111 [PMID: 7084029]

Gasper 2003 {published data only}

Gasper K, St Anna L, Montgomery L. Are antibiotics effective for otitis media with effusion? Journal of Family Practice 2003;52(4):321-3. 12618373 [EMBASE: 36427691]

Gibson 1996 {published data only}

Gibson PG, Stuart JE, Wlodarczyk J, Olson LG, Hensley MJ. Nasal inflammation and chronic ear disease in Australian Aboriginal children. Journal of Paediatrics and Child Health 1996;32(2):143-7. [CENTRAL: CN-00131589] 1066176 [PMID: 8860389]

Giebink 1990 {published data only}

Giebink GC, Batalden PB, Le CT, Russ JN, Knox JK, Anderson RS. Randomized controlled trial comparing trimethoprim-sulfamethoxazole, prednisone, ibuprofen, and no treatment in chronic otitis media with effusion. In: Lim DJ, Bluestone CD, Klein JO, editors(s). Recent Advances Otitis Media: Proceedings of the Fourth International Symposium; 1988 Jun 1-4 Toronto (Canada). 1988:240-4. [CENTRAL: CN-00452593] 1305026

Giebink GS, Batalden PB, Le CT, Lassman FM, Buran DJ, Seltz AE. A controlled trial comparing three treatments for chronic otitis media with effusion. Pediatric Infectious Disease Journal 1990;9(1):33-40. [CENTRAL: CN-00065358] 1000394 [PMID: 2405348]

Hozawa 2001 {published data only}

Hozawa T. Evidence-based macrolide therapy for children with serous otitis media. Japanese Journal of Antibiotics 2001;54(Suppl C):30-2. 12618393 [EMBASE: 36495134]

Iino 1989 {published data only}

Iino Y, Ishitoya J, Ikeda M, Ito Y, Usami M, Kawashiro N, et al. Factors on delayed recovery of otitis media with effusion in children--clinical and bacteriological study. Nihon Jibiinkoka Gakkai Kaiho 1989;92(8):1183-91. [CENTRAL: CN-00063873] 998912 [PMID: 2685215]

Iino 2001 {published data only}

Iino Y. Efficacy of macrolide therapy for children with serous otitis media. Japanese Journal of Antibiotics 2001;54 Suppl C:23-5. 12615763 [EMBASE: 36495133] [PMID: 12575412]

Kobayashi 2001 {published data only}

Kobayashi K. Applicability of long-term low-dosage macrolide therapy for children with serous otitis media. Japanese Journal of Antibiotics 2001;54 Suppl C:26-9. 12615762 [PMID: 12627599]

Kuriyama 1980 {published data only}

Kuriyama K. Synergistic effect of antibiotics and Chinese drug on recurrent otitis media. Otolaryngology 1980;52(9):617-22. 12618642 [EMBASE: 11228874]

Leonetti 1988 {published data only}

Leonetti JP, Stankiewicz JA. Antimicrobial prophylaxis for recurrent otitis media. Otolaryngology - Head & Neck Surgery 1988;99(1):81-2. 12616223 [PMID: 3140190]

Marks 1981 {published data only}

Marks NJ, Mills RP, Shaheen OH. A controlled trial of cotrimoxazole therapy in serous otitis media. Journal of Laryngology and Otology 1981;95(10):1003-9. [CENTRAL: CN-00026372] 961441 [EMBASE: 1982075258] [PMID: 7028896]

Paradise 1997 {published data only}

Paradise J, Campbell T, Dollaghan C, Feldman H, Bernard B, Colborn K, et al. Receptive vocabulary, cognition, and parent-rated behavior at age 3 years in relation to otitis media in the first 3 years of life. In: Abstract Book of the Association of Health Service Research. Vol. 14. 1997:350-1. [CENTRAL: CN-00452820] 1305231

Parlea 2012 {published data only}

Parlea E, Georgescu M, Calarasu R. Tympanometry as a predictor factor in the evolution of otitis media with effusion. Journal of Medicine and Life 2012;5(4):452-4. [CENTRAL: CN-00850240] 1626099 [EMBASE: 369159817] [PMID: 23346249]

Perrin 1974 {published data only}

Perrin JM, Charney E, MacWhinney JBJ, McInerny TK, Miller RL, Nazarian LF. Sulfisoxazole as chemoprophylaxis for recurrent otitis media. A double-blind crossover study in pediatric practice. New England Journal of Medicine 1974;291(13):664-7. [CENTRAL: CN-00010786] 947282 [PMID: 4153093]

Persico 1978 {published data only}

Persico M, Podoshin L, Fradis M, Fradis M. Otitis media with effusion: a steroid and antibiotic therapeutic trial before surgery. Annals of Otology, Rhinology, and Laryngology 1978;87:191-5. [CENTRAL: CN-00449363] 1302503 [PMID: 646286]

Principi 1989 {published data only}

Principi N, Marchisio P, Massironi E, Grasso RM, Filiberti G. Prophylaxis of recurrent acute otitis media and middle-ear effusion. Comparison of amoxicillin with sulfamethoxazole and trimethoprim. American Journal of Diseases of Children 1989;143(12):1414-8. [CENTRAL: CN-00063984] 999023 [PMID: 2589274]

Roark 1997 {published data only}

Roark R, Berman S. Continuous twice daily or once daily amoxicillin prophylaxis compared with placebo for children with recurrent acute otitis media. Pediatric Infectious Disease Journal 1997;16(4):376-81. [CENTRAL: CN-00138754] 1073325 [PMID: 9109139]

Rohail 2006 {published data only}

Rohail A, Gill ZI, Butt MR. A comparison of medical treatment versus surgical treatment for the management of otitis media with effusion. Annals of King Edward Medical College 2006;12(1):64-7. [CENTRAL: CN-00597368] 1421949

Schloss 1988 {published data only}

Schloss MD, Dempsey EE, Rishikof E, Sorga S, Grace MGA. Double blind study comparing erythromycin-sulfisoxazole (Pediazole) TID to placebo in chronic otitis media with effusion. In: Lim DJ, Bluestone CD, Klein JO, editors(s). Recent Advances on Otitis Media: Proceedings of the 4th International Symposium; 1987 Jun 1-4; Toronto (ON). 1988:261-3. [CENTRAL: CN-00452893] 1305287

Schloss MD, Rishikof E, Sorger S, Dempsey EE, Grace M. A double-blind study comparing erythromycin-sulfisoxazole (Pediazole (R)) t.i.d. with placebo in chronic otitis media with effusion. Today's Therapeutic Trends 1988;5(4):43-56. [CENTRAL: CN-00192403] 1119256 [EMBASE: 1988100915]

Schwartz 1982 {published data only}

Schwartz RH, Rodriguez WJ. Trimethoprim-sulfamethoxazole treatment of persistent otitis media with effusion. Pediatric Infectious Disease Journal 1982;1(5):333-5. [CENTRAL: CN-00030082] 965147 [PMID: 7155965]

Schwartz 1982a {published data only}

Schwartz RH, Puglise J, Rodriguez WJ. Sulphamethoxazole prophylaxis in the otitis-prone child. Archives of Disease in Childhood 1982;57(8):590-3. [CENTRAL: CN-00028780] 963848 [PMID: 7051984]

Shubich 1996 {published data only}

Shubich I. Otitis media with effusion and allergy control in children: a prospective study. In: Sixth International Symposium on Otitis Media; 1996; Fort Lauderdale (FL). 1996:173-4. [CENTRAL: CN-00452904] 1305298

Smales 1992 {published data only}

Smales O. Antibiotics for otitis media with effusion. New Zealand Medical Journal 1992;105(927):42. 12616129 [PMID: 1538867]

Stenstrom 2005 {published data only}

Stenstrom R, Pless IB, Bernard P. Hearing thresholds and tympanic membrane sequelae in children managed medically or surgically for otitis media with effusion.

Archives of Pediatrics & Adolescent Medicine 2005;159(12):1151-6. [CENTRAL: CN-00532329] 1373954 [PMID: 16330739]

Tracy 1995 {published data only}

Tracy JM, Demain JG, Hoffman K, Goetz DW. Intranasal beclomethasone as an adjunct to treatment of chronic middle ear effusion. Annals of Allergy, Asthma & Immunology 1995;74:59. [CENTRAL: CN-00285148] 1179750

Tracy JM, Demain JG, Hoffman KM, Goetz DW. Intranasal beclomethasone as an adjunct to treatment of chronic middle ear effusion. Annals of Allergy, Asthma & Immunology 1998;80(2):198-206. [CENTRAL: CN-00148310] 1082706 [PMID: 9494455]

van Balen 1997 {published data only}

van Balen FA. Antibiotics in otitis media with effusion [Antibiotica bij otitis media met effusie]. Nederlands Tijdschrift voor Geneeskunde 1997;141(8):401-2. 12615946 [PMID: 9157309]

Varsano 1985 {published data only}

Varsano I, Volovitz B, Mimouni F. Sulfisoxazole prophylaxis of middle ear effusion and recurrent acute otitis media. American Journal of Diseases of Children 1985;139(6):632-5. [CENTRAL: CN-00038335] 973391 [PMID: 3890523]

Velepic 2011 {published data only}

Velepic M, Starcevic R, Bonifacic M, Ticac R, Kujundzic M, Udovic DS, et al. The clinical status of the eardrum: an inclusion criterion for the treatment of chronic secretory otitis media in children. International Journal of Pediatric Otorhinolaryngology 2011;75(5):686-90. [CENTRAL: CN-00784332] 1581204 [EMBASE: 51315541] [PMID: 21397957]

Yeldandi 2001 {published data only}

Yeldandi V, MacLeod C, Mulvaney AM. Open-label, randomised, comparative study of usual care with or without clarithromycin suspension in serous otitis media with inflammation. In: 22nd International Congress of Chemotherapy; 2001 Jun 30-Jul 3; Amsterdam (the Netherlands). 2001. [ABSTRACT NO.: P10.009] [CENTRAL: CN-00453008] 1305387

Yin 2002 {published data only}

Yin TF, Tang QL, Xie DH, Lu YD. Efficacy of cefaclor in treating children with secretory otitis media. Shanghai Medicine 2002;23(2):65-6. [CENTRAL: CN-00416980] 1276330

Zocconi 1994 {published data only}

Zocconi E. Antibiotics and oral steroids in the treatment of otitis media with effusion. Pediatria Medica e Chirurgica 1994;16(3):273-5. 3565130

References to studies awaiting assessment

Koay 1998 {published data only}

Koay B, Commins DJ, Bates S, Mitchell B, Moore A, Bates G, et al. In search of a medical treatment for otitis media with effusion (OME): a randomised double-blind controlled trial (RCT). In: 7th International Congress of Pediatric Otorhinolaryngology. Helsinki, Finland, 7-10 June, 1998. 1998:64. [ABSTRACT NUMBER: 289] [CENTRAL: CN-00292550] 1181636

Tawfik 2002 {published data only}

Tawfik S, Belal A, Sorour W. A comparative study of the different treatment modalities of otitis media with effusion in children. In: 8th International Congress of Paediatric Otorhinolaryngology (ESPO). Oxford, UK, 11-14 September, 2002. 2002:151, Abstract No. P2.26. [CENTRAL: CN-00508402] 1352190

Additional references

Abidin 1995

Abidin RR. Parenting Stress Index: Professional Manual. Odessa, FL: Psychological Assessment Resources, 1995.

Achenbach 2011

Achenbach T M. Child Behavior Checklist. In: Kreutzer JS, DeLuca J, Caplan B, editors(s). Encyclopedia of Clinical Neuropsychology. New York, NY: Springer, 2011.

Bayley 2006

Bayley N. Bayley Scales of Infant and Toddler Development. San Antonio, TX: Harcourt Assessment, Inc, 2006.

Bruce 2015

Bruce I, Harman N, Williamson P, Tierney S, Callery P, Mohiuddin S, et al. The management of Otitis Media with Effusion in children with cleft palate (mOMEnt): a feasibility study and economic evaluation. Health Technology Assessment 2015;19(68):1-374. [DOI: 10.3310/hta19680]

Cantekin 1983

Cantekin EI. Algorithm for diagnosis of otitis media with effusion. Annals of Otology, Rhinology & Laryngology 1983;92(6 Suppl):6-6. [DOI: 10.1177/00034894830920S603]

Cochrane ENT 2020

Cochrane ENT. Otitis media with effusion: a project to prioritise Cochrane systematic reviews. https://ent.cochrane.org/otitis-media-effusion-ome-glue-ear 2020.

Daniel 2012

Daniel M, Imtiaz-Umer S, Fergie N, Birchall JP, Bayston R. Bacterial involvement in otitis media with effusion. International Journal of Pediatric Otorhinolaryngology 2012;76:1416-22. [DOI: 10.1016/j.ijporl.2012.06.013]

Dunn 2007

Dunn LM, Dunn DM. Peabody Picture Vocabulary Test (PPVT™-4). 4th edition. Pearson Education, 2007.

Fekkes 2000

Fekkes M, Theunissen NC, Brugman E, Veen S, Verrips EG, Koopman HM, et al. Development and psychometric evaluation of the TAPQOL: a health-related quality of life instrument for 1–5-year-old children. Quality of Life Research 2000;9:961-72.

Flynn 2009

Flynn T, Möller C, Jönsson R, Lohmander A . The high prevalence of otitis media with effusion in children with cleft lip and palate as compared to children without clefts. International Journal of Pediatric Otorhinolaryngology 2009;73:1441-6. [DOI: 10.1016/j.ijporl.2009.07.015]

Galbraith 2022

Galbraith K, Mulvaney CA, MacKeith S, Marom T, Daniel M, Venekamp RP, et al. Autoinflation for otitis media with effusion (OME) in children. Cochrane Database of Systematic Reviews 2022, Issue 4. Art. No: CD015253. [DOI: 10.1002/14651858.CD015253]

Goodman 1997

Goodman R. The Strengths and Difficulties Questionnaire: a research note. Journal of Child Psychology and Psychiatry 1997;38:581-6.

Gresham 1990

Gresham FM, Elliott SN. Social Skills Rating System. Circle Pines, MN: American Guidance Service, 1990.

Griffiths 1996

Griffiths R. The Griffiths Mental Development Scales from Birth to Two Years, Manual, the 1996 revision. Henley: Association for Research in Infant and Child Development, Test Agency, 1996.

Haggard 2003

Haggard MP, Smith SC, Nicholls EE. Quality of life and child behaviour. In: Rosenfeld RM, Bluestone CD, editors(s). Evidence-Based Otitis Media. 2nd edition. Hamilton, Ontario: BC Decker Inc, 2003:401-29. [https://researchonline.lshtm.ac.uk/id/eprint/15108]

Handbook 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hedrick 1984

Hedrick DL, Prather EM, Tobin AR. Sequenced Inventory of Communication Development. Seattle, WA: University of Washington Press, 1984.

Higgins 2021

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Jellinek 1988

Jellinek MS, Murphy JM, Robinson J, Feins A, Lamb S, Fenton T. Pediatric Symptom Checklist: screening school-age children for psychosocial dysfunction. Journal of Pediatrics 1988;112(2):201-9. [DOI: 10.1016/s0022-3476(88)80056-8]

Kreiner-Møller 2012

Kreiner-Møller E, Chawes BL, Caye-Thomasen P, Bønnelykke K, Bisgaard H. Allergic rhinitis is associated with otitis media with effusion: a birth cohort study. Clinical

and Experimental Allergy 2012;42(11):1615-20. [DOI: 10.1111/j.1365-2222.2012.04038.x]

Landgraf 1994

Landgraf JM. The Infant/Toddler Child Health Questionnaire: conceptual framework, logic content, and preliminary psychometric results. Boston: Health Act, 1994.

Landgraf 1996

Landgraf JL, Abetz L, Ware JE. The CHQ User's Manual. Boston: The Health Institute, New England Medical Center, 1996.

Lefebvre 2020

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Liu 2020

Liu PZ, Ismail-Koch H, Stephenson K, Donne AJ, Fergie N, Derry J, et al. A core outcome set for research on the management of otitis media with effusion in otherwise-healthy children. International Journal of Pediatric Otorhinolaryngology 2020;134:110029. [DOI: 10.1016/j.ijporl.2020.110029]

MacKeith 2022a

MacKeith S, Mulvaney CA, Galbraith K, Marom T, Daniel M, Venekamp RP, et al. Adenoidectomy for otitis media with effusion (OME) in children. Cochrane Database of Systematic Reviews 2022, Issue 4. Art. No: CD015252. [DOI: 10.1002/14651858.CD015252]

MacKeith 2022b

MacKeith S, Mulvaney CA, Galbraith K, Marom T, Daniel M, Venekamp RP, et al. Ventilation tubes (grommets) for otitis media with effusion (OME) in children. Cochrane Database of Systematic Reviews 2022, Issue 3. Art. No: CD015215. [DOI: 10.1002/14651858.CD015215]

Maris 2014

Maris M, Wojciechowski M, Van de Heyning P, Boudewyns A. A cross-sectional analysis of otitis media with effusion in children with Down syndrome. European Journal of Pediatrics 2014;173:1319-25. [DOI: 10.1007/s00431-014-2323-5]

Marseglia 2008

Marseglia GL, Pagella F, Caimmi D, Caimmi S, Castellazzi AM, Poddighe D, et al. Increased risk of otitis media with effusion in allergic children presenting with adenoiditis. Otolaryngology – Head and Neck Surgery 2008;138(5):572-5. [DOI: 10.1016/j.otohns.2008.01.020]

Marshall 2018

Marshall J, Noel-Storr AH, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying randomized controlled trials: an evaluation and practitioner's guide. Research Synthesis Methods 2018;9(4):602-14.

McCarthy 1972

McCarthy D. Manual for the McCarthy Scales of Children's Abilities. New York: Psychological Corp, 1972.

McDonald 2017

McDonald S, Noel-Storr AH, Thomas J. Harnessing the efficiencies of machine learning and Cochrane Crowd to identify randomised trials for individual Cochrane reviews. In: Global Evidence Summit; 2017 Sep 13-17; Cape Town, South Africa. 2017.

Mulvaney 2022a

Mulvaney CA, Galbraith K, MacKeith S, Marom T, Daniel M, Venekamp RP, et al. Topical and oral steroids for otitis media with effusion (OME) in children. Cochrane Database of Systematic Reviews 2022, Issue 4. Art. No: CD015255. [DOI: 10.1002/14651858.CD015255]

NICE 2008

NICE. Otitis media with effusion in under 12s: Otitis media with effusion in under 12s: surgery (CG60). https://www.nice.org.uk/guidance/cg60 2008.

Noel-Storr 2018

Noel-Storr AH. Cochrane Crowd: new ways of working together to produce health evidence. In: Evidence Live; 2018 Jun 18-20; Oxford, UK. 2018.

Park 2004

Park C-W, Han J-H, Jeong J-H, Cho S-H, Kang M-J, Tae K, et al. Detection rates of bacteria in chronic otitis media with effusion in children. Journal of Korean Medical Science 2004;19:735-8. [DOI: 10.3346/jkms.2004.19.5.735]

Poetker 2005

Poetker DM, Lindstrom DR, Edmiston CE, Krepel CJ, Link TR, Kerschner JE. Microbiology of middle ear effusions from 292 patients undergoing tympanostomy tube placement for middle ear disease. International Journal of Pediatric Otorhinolaryngology 2005;69(6):799-804. [DOI: 10.1016/j.ijporl.2005.01.012]

Rabin 2001

Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Annals of Medicine 2001;33(5):337-43.

RevMan 2014 [Computer program]

Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Reynell 1985

Reynell JH. Reynell Development Language Scales Manual. Windsor, UK: NFER-NELSON, 1985.

Rosenfeld 1997

Rosenfeld RM, Goldsmith AJ, Tetlus L, Balzano A. Quality of life for children with otitis media. Archives of Otolaryngology--Head & Neck Surgery 1997;123:1049-54. [DOI: 10.1001/archotol.1997.01900100019002]

Rosenfeld 2000

Rosenfeld RM, Bhaya MH, Bower CM, Brookhouser PE, Casselbrant ML, Chan KH, et al. Impact of tympanostomy tubes on child quality of life. Archives of Otolaryngology--Head & Neck Surgery 2000;126:585-92.

Rosenfeld 2003

Rosenfeld RM, Kay D. Natural history of untreated otitis media. Laryngoscope 2003;113:1645-57. [DOI: 10.1097/00005537-200310000-00004]

Rosenfeld 2016

Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, et al. Clinical practice guideline: otitis media with effusion (update). Otolaryngology - Head & Neck Surgery 2016;154(1 Suppl):S1-S41.

Schlichting 2007

Schlichting JEPT, Lutje Spelberg HC. Lexilijst Begrip: an instrument to investigate language comprehension in children aged 15-25 months in the context of early identification. Amsterdam: Pearson Assessment & Information BV, 2007.

Schlichting 2010

Schlichting JEPT, Lutje Spelberg HC. Schlichting Test for Language Comprehension; Instruction Manual. Woooden: Bohn Stafleu van Loghum, 2010.

Schmalbach 2021

Schmalbach CE, Brereton J, Bowman C, Denneny III JC. American Academy of Otolaryngology–Head and Neck Surgery/Foundation Reg-ent Registry: Purpose, Properties, and Priorities. Otolaryngology–Head and Neck Surgery 2021;164(5):964-71.

Seppanen 2020

Seppanen E, Thornton R, North H, Corscadden KJ, Wiertsema S, Vijayasekaran S, et al. Bacterial reservoirs in the middle ear of otitis-prone children are associated with repeat ventilation tube insertion. Pediatric Infectious Disease Journal 2020;39(2):91-6. [DOI: 10.1097/INF.0000000000002541]

Thomas 2017

Thomas J, Noel-Storr AH, Marshall I, Wallace B, McDonald S, Mavergames C, et al, Living Systematic Review Network. Living systematic reviews 2: combining human and machine effort. Journal of Clinical Epidemiology 2017;91:31-7.

TNO 1997

TNO—Prevention and Health/LUMC. TAIQOL—Questionnaire for parents of children aged 1—5 years. Leiden, The Netherlands: Leiden University Medical Center, 1997.

Venekamp 2016

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]

Verrips 1998

Verrips GH, Vogels AGC, Verloove-Vanhorick SP, Fekkes M, Koopman HM, Kamphuis RP, et al. Health-related quality of life measure for children - the TACQOL. Journal

of Applied Therapeutics 1998;1(4):357-60.

Wallace 2017

Wallace BC, Noel-Storr AH, Marshall IJ, Cohen AM, Smalheiser NR, Thomas J. Identifying reports of randomized controlled trials (RCTs) via a hybrid machine learning and crowdsourcing approach. Journal of the American Medical Informatics Association 2017;24(6):1165-8. [DOI: 10.1093/jamia/ocx053]

Williamson 2011

Williamson I. Otitis media with effusion in children. BMJ Clinical Evidence 2011;2011:0502. [PMID: 21477396]

Zernotti 2017

Zernotti ME, Pawankar R, Ansotegui I, Badellino H, Croce JS, Hossny E, et al. Otitis media with effusion and atopy: is there a causal relationship? World Allergy Organization Journal 2017;10(1):37. [DOI: 10.1186/s40413-017-0168-x]

Zimmerman 1992

Zimmerman IL, Steiner VG, Pond RE. Preschool Language Scale-3. San Antonio, TX: The Psychological Corporation, 1992.

References to other published versions of this review

Mulvaney 2022b

Mulvaney CA, Galbraith K, MacKeith S, Marom T, Daniel M, Venekamp RP, et al. Antibiotics for otitis media with effusion (OME) in children. Cochrane Database of Systematic Reviews 2022, Issue 4. Art. No: CD015254. [DOI: 10.1002/14651858.CD015254]

Figures and tables

Additional tables

Table 1

Sensitivity analyses

Outcome	Main analysis result	Sensitivity analysis	Sensitivity analysis result
Antibiotics versus placebo			
1.2 Hearing threshold: speech reception threshold (short-term)	MD -2.58 (-4.52 to -0.65)	Fixed-effect model	MD -2.58 (-4.52 to -0.65)
1.6 Persistence of OME (short-term)	RR 0.88 (0.78 to 1.00)	Exclusion of studies with any concerns over trustworthiness	RR 0.92 (0.85 to 1.00)
1.6 Persistence of OME (short-term)	RR 0.88 (0.78 to 1.00)	Fixed-effect model	RR 0.90 (0.84 to 0.96)
1.10 Persistence of OME (medium-term)	RR 0.89 (0.68 to 1.17)	Exclusion of studies with any concerns over trustworthiness	RR 1.06 (0.73 to 1.53)
1.10 Persistence of OME (medium-term)	RR 0.89 (0.68 to 1.17)	Fixed-effect model	RR 0.87 (0.70 to 1.09)
1.14 Episodes of acute otitis media	RR 0.68 (0.42 to 1.10)	Fixed-effect model	RR 0.67 (0.42 to 1.09)
Antibiotics versus no treatment			
2.3 Persistence of OME (short-term)	RR 0.64 (0.50 to 0.80)	Fixed-effect model	RR 0.60 (0.53 to 0.68)
2.3 Persistence of OME (short-term)	RR 0.64 (0.50 to 0.80)	Exclusion of studies at high risk of bias	RR 0.66 (0.50 to 0.86)

MD: mean difference; OME: otitis media with effusion; RR: risk ratio

Table 2

Comparison of studies

Study	Participants	Setting	Intervention	Comparator	Concomitant treatment	Follow-up (main outcomes reported at this time)	Note
Ardehali 2008	Children aged 2 to 12 years with chronic OME (≥ 3 months), without response to 3 courses of antibiotics (n = 60)	Single-centre study from Iran	Co-amoxiclav, 40 mg/kg/day in 3 divided doses for 3 months	No treatment	None reported	3 months	A third a received reflux medicati but this v not relev this revie therefore were not extracte
Balle 1990	Children aged 1 to 10 years with at least 3 months duration of uni- or bilateral OME (n = 264)	Study conducted in Denmark. No details on participants recruitment.	4 weeks treatment with amoxicillin and clavulanate potassium. Concentration not stated. Children aged 1 to 5 had 5 mL 3 times daily, children aged 6 to 10 had 7.5 mL 3 times daily.	Placebo	None reported	12 months	Note tha study did provide a data for outcome interest i review
Chen 2013	Children aged 3 to 14 years with OME for less than 3 months (n = 84)	Single-centre, university ENT department in China	Clarithromycin 15 mg/kg/day in 2 divided doses for 1 week, then 5 to 8 mg/kg/day until the tympanogram was type A (range of treatment 5 to 12 weeks)	No treatment	Topical glucocorticoid spray was given to all participants for 12 weeks It appears that all participants underwent tympanocentesis at the start of the trial	12 weeks	Two chil in the intervent group ac received azithrom instead clarithro
Endo 1997	Children with bilateral OME, aged less than 2 years (n = 26)	Single-centre study from Brazil	Sulfamethoxazole-trimethoprim 20 mg/kg/day in a single night-time dose for 30 days	Stated to be placebo, but no information on the nature of the placebo is provided	None reported	4 weeks	Note tha trial also included children, they rec a differe intervent not relev for this r
Ernston 1985	Children aged < 12 years with uni- or bilateral OME for at least 3 months (n = 91)	Single-centre study from Sweden	Cefaclor 20 mg/kg twice daily for 10 days	No treatment	None reported	10 days	—
Healy 1984	Children aged 2 to 5 years with OME for ≤ 6 weeks (n = 200)	Single-centre, University hospital study from USA	Trimethoprim-sulfamethoxazole (8 mg and 40 mg/kg/day respectively) in 2 divided doses for 4 weeks	No treatment	None reported	4 weeks	—
Hemlin 1997	Children aged 2 to 12	Single-centre study	Cefixime 8 mg/kg per day in 2 divided	Placebo suspension	None reported	12 to 21 days	Note tha third arm

	years with uni- or bilateral OME for at least 3 months (n = 81)	from Sweden	doses for 10 days	of similar appearance			received antibiotic steroids. are not relevant this revie have not included here.
Karlidag 2002	Children aged 2 to 12 years with uni- or bilateral OME (n = 42)	Single-centre study from Turkey	Ampicillin/sulbactam 25 mg/kg/day, in 2 divided doses for 8 weeks	No treatment	None reported	8 weeks	Note tha third arm received antibiotic steroids. are not relevant this revie have not included here.
Leach 2008	Aboriginal infants aged < 12 months with OME (n = 103)	Recruited from 3 Aboriginal communities in Australia	Amoxicillin 50 mg/kg/day for 24 weeks, or until bilateral normal middle ear status	Placebo suspension of equivalent volume	None reported	24 weeks	—
Mandel 1987	Children aged 7 months to 12 years with OME (n = 340)	Single-centre study from the USA	Amoxicillin 40 mg/kg per day in 3 divided doses for 2 weeks	Placebo	Both groups also received an additional placebo for the third arm of this study	4 weeks	A third treatmer received antibiotic antihista Data we relevant this revie therefore included
Mandel 1991	Children aged 7 months to 12 years with OME (n = 331)	Single-centre study from the USA	Erythromycin and sulfisoxazole (50 mg and 150 mg/kg/day respectively) in 4 divided doses for 2 weeks or Cefaclor 40 mg/kg/day in 3 divided doses for 2 weeks or Amoxicillin 40 mg/kg/day in 3 divided doses for 2 weeks	Placebo	None reported	4 weeks	Note tha from all arms receiving antibiotic have bee pooled f purpose analysis.
Manrique 1987	Children aged 8 months to 13 years with unilateral or bilateral OME for at least 3 months (52 ears	Single-centre study from Spain	Amoxicillin 50 mg/kg/day for 8 days	No treatment	Participants in both groups received a daily dose of a decongestant syrup (chlorhydrate ambroxol, dose dependent on age) for the	3 months	—

	assessed, number of children unclear)				duration of the trial		
Marchisio 1998	Children aged 5 to 7 years with OME for at least 3 months (n = 120)	Multicentre study from Italy	Ceftibuten 9 mg/kg/day in 1 daily dose for 14 days	Placebo (nasal saline drops)	None reported	8 weeks	—
Møller 1990	Children aged 1 to 15 years with bilateral OME for at least 3 months, awaiting ventilation tube insertion (n = 147)	Single-centre study from Norway	Erythromycin 50 mg/kg/day in 2 divided doses for 14 days	Placebo	None reported	1 month	—
Podoshin 1990	Children aged 4 to 8 years with OME for ≥ 2 months, who had received no previous treatment (n = 86)	Single-centre study from Israel	Amoxicillin 50 mg/kg/day for 14 days	Lactose powder placebo	Both groups received an additional placebo to account for the third intervention in this study (antibiotics plus prednisone)	2 months	Note tha there wa third arm this stud where participa received antibiotic steroids. have not extracte this revie
Puhakka 1985	Children aged 7 months to 11 years with OME (n = 46)	Single-centre study from Finland	6 mg trimethoprim and 18.5 mg sulfadiazine/kg/day in 2 divided doses for 10 days	Placebo	Both groups received an additional placebo to account for the third intervention in this study (antibiotics plus prednisone)	8 weeks	Note tha there wa third arm this stud where participa received antibiotic steroids. have not extracte this revie
Sundberg 1984	Children aged 1.5 to 11 years with unilateral or bilateral OME for at least 3 months (n = 75)	Single-centre study from Sweden	Erythromycin ethylsuccinate 20 to 30 mg/kg twice daily for 10 days	No treatment	None reported	10 days	Note tha study did provide a data for outcome interest i review
Thomsen 1989	Children aged 1 to 10 years with at least 3 months of unilateral or bilateral OME (n = 264)	Single-centre study from Denmark	Amoxicillin and clavulanate potassium with 125 mg/31.25 mg 3 times daily (if aged 1 to 5) or 187 mg/46.9 mg 3 times daily (if aged 6 to 10) for 1 month	Placebo	In patients with bilateral disease, a ventilation tube was inserted in the right ear, and the left ear was included in the study	3 months	—
van Balen 1996	Children aged ≤ 6 years with at least 3	Single-centre study from the Netherlands	Amoxicillin 20 mg/kg/day plus 5 mg/kg/day clavulanic acid in 3	Placebo	One drop of decongestant (oxymetazoline	2 weeks	—

	months of OME (n = 162)		divided doses for 14 days		0.25%) 3 times daily		

OME: otitis media with effusion

Table 3

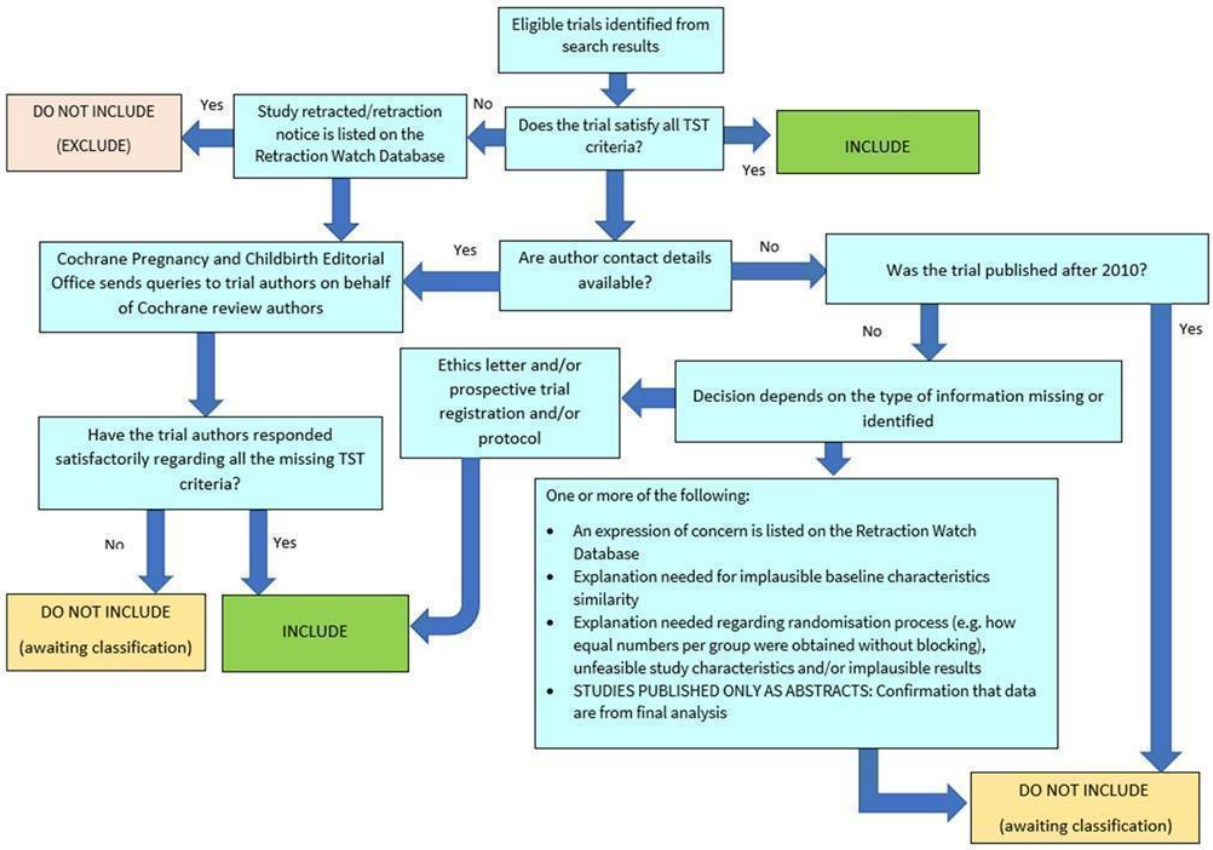
Adverse effects

Adverse event	Trial(s)	Reported data
Anaphylaxis	Ardehali 2008; Hemlin 1997; Leach 2008; Marchisio 1998; Thomsen 1989	Without referring directly to anaphylaxis, 5 trials provided sufficient information to reasonably assume there were no such cases. • Ardehali 2008 and Marchisio 1998 reported that no participants experienced adverse effects. • Thomsen 1989 reported that there were no unwanted side effects from the drug (antibiotic) itself. • Hemlin 1997 did not list anaphylaxis amongst the adverse events that were reported as "probably or possibly related to active treatment". • Leach 2008 reported that "no infant was withdrawn as a result of direct adverse reaction due to medication".
Gastrointestinal upset	Chen 2013; Hemlin 1997; Mandel 1987; Mandel 1991; Thomsen 1989; van Balen 1996	• Chen 2013 reported that one child amongst 36 (2.8%) who received macrolide antibiotics had vomiting. • Hemlin 1997 reported vomiting in 3 children of 61 who received cefixime (4.9%), gastroenteritis in 1 (1.6%), stomach pain in 2 (3.3%), loose stools in 2 (3.3%) and diarrhoea in 2 (3.3%). • Mandel 1987 reported that 3 children receiving amoxicillin for 2 weeks had diarrhoea, compared to none of those receiving placebo. The number of children with available data was not reported. • Mandel 1991 reported abdominal cramps, nausea, vomiting, diarrhoea, irritability, nappy rash or combinations of these symptoms, in 3 participants receiving erythromycin-sulfisoxazole, 4 participants receiving cefaclor, one participants receiving amoxicillin and 4 participants receiving placebo. The number of children with available data was not reported. • Thomsen 1989 reported that 2 of 131 children (1.5%) given amoxicillin-clavulanate potassium dropped out because of diarrhoea. • van Balen 1996 reported that 25 of 79 children who received co-amoxiclav (30%) developed 'gastrointestinal' side effects, compared to 14 of 74 (18%) who received placebo. The RR was 1.67 (95%CI 0.94 to 2.96) (Analysis 1.13).
Skin rash or irritation	Mandel 1987; Mandel 1991; Thomsen 1989; van Balen 1996	• Mandel 1987 reported skin rash in 3 children who had received 2 weeks of amoxicillin, compared to none of those who received placebo. The number of children with available data was not reported. • Mandel 1991 reported urticaria in 2 children receiving cefaclor, one of whom also had joint swelling. The number of children with available data was not reported. • Thomsen 1989 reported that 3 of 131 children (2.3%) given amoxicillin-clavulanate potassium dropped out because of skin reaction. • van Balen 1996 reported that 4 children of 79 who received co-amoxiclav (5%) developed itching/rash, compared with one of 74 (1.3%) who received placebo.
Mild sedation, irritability or both	Mandel 1987	• Mandel 1987 reported that 5% of children who received 2 weeks of amoxicillin and placebo had mild sedation,

		irritability or both at 2 weeks, compared to 6% of those receiving placebo. The number of children with available data was not reported. At 4 weeks, less than 1.5% in each group reported these symptoms. • Mandel 1991 reported irritability, various gastrointestinal symptoms or combinations of these occurred amongst 3 children receiving erythromycin-sulfisoxazole, 4 participants receiving cefaclor, one participant receiving amoxicillin and 4 participants receiving placebo. The number of children with available data was not reported.
Ear drum perforation	Leach 2008	• Leach 2008 reported that 6 of 52 (11.5%) children who received amoxicillin had any perforation (including acute otitis media with perforation, dry perforation or chronic suppurative otitis media) as worst ear status at the end of therapy (up to 24 weeks), compared with 14 of 51 (27.4%) children who received placebo. The RR was 0.42 (95% CI 0.18 to 1.01) (Analysis 1.12).

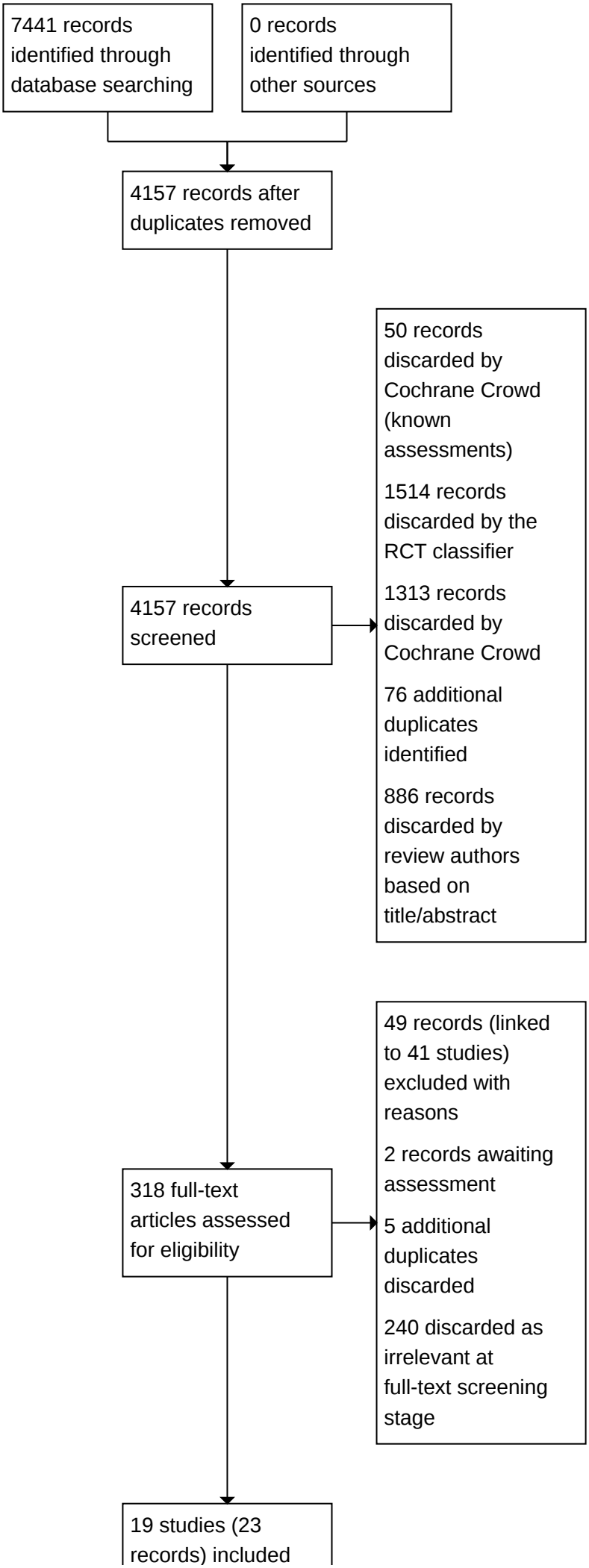
CI: confidence interval; RR: risk ratio

Figure 1



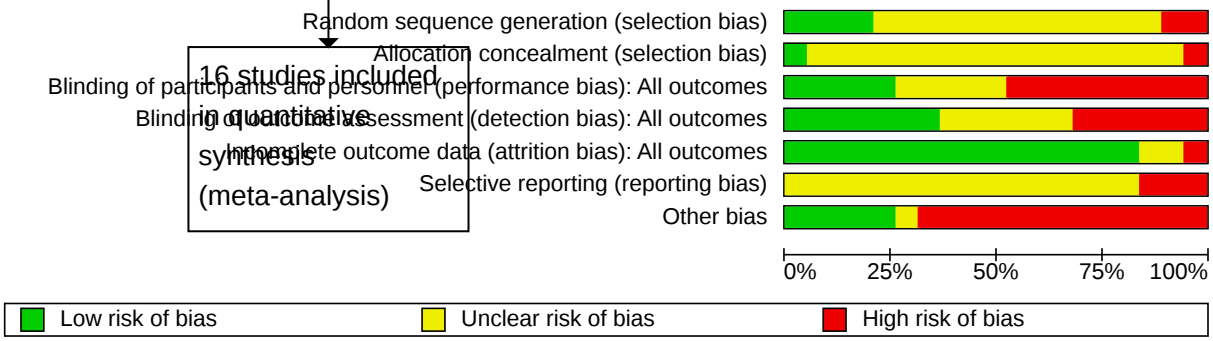
The Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool

Figure 2


7441 records identified through database searching
0 records identified through other sources
4157 records after duplicates removed
4157 records screened
50 records discarded by Cochrane Crowd (known assessments)
1514 records discarded by the RCT classifier
1313 records discarded by Cochrane Crowd
76 additional duplicates identified
886 records discarded by review authors based on title/abstract
318 full-text articles assessed for eligibility
49 records (linked to 41 studies) excluded with reasons
2 records awaiting assessment
5 additional duplicates discarded
240 discarded as irrelevant at full-text screening stage
19 studies (23 records) included

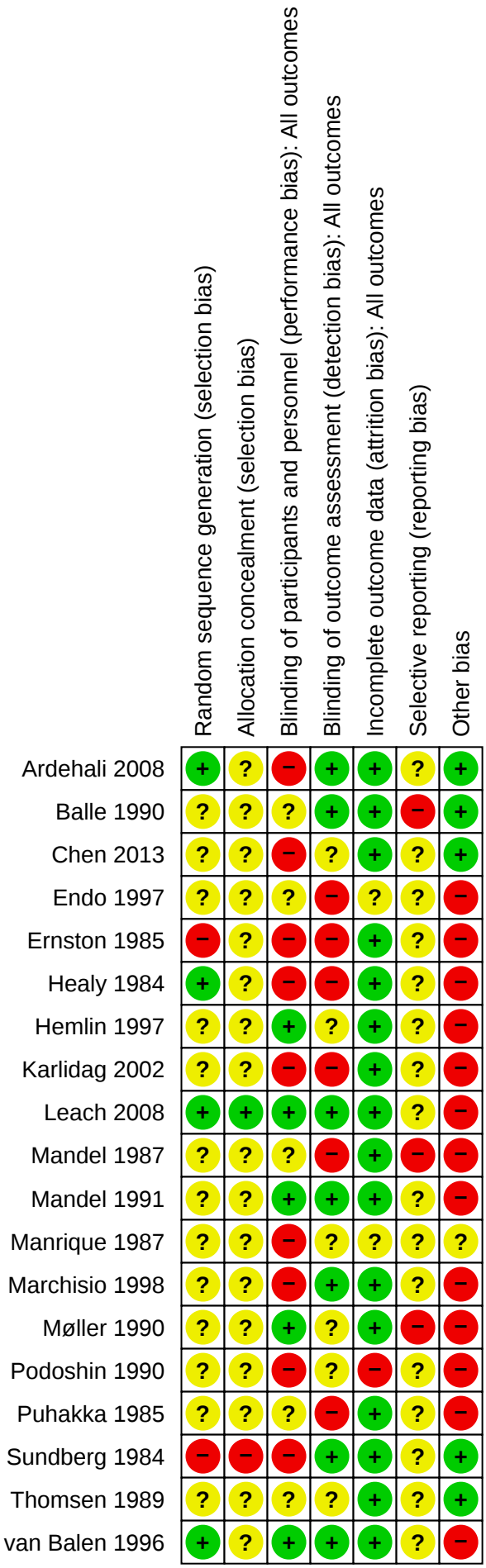
A flow chart of study retrieval and selection.

Figure 3



Risk of bias graph (our judgements about each risk of bias item presented as percentages across all included studies).

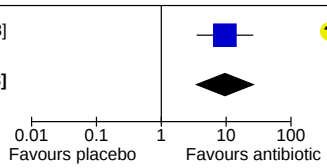
Figure 4



Risk of bias summary (our judgements about each risk of bias item for each included study).

Analysis 1.1

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Risk of Bias A B C D E F G
Podoshin 1990 (1)	20	49	0	37	100.0%	9.59 [3.51 , 26.18]	? ? − ? − ? −
Total (95% CI)		**49**		**37**	**100.0%**	**9.59 [3.51 , 26.18]**	
Total events:	20		0				



Heterogeneity: Not applicable
Test for overall effect: Z = 4.41 (P < 0.0001)
Test for subgroup differences: Not applicable

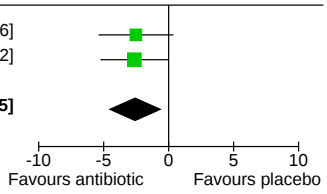
Footnotes
(1) 2 months. Analysis by child.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Antibiotic versus placebo, Outcome 1: Normal hearing (as complete improvement in air-bone gap in worst ear): short-term

Analysis 1.2

Study or Subgroup	antibiotic Mean	antibiotic SD	antibiotic Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Random, 95% CI
Mandel 1987 (1)	14.16	9.5	98	16.68	10.62	91	45.1%	-2.52 [-5.40 , 0.36]
Mandel 1991 (2)	14.465106	9.337095	235	17.1	10.26	75	54.9%	-2.63 [-5.25 , -0.02]
Total (95% CI)			**333**			**166**	**100.0%**	**-2.58 [-4.52 , -0.65]**



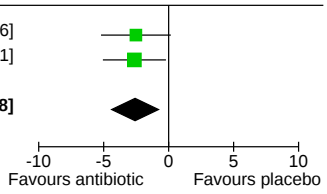
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)
Test for subgroup differences: Not applicable

Footnotes
(1) 4 weeks. Right and left ear data combined.
(2) 4 weeks. Right and left ear data combined. Three antibiotic arms combined (erythromycin-sulfisoxazole, cefaclor and amoxicillin)

Comparison 1: Antibiotic versus placebo, Outcome 2: Hearing threshold: speech reception threshold (short-term). Correction of variance assuming correlation coefficient of 0.5

Analysis 1.3

Study or Subgroup	antibiotic Mean	antibiotic SD	antibiotic Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Random, 95% CI
Mandel 1987 (1)	14.16	8.86	98	16.68	9.89	91	45.0%	-2.52 [-5.20 , 0.16]
Mandel 1991 (2)	14.465106	8.583711	235	17.1	9.56	75	55.0%	-2.63 [-5.06 , -0.21]
Total (95% CI)			**333**			**166**	**100.0%**	**-2.58 [-4.38 , -0.78]**



Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.81 (P = 0.005)
Test for subgroup differences: Not applicable

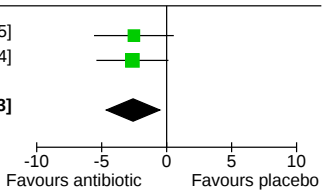
Footnotes
(1) 4 weeks. Right and left ear data combined.
(2) 4 weeks. Right and left ear data combined. Three antibiotic arms combined (erythromycin-sulfisoxazole, cefaclor and amoxicillin)

Comparison 1: Antibiotic versus placebo, Outcome 3: Sensitivity analysis: speech reception threshold: assuming correlation coefficient of 0.3

Analysis 1.4

Study or Subgroup	antibiotic Mean	SD	Total	placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mandel 1987 (1)	14.16	10.13	98	16.68	11.31	91	44.9%	-2.52 [-5.59 , 0.55]
Mandel 1991 (2)	14.465106	9.775053	235	17.1	10.93	75	55.1%	-2.63 [-5.41 , 0.14]
Total (95% CI)			**333**			**166**	**100.0%**	**-2.58 [-4.64 , -0.53]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 2.46 (P = 0.01)
Test for subgroup differences: Not applicable

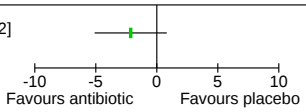


Footnotes
(1) 4 weeks. Right and left ear data combined. Correction of variance assuming correlation coefficient of 0.7
(2) 4 weeks. Three antibiotic arms combined (erythromycin-sulfisoxazole, cefaclor and amoxicillin)

Comparison 1: Antibiotic versus placebo, Outcome 4: Sensitivity analysis: speech reception threshold: assuming correlation coefficient of 0.7

Analysis 1.5

Study or Subgroup	antibiotic Mean	SD	Total	placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Mandel 1987 (1)	17	7.07	50	19.14	8.15	52	-2.14 [-5.10 , 0.82]	? ? ? − + − −

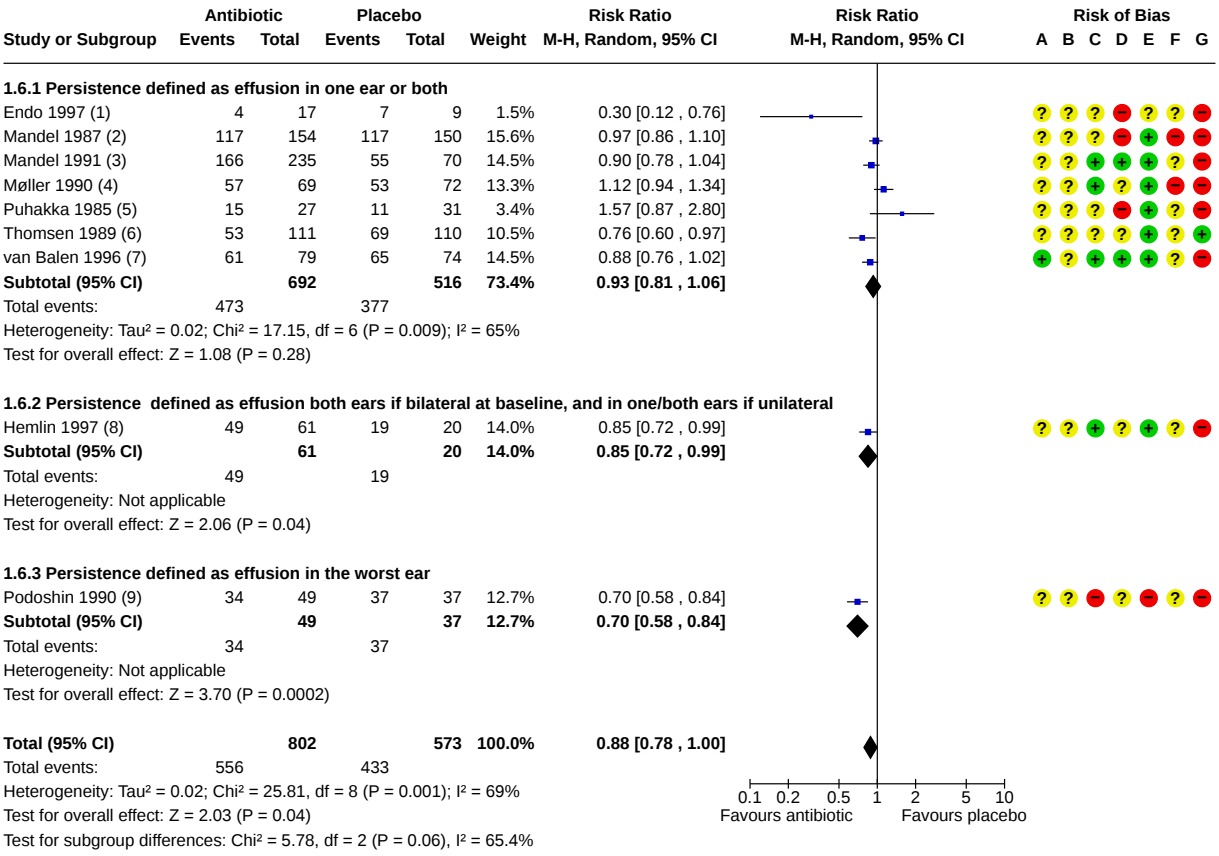


Footnotes
(1) 4 weeks. Children under 2 years old or who could not be tested by other methods

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Antibiotic versus placebo, Outcome 5: Hearing threshold: speech awareness threshold (short-term)

Analysis 1.6



Footnotes

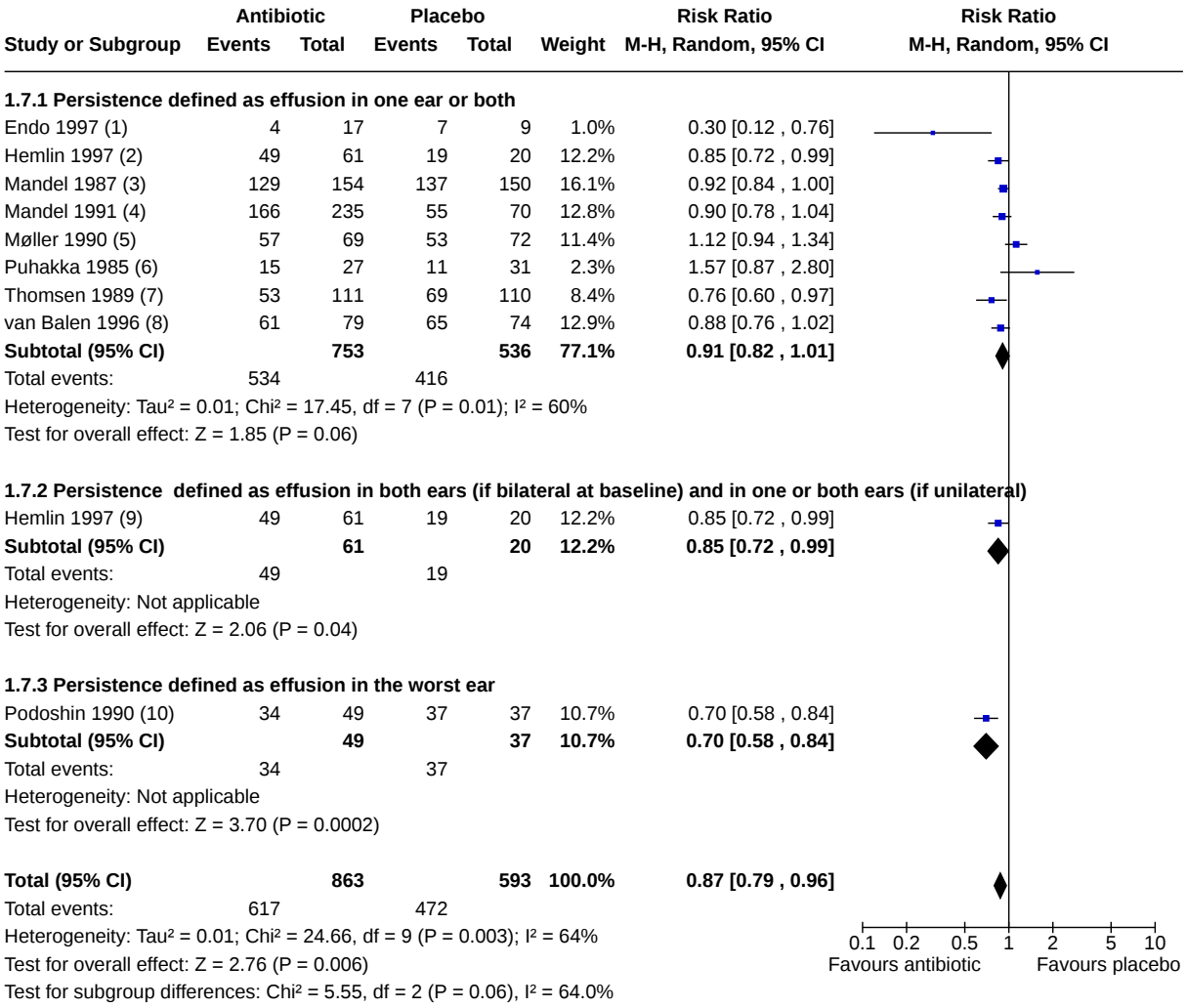
(1) 4 weeks. Bilateral OME. Failure to resolve bilaterally (assumed from text)
(2) 4 weeks. Mixed uni-and bilateral. Excluding cases of acute otitis.
(3) 4 weeks. Mixed uni-and bilateral. 3 antibiotic groups combined.
(4) 4 weeks. Bilateral OME.
(5) 8 weeks. Mixed uni- and bilateral. Analysed by ear (assumed ICC of 0.5)
(6) 3 months. Mixed uni- and bilateral.
(7) 2 weeks. Bilateral OME. Persistence = effusion in one or both ears.
(8) 12 to 21 days. Mixed uni- and bilateral.
(9) 8 weeks. Laterality of effusion at baseline not reported.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Antibiotic versus placebo, Outcome 6: Persistence of OME (short-term)

Analysis 1.7

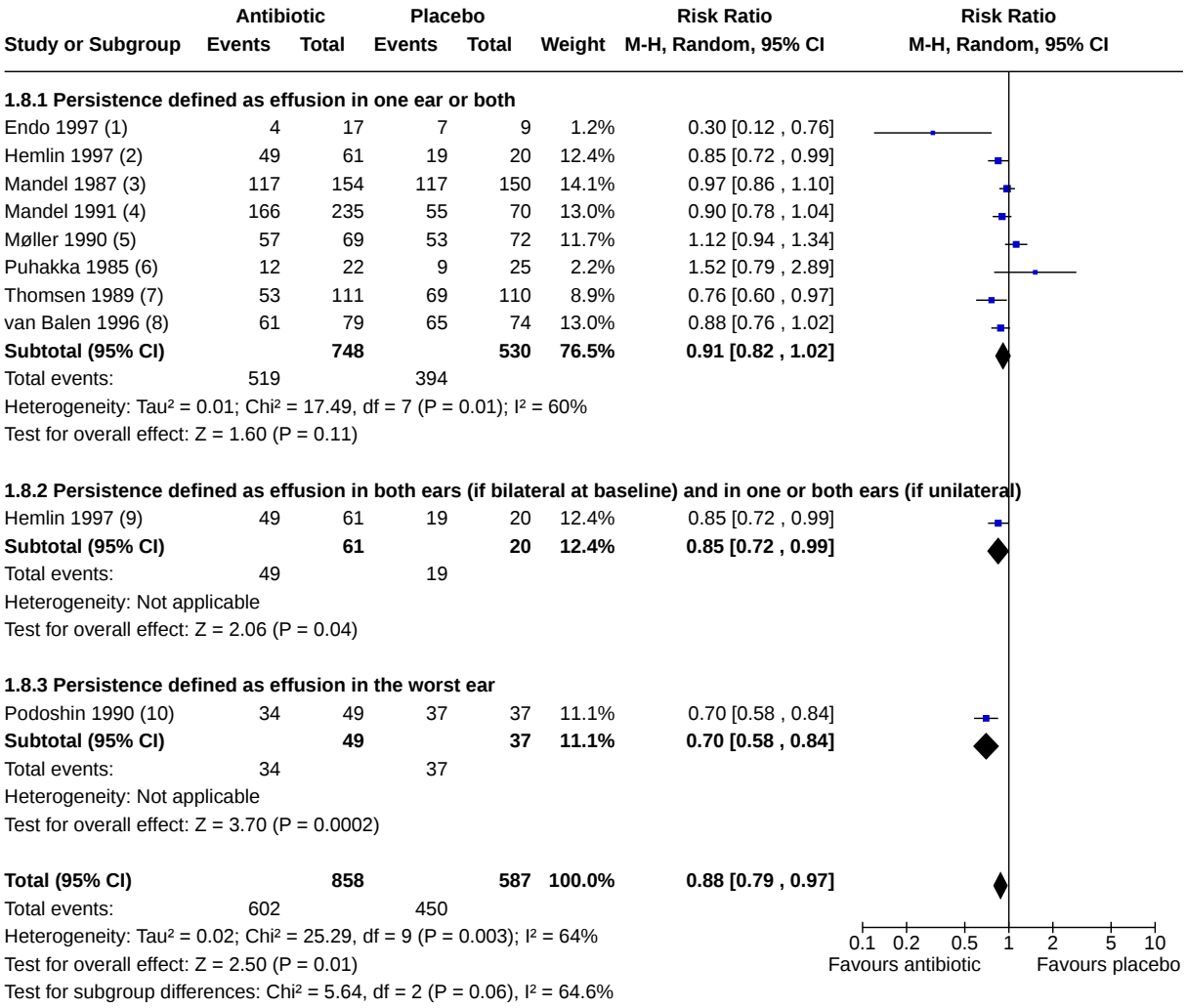


Footnotes

(1) 4 weeks. Bilateral OME. Failure to resolve bilaterally (assumed from text)
(2) At 12 to 21 days. Mixed uni- and bilateral.
(3) 4 weeks. Mixed uni-and bilateral. Including cases of acute otitis.
(4) 4 weeks. Mixed uni-and bilateral. 3 antibiotic groups combined.
(5) 4 weeks. Bilateral OME.
(6) 8 weeks. Mixed uni- and bilateral. Analysed by ear (assumed ICC of 0.5)
(7) 3 months. Mixed uni- and bilateral.
(8) 2 weeks. Bilateral OME. Persistence = effusion in one or both ears.
(9) 12 to 21 days. Mixed uni- and bilateral.
(10) 8 weeks. Laterality of effusion at baseline not reported.

Comparison 1: Antibiotic versus placebo, Outcome 7: Sensitivity analysis: persistence (short-term) including cases of acute otitis (Mandel 1987)

Analysis 1.8

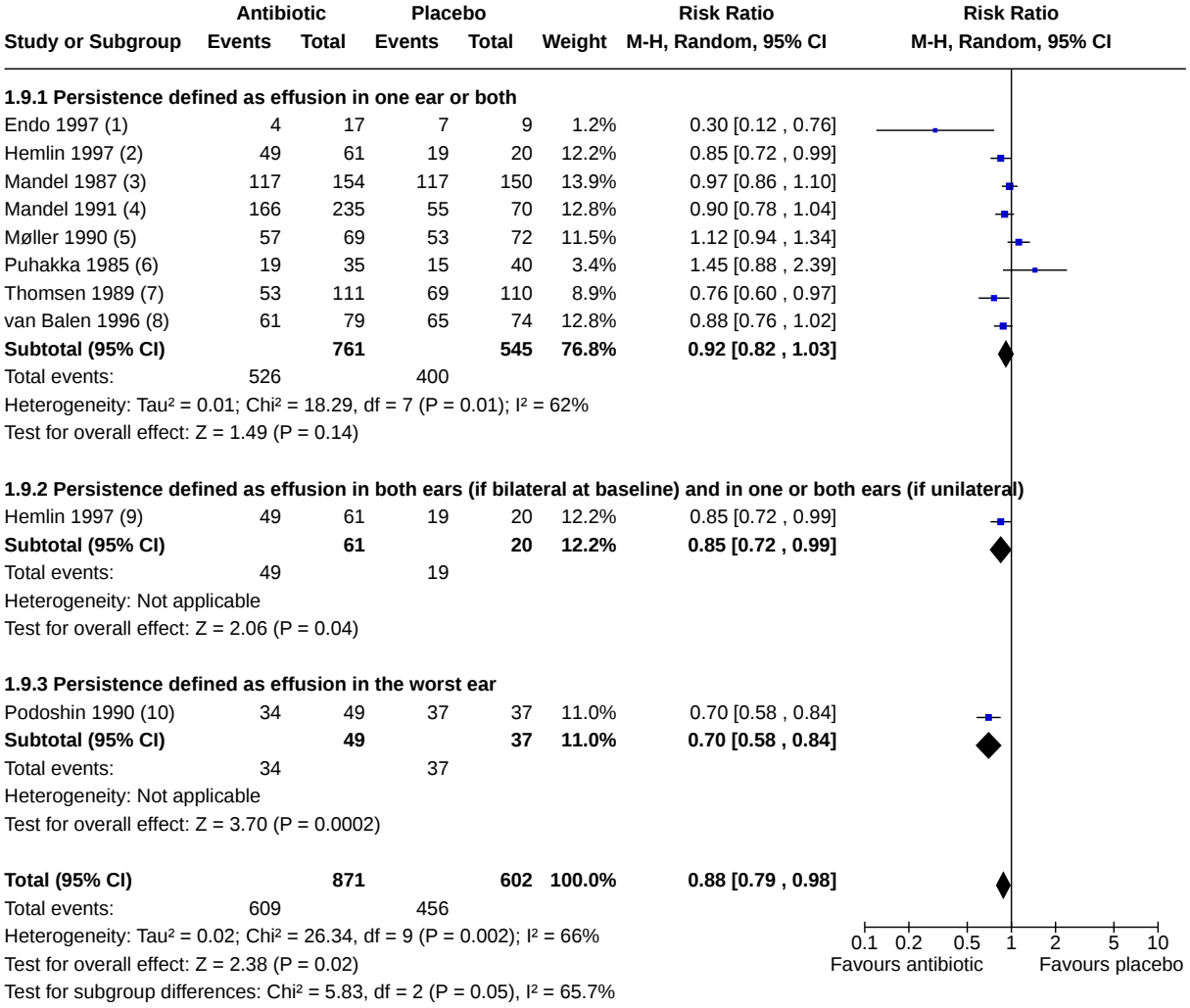


Footnotes

(1) 4 weeks. Bilateral OME. Failure to resolve bilaterally (assumed from text)
(2) At 12 to 21 days. Mixed uni- and bilateral.
(3) 4 weeks. Mixed uni-and bilateral. Excluding cases of acute otitis.
(4) 4 weeks. Mixed uni-and bilateral. 3 antibiotic groups combined.
(5) 4 weeks. Bilateral OME.
(6) 8 weeks. Mixed uni- and bilateral. Analysed by ear (assumed ICC of 1.0)
(7) 3 months. Mixed uni- and bilateral.
(8) 2 weeks. Bilateral OME. Persistence = effusion in one or both ears.
(9) 12 to 21 days. Mixed uni- and bilateral.
(10) 8 weeks. Laterality of effusion at baseline not reported.

Comparison 1: Antibiotic versus placebo, Outcome 8: Sensitivity analysis: persistence (short-term) assuming ICC of 1.0 [complete correlation between ears] (Puhakka 1985)

Analysis 1.9

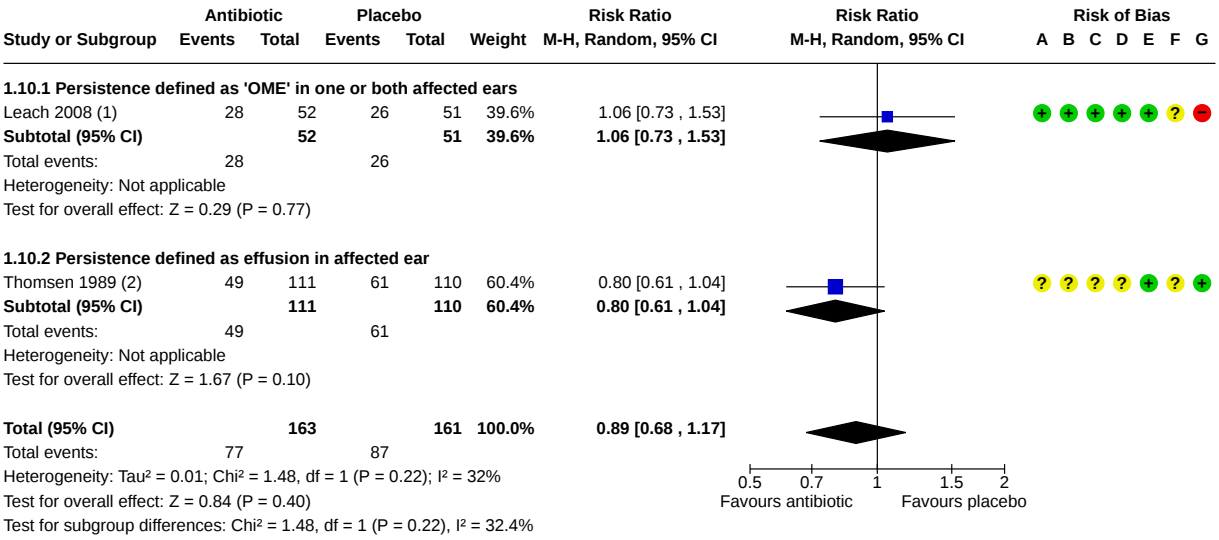


Footnotes

(1) 4 weeks. Bilateral OME. Failure to resolve bilaterally (assumed from text)
(2) At 12 to 21 days. Mixed uni- and bilateral.
(3) 4 weeks. Mixed uni-and bilateral. Excluding cases of acute otitis.
(4) 4 weeks. Mixed uni-and bilateral. 3 antibiotic groups combined.
(5) 4 weeks. Bilateral OME.
(6) 8 weeks. Mixed uni- and bilateral. Analysed by ear (assumed ICC of zero)
(7) 3 months. Mixed uni- and bilateral.
(8) 2 weeks. Bilateral OME. Persistence = effusion in one or both ears.
(9) 12 to 21 days. Mixed uni- and bilateral.
(10) 8 weeks. Laterality of effusion at baseline not reported.

Comparison 1: Antibiotic versus placebo, Outcome 9: Sensitivity analysis: persistence (short-term) assuming ICC of zero [no correlation between ears] (Puhakka 1985)

Analysis 1.10



Footnotes

(1) 6 months. Mixed uni- and bilateral. Persistence = OME in one or both affected ears

(2) 12 months. Mixed uni- and bilateral. If bilateral, VT placed in right and only left ear observed. Persistence = effusion in affected ear.

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

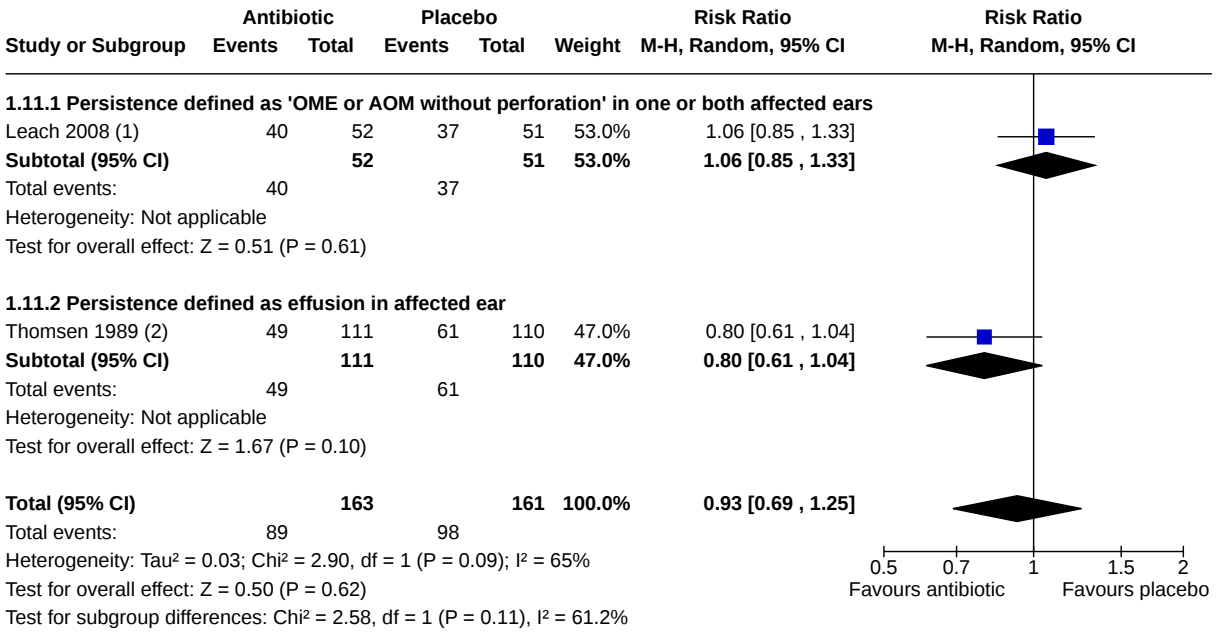
(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

(G) Other bias

Comparison 1: Antibiotic versus placebo, Outcome 10: Persistence of OME (medium-term)

Analysis 1.11



Footnotes

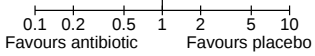
(1) 6 months. Mixed uni- and bilateral. Persistence = OME or AOM without perforation in one or both affected ears

(2) 12 months. Mixed uni- and bilateral. If bilateral, VT placed in right and only left ear observed. Persistence = effusion in affected ear.

Comparison 1: Antibiotic versus placebo, Outcome 11: Sensitivity analysis: persistence of OME (medium-term); defined as 'OME' or 'AOM without perforation' (Leach 2008)

Analysis 1.12

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Leach 2008 (1)	6	52	14	51	100.0%	0.42 [0.18 , 1.01]		+ + + + + ? −
Total (95% CI)		**52**		**51**	**100.0%**	**0.42 [0.18 , 1.01]**		
Total events:	6		14					



Heterogeneity: Not applicable
Test for overall effect: Z = 1.94 (P = 0.05)
Test for subgroup differences: Not applicable

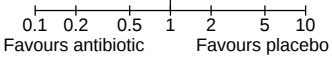
Footnotes
(1) 6 months. Worst ear status at the end of therapy. Includes AOM with perforation, dry perforation or CSOM.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Antibiotic versus placebo, Outcome 12: Adverse event: eardrum perforation

Analysis 1.13

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
van Balen 1996 (1)	25	79	14	74	1.67 [0.94 , 2.96]		+ ? + + + ? −



Test for subgroup differences: Not applicable

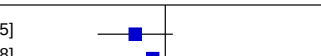
Footnotes
(1) 2 weeks.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Antibiotic versus placebo, Outcome 13: Adverse event: 'gastrointestinal'

Analysis 1.14

Study or Subgroup	Antibiotic Events	Antibiotic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Mandel 1987 (1)	12	155	20	150	50.5%	0.58 [0.29 , 1.15]		? ? ? − + − −
Mandel 1991 (2)	25	235	10	75	49.5%	0.80 [0.40 , 1.58]		? ? + + + ? −
Total (95% CI)		**390**		**225**	**100.0%**	**0.68 [0.42 , 1.10]**		
Total events:	37		30					



Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.57 (P = 0.12)
Test for subgroup differences: Not applicable

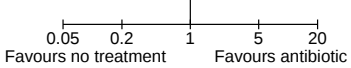
Footnotes
(1) 4 weeks. One or more episodes. Data from the same study, reported in Cantekin 1991.
(2) 4 weeks. One or more episodes. Data from 3 antibiotic arms combined (erythromycin-sulfisoxazole, cefaclor and amoxicillin).

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 1: Antibiotic versus placebo, Outcome 14: Episodes of acute otitis media

Analysis 2.1

Study or Subgroup	Antibiotic Events	Antibiotic Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Ernston 1985 (1)	24	46	5	45	100.0%	4.70 [1.96 , 11.22]		
Total (95% CI)		**46**		**45**	**100.0%**	**4.70 [1.96 , 11.22]**		
Total events:	24		5					



Heterogeneity: Not applicable
Test for overall effect: Z = 3.48 (P = 0.0005)
Test for subgroup differences: Not applicable

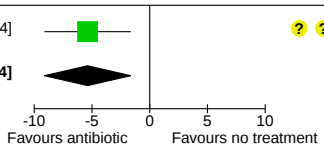
Footnotes
(1) 10 days. "Normal thresholds of hearing" and bilateral resolution of OME.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2: Antibiotic versus no treatment, Outcome 1: Hearing returned to normal (very short-term)

Analysis 2.2

Study or Subgroup	Antibiotic Mean	Antibiotic SD	Antibiotic Total	No treatment Mean	No treatment SD	No treatment Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Chen 2013 (1)	8.72	7.52	36	14.1	8.76	37	100.0%	-5.38 [-9.12 , -1.64]		
Total (95% CI)			**36**			**37**	**100.0%**	**-5.38 [-9.12 , -1.64]**		



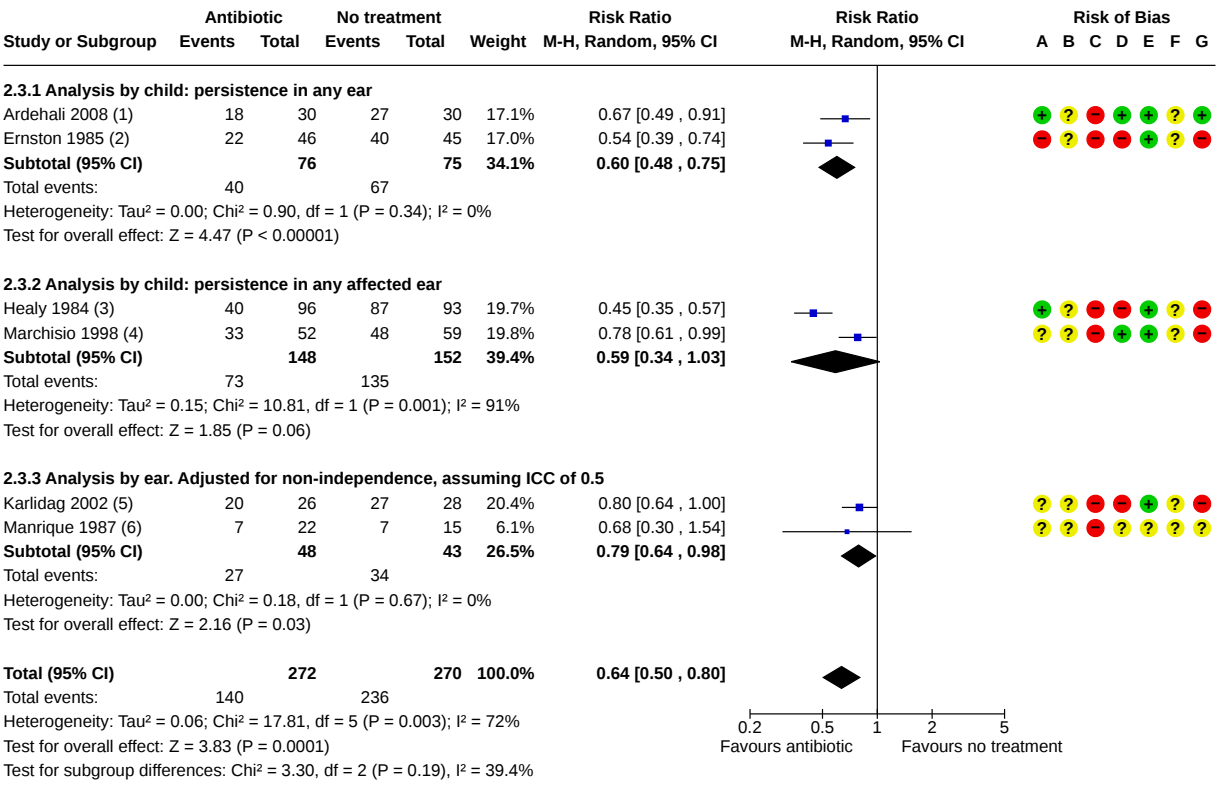
Heterogeneity: Not applicable
Test for overall effect: Z = 2.82 (P = 0.005)
Test for subgroup differences: Not applicable

Footnotes
(1) At 3 months. Air bone gap.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2: Antibiotic versus no treatment, Outcome 2: Final hearing threshold (short-term)

Analysis 2.3



Footnotes

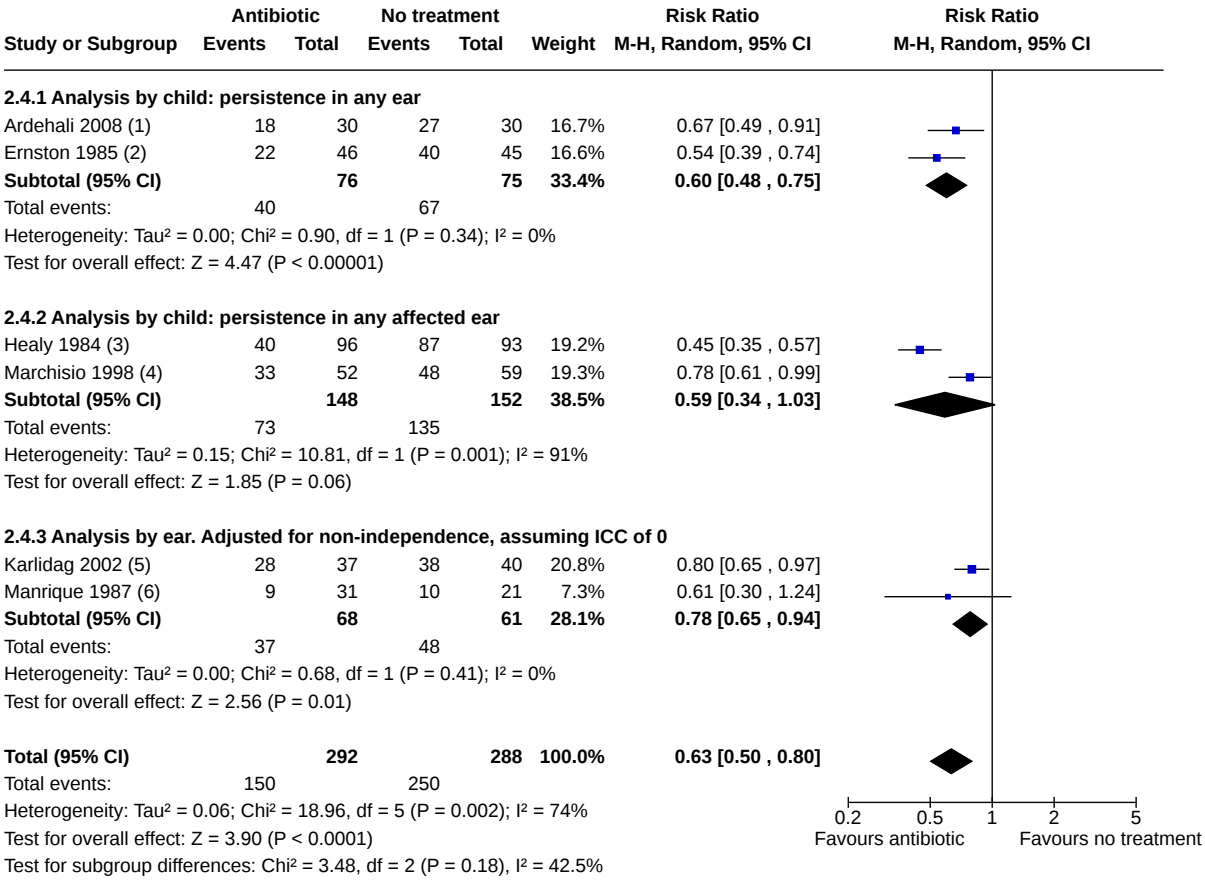
(1) 3 months. Mixed uni- and bilateral.
(2) 10 days. Mixed uni- and bilateral. Only includes participants who also had "normal thresholds of hearing".
(3) 4 weeks. Mixed uni- and bilateral.
(4) 8 weeks. Mixed uni- and bilateral.
(5) 8 weeks. Mixed uni- and bilateral. Ave cluster size=1.83. DE=1.42
(6) 3 months. Mixed uni- and bilateral. Ave cluster size=1.76. DE=1.38

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2: Antibiotic versus no treatment, Outcome 3: Persistence of OME (short-term)

Analysis 2.4

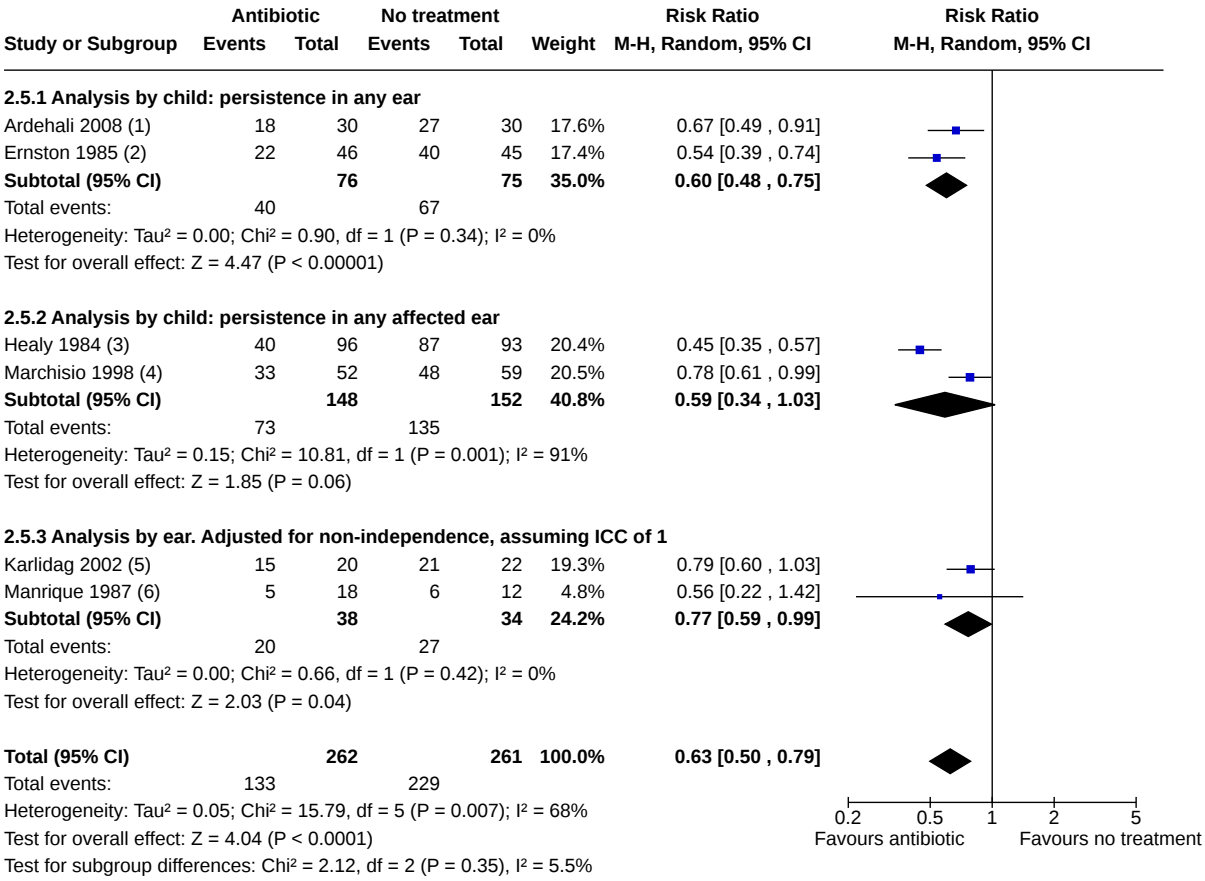


Footnotes

(1) 3 months. Mixed uni- and bilateral.
(2) 10 days. Mixed uni- and bilateral. Only includes participants who also had "normal thresholds of hearing".
(3) 4 weeks. Mixed uni- and bilateral.
(4) 8 weeks. Mixed uni- and bilateral.
(5) 8 weeks. Mixed uni- and bilateral. Ave cluster size=1.83. DE=1.0
(6) 3 months. Mixed uni- and bilateral. Ave cluster size=1.76. DE=1.0

Comparison 2: Antibiotic versus no treatment, Outcome 4: Sensitivity analysis 1: persistence of OME (short-term). ICC = zero

Analysis 2.5

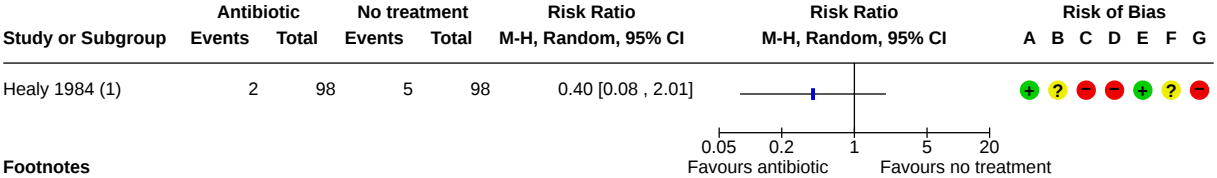


Footnotes

(1) 3 months. Mixed uni- and bilateral.
(2) 10 days. Mixed uni- and bilateral. Only includes participants who also had "normal thresholds of hearing".
(3) 4 weeks. Mixed uni- and bilateral.
(4) 8 weeks. Mixed uni- and bilateral.
(5) 8 weeks. Mixed uni- and bilateral. Ave cluster size=1.83. DE=1.83
(6) 3 months. Mixed uni- and bilateral. Ave cluster size=1.76. DE=1.76

Comparison 2: Antibiotic versus no treatment, Outcome 5: Sensitivity analysis 2: persistence of OME (short-term). ICC = 1.0

Analysis 2.6



Footnotes

(1) One or more episodes within 4 weeks. Definition of AOM unclear.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Comparison 2: Antibiotic versus no treatment, Outcome 6: Episodes of acute otitis media (short-term)