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Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion (Review)

Venekamp RP, Javed F, van Dongen TMA, Waddell A, Schilder AGM

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[Intervention Review]

Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

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ABSTRACT

Background

Ear discharge (otorrhoea) is common in children with grommets (ventilation/tympanostomy tubes); the proportion of children developing discharge ranges from 25% to 75%. The most common treatment strategies include oral broad-spectrum antibiotics, antibiotic eardrops or those containing a combination of antibiotic(s) and a corticosteroid, and initial observation. Important drivers for one strategy over the other are concerns over the side effects of oral antibiotics and the potential ototoxicity of antibiotic eardrops.

Objectives

To assess the benefits and harms of current treatment strategies for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion.

Search methods

The Cochrane ENT Information Specialist searched the ENT Trials Register, CENTRAL (2016, Issue 5), multiple databases and additional sources for published and unpublished trials (search date 23 June 2016).

Selection criteria

Randomised controlled trials comparing at least two of the following: oral antibiotics, oral corticosteroids, antibiotic eardrops (with or without corticosteroid), corticosteroid eardrops, microsuction cleaning of the ear canal, saline rinsing of the ear canal, placebo or no treatment. The main comparison of interest was antibiotic eardrops (with or without corticosteroid) *versus* oral antibiotics.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. Primary outcomes were: proportion of children with resolution of ear discharge at short-term follow-up (less than two weeks), adverse events and serious complications. Secondary outcomes were: proportion of children with resolution of ear discharge at intermediate- (two to four weeks) and long-term (four to 12 weeks) follow-up, proportion of children with resolution of ear pain and fever at short-term follow-up, duration of ear discharge, proportion of children with chronic ear discharge, ear discharge recurrences, tube blockage, tube extrusion, health-related quality of life and hearing. We used GRADE to assess the quality of the evidence for each outcome; this is indicated in *italics*.

Main results

We included nine studies, evaluating a range of treatments, with 2132 children who developed acute ear discharge beyond the immediate postoperative period. We judged the risk of bias to be low to moderate in most studies.

Antibiotic eardrops (with or without corticosteroid) *versus oral antibiotics*

Antibiotic eardrops with or without corticosteroid were more effective than oral antibiotics in terms of:

- resolution of discharge at one week (one study, 42 children, ciprofloxacin eardrops *versus* amoxicillin: 77% versus 30%; risk ratio (RR) 2.58, 95% confidence interval (CI) 1.27 to 5.22; *moderate-quality evidence*);

- resolution of discharge at two weeks (one study, 153 children, bacitracin-colistin-hydrocortisone eardrops *versus* amoxicillin-clavulanate: 95% versus 56%; RR 1.70, 95% CI 1.38 to 2.08; *moderate-quality evidence*);

- duration of discharge (two studies, 233 children, ciprofloxacin eardrops *versus* amoxicillin: median 4 days versus 7 days and bacitracin-colistin-hydrocortisone eardrops *versus* amoxicillin-clavulanate: 4 days versus 5 days; *moderate-quality evidence*);

- ear discharge recurrences (one study, 148 children, bacitracin-colistin-hydrocortisone eardrops *versus* amoxicillin-clavulanate: 0 versus 1 episode at six months; *low-quality evidence*); and

- disease-specific quality of life (one study, 153 children, bacitracin-colistin-hydrocortisone eardrops *versus* amoxicillin-clavulanate: difference in change in median Otitis Media-6 total score (range 6 to 42) at two weeks: -2; *low-quality evidence*).

We found no evidence that antibiotic eardrops were more effective in terms of the proportion of children developing chronic ear discharge or tube blockage, generic quality of life or hearing.

Adverse events occurred at similar rates in children treated with antibiotic eardrops and those treated with oral antibiotics, while no serious complications occurred in either of the groups.

Other comparisons

(a) *Antibiotic eardrops with or without corticosteroid* were more effective than*corticosteroid eardrops* in terms of:

- duration of ear discharge (one study, 331 children, ciprofloxacin *versus* ciprofloxacin-fluocinolone acetonide *versus* fluocinolone acetonide eardrops: median 5 days versus 7 days versus 22 days; *moderate-quality evidence*).

(b) *Antibiotic eardrops* were more effective than *saline rinsing of the ear canal* in terms of:

- resolution of ear discharge at one week (one study, 48 children, ciprofloxacin eardrops *versus* saline rinsing: 77% versus 46%; RR 1.67, 95% CI 1.04 to 2.69; *moderate-quality evidence*);

but not in terms of tube blockage. Since the lower limit of the 95% CI for the effect size for resolution of ear discharge at one week approaches unity, a trivial or clinically irrelevant difference cannot be excluded.

(c) *Eardrops containing two antibiotics and a corticosteroid* (bacitracin-colistin-hydrocortisone) were more effective than *no treatment* in terms of:

- resolution of discharge at two weeks (one study; 151 children: 95% versus 45%; RR 2.09, 95% CI 1.62 to 2.69; *moderate-quality evidence*);

- duration of discharge (one study; 147 children, median 4 days versus 12 days; *moderate-quality evidence*);

- chronic discharge (one study; 147 children; RR 0.08, 95% CI 0.01 to 0.62; *low-quality evidence*); and

- disease-specific quality of life (one study, 153 children, difference in change in median Otitis Media-6 total score (range 6 to 42) between groups at two weeks: -1.5; *low-quality evidence*).

We found no evidence that antibiotic eardrops were more effective in terms of ear discharge recurrences or generic quality of life.

(d) *Eardrops containing a combination of an antibiotic and a corticosteroid* were more effective than *eardrops containing antibiotics (low-quality evidence)* in terms of:

- resolution of ear discharge at short-term follow-up (two studies, 590 children: 35% versus 20%; RR 1.76, 95% CI 1.33 to 2.31); and

- duration of discharge (three studies, 813 children);

but not in terms of resolution of discharge at intermediate-term follow-up or proportion of children with tube blockage. However, there is a substantial risk of publication bias, therefore these findings should be interpreted with caution.

Authors' conclusions

We found moderate to low-quality evidence that antibiotic eardrops (with or without corticosteroid) are more effective than oral antibiotics, corticosteroid eardrops and no treatment in children with ear discharge occurring at least two weeks following grommet insertion. There is some limited, inconclusive evidence that antibiotic eardrops are more effective than saline rinsing. There is uncertainty whether antibiotic-corticosteroid eardrops are more effective than eardrops containing antibiotics only.

PLAIN LANGUAGE SUMMARY

Interventions for children with ear discharge occurring at least two weeks following grommet placement

Review question

This review compares the effects and safety of interventions in children with grommets who develop ear discharge beyond the immediate postoperative period.

Background

The insertion of grommets (1 to 2 mm plastic tubes placed into the eardrum) is one of the commonest surgical procedures performed in children worldwide. Up to three in four children with grommets develop episodes of ear discharge. When this occurs beyond the immediate postoperative period, it is thought to be a symptom of a middle ear infection. The most common treatments include oral antibiotics (i.e. by mouth), antibiotic eardrops or those containing a combination of antibiotic(s) and a corticosteroid, and initial observation. Important reasons for physicians to choose one treatment over another are concerns over the side effects of oral antibiotics and the potential risk of damage to the inner ear and hearing loss due to the use of antibiotic eardrops.

Study characteristics

This review includes evidence up to 23 June 2016. We included nine studies with a total of 2132 children who developed acute ear discharge beyond the immediate postoperative period. The studies evaluated a range of treatments.

Key results

We primarily looked at the difference in the proportion of children whose ear discharge had resolved within two weeks after treatment was started, adverse events and serious complications. Secondary outcomes were the proportion of children whose discharge had resolved at two to four weeks and four to 12 weeks, the proportion of children whose ear pain and fever had resolved within two weeks, the duration of discharge, the proportion of children with chronic discharge, discharge recurrences, tube blockage, tube extrusion, health-related quality of life and hearing.

Antibiotic eardrops (with or without corticosteroid) *versus* oral antibiotics

Antibiotic eardrops with or without corticosteroid were more effective than oral antibiotics in terms of resolution of ear discharge at one week (*moderate-quality evidence*) and two weeks (*moderate-quality evidence*), ear discharge recurrences (*low-quality evidence*) and disease-specific quality of life (*low-quality evidence*). We found no evidence that antibiotic eardrops were more effective in reducing the risk of chronic ear discharge (*low-quality evidence*), tube blockage (*low-quality evidence*), general quality of life (*low-quality evidence*) or hearing (*very low-quality evidence*). Adverse events occurred at similar rates (*low-quality evidence*), while no serious complications occurred in either of the groups (*very low-quality evidence*).

Other comparisons

Antibiotic eardrops with or without corticosteroid were more effective than *corticosteroid eardrops* in terms of duration of ear discharge (*moderate-quality evidence*).

Antibiotic eardrops were more effective than *saline rinsing* in terms of resolution of ear discharge at one week (*moderate-quality evidence*), but not in terms of tube blockage (*low-quality evidence*). Also, we cannot exclude an unimportant difference between antibiotic eardrops and saline rinsing in terms of resolution of discharge at one week.

Eardrops containing two antibiotics and a corticosteroid were more effective than *no treatment* in terms of resolution of ear discharge at two weeks (*moderate-quality evidence*), duration of ear discharge (*moderate-quality evidence*), reducing the risk of chronic ear discharge (*low-quality evidence*) and disease-specific quality of life (*low-quality evidence*). We found no evidence that antibiotic eardrops were more effective in terms of ear discharge recurrences (*low-quality evidence*) or general quality of life (*low-quality evidence*).

Low-quality evidence suggests that *antibiotic and corticosteroid combination eardrops* are more effective than *eardrops containing antibiotics only* in terms of resolution of ear discharge within two weeks and duration of ear discharge, but not in terms of resolution of ear discharge at two to four weeks or tube blockage. There is a substantial risk of publication bias, therefore these findings should be interpreted with caution.

Quality of evidence and conclusion

We found moderate to low-quality evidence that antibiotic eardrops (with or without corticosteroid) are more effective than oral antibiotics, corticosteroid eardrops and no treatment in children with ear discharge occurring at least two weeks following grommet placement. There is some limited, inconclusive evidence that antibiotic eardrops are more effective than saline rinsing. There is uncertainty whether antibiotic-corticosteroid eardrops are more effective than eardrops containing antibiotics only.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics for children with grommets (ventilation tubes) who develop ear discharge beyond the immediate postoperative period

Patients: children with grommets who develop ear discharge beyond the immediate postoperative period
Setting: primary and secondary care
Intervention: antibiotic eardrops (with or without a corticosteroid)
Control: oral antibiotics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oral antibiotics	Risk with antibiotic eardrops				
Resolution of ear discharge at short-term follow-up (1 week)	Study population		RR 2.58 (1.27 to 5.22)	42 (1 RCT)	⊕⊕⊕◯ **moderate** [1]	The NNTB based on the study population risk was 1/ (774-381)* 1000 = 2.55
	300 per 1000	774 per 1000 (381 to 1000)				
Adverse events	Study population		RR 0.37 (0.12 to 1.09)	705 (3 RCTs)	⊕⊕◯◯ **low** [2]	-
	317 per 1000	117 per 1000 (38 to 345)				
Serious complications	Study population		n/a	153 (1 RCT)	⊕◯◯◯ **very low** [3]	-
	0 per 1000	0 per 1000 (0 to 0)				
Resolution of ear discharge at intermediate-term follow-up (2 weeks)	Study population		RR 1.70 (1.38 to 2.08)	153 (1 RCT)	⊕⊕⊕◯ **moderate** [4]	-
	558 per 1000	949 per 1000 (771 to 1000)				

Duration of ear discharge	Antibiotic eardrops versus oral antibiotics: Median 4 days (range 1 to 28) versus 5 days (range 1 to 36) Median 4 days (range not reported) versus 7 days (range not reported)	n/a	232 (2 RCTs)	⊕⊕⊕◯ **moderate** [4]	-
Tube blockage	Study population 50 per 1000 — 60 per 1000 (17 to 223)	RR 1.20 (0.33 to 4.45)	121 (2 RCTs)	⊕⊕◯◯ **low** [5]	-
Health-related quality of life					
Generic - CHQ	At 2 weeks, the change in CHQ scores did not differ significantly between the groups. The change in Otitis Media-6 total score (range 6 to 42) at 2 weeks was small but favoured antibiotic-corticosteroid eardrops (difference in median difference between treatment groups: -2, P < 0.01)	n/a	153 (1 RCT)	⊕⊕◯◯ **low** [6]	-
Disease-specific - OM-6 (range 6 to 42)	Change in median score: +1 (baseline: 15.5; 2 weeks: 16.5) — Change in median score: -1 (baseline: 15.5; 2 weeks: 14.5)	Difference in change in median OM-6 scores: -2 (in favour of antibiotic eardrops)	153 (1 RCT)	⊕⊕◯◯ **low** [6]	-

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CHQ: Child Heath Questionnaire; **CI:** confidence interval; n/a: not applicable; **NNTB:** number needed to treat to benefit; **OM-6:** Otitis Media-6; **RCT:** randomised controlled trial; **RR:** risk ratio

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

[1]We downgraded the evidence from high to moderate quality due to imprecise effect estimate (small sample size).

[2]We downgraded the evidence from high to low quality due to study limitations (risk of bias) and inconsistency of effect estimates across individual trials.

[3]We downgraded the evidence from high to very low quality due to study limitations (risk of bias) and imprecise effect estimate (small sample size and infrequent occurrence of outcome).

[4]We downgraded the evidence from high to moderate quality due to study limitations (risk of bias).

[5]We downgraded the evidence from high to low quality due to study limitations (risk of bias) and imprecise effect estimate (infrequent occurrence of outcome).

[6]We downgraded the evidence from high to low quality due to study limitations (risk of bias) and imprecise effect estimate (small sample size).

BACKGROUND

Description of the condition

The insertion of grommets (also known as ventilation tubes or tympanostomy tubes) is one of the most common surgical procedures performed in children worldwide, with 25,000 procedures performed in the UK (Position Paper ENT UK 2009), and 700,000 in the USA each year (Cullen 2009). The two main indications for this operation are restoration of hearing in children with persistent bilateral otitis media with effusion (also called 'glue ear') and prevention of further middle ear infections in children suffering from recurrent acute otitis media.

Ear discharge (also called otorrhoea) is a common sequela in patients with grommets; it is generally considered to be a symptom of a middle ear infection whereby inflammatory secretions that have built up in the middle ear drain through the grommet into the ear canal. Clinically a distinction is made between ear discharge occurring during the postoperative period (that is, within two weeks after grommet insertion), where treatment focuses on prevention (Syed 2013), and ear discharge developing beyond this period, which is considered a symptom of a new middle ear infection. Depending on the age range of children studied, their indication for grommets and the study design, the proportion of children developing ear discharge ranges from 25% to 75% (Ah-Tye 2001; Kay 2001; van Dongen 2013). Ear discharge is unpleasant and can smell bad, while the underlying middle ear infection can cause general illness, fever and ear pain. Ear discharge persisting for three days or more has a negative impact on children's quality of life (Rosenfeld 2000). Although most episodes of ear discharge last only days to weeks, some children with grommets develop chronic ear discharge, which may be associated with considerable morbidity and hearing loss.

Description of the intervention

Various treatments and combinations of treatments are currently used in children with grommets who develop ear discharge. Preferences vary across countries and healthcare settings. The most common strategies include oral broad-spectrum antibiotics, antibiotic eardrops or those containing a combination of antibiotic(s) and a corticosteroid, and initial observation. Less common treatments are systemic or ototopical corticosteroids and interventions like cleaning of the ear canal using microsuction equipment (in an ENT setting) and saline rinsing of the ear canal (in a primary care or ENT setting).

Most ENT surgeons prefer ototopical treatment with antibiotic eardrops (with or without a corticosteroid) (Badalyan 2013). Paediatricians and general practitioners, on the other hand, tend to prescribe oral antibiotics or advise to wait and see, driven by guidance and concerns over the potential ototoxicity of ototopical antibiotics when used in children with a non-intact eardrum (including grommets) (British National Formulary 2014). Aminoglycosides and chloramphenicol are indeed potentially ototoxic; when applied locally onto the round window they may penetrate into the inner ear and cause hair cell damage and sensorineural hearing loss. Whilst this has been documented in animal studies, there is little evidence to suggest that similar processes occur when humans with middle ear disease are treated with these drops; middle ear secretions and thickened mucosa likely protect the round window and inner ear from the ototoxic effects of the drops (Pappas 2006; Phillips 2007).

Quinolones are considered non-ototoxic (Pappas 2006) and they became widely available as eardrops in the 1990s. The recent clinical practice guideline on tympanostomy tubes in children recommends quinolone drops as the first-line treatment in children with grommets who develop ear discharge (Rosenfeld 2013). In many countries, such as the UK, however, otic quinolone formulations are not widely available (in contrast to ophthalmic formulations).

In this review we will assess the effectiveness and safety of current interventions for children with grommets who develop ear discharge beyond the immediate postoperative period, with a particular focus on oral versus ototopical antibiotics.

Treatment strategies for (the prevention of) ear discharge occurring shortly after the insertion of grommets (also called early postoperative ear discharge) are beyond the scope of this review and are addressed in a separate Cochrane Review (Syed 2013).

How the intervention might work

Ear discharge in children with grommets is generally a symptom of an infection of the middle ear. In addition to the most common bacteria causing acute otitis media, non-typeable*Haemophilus influenzae*, *Streptococcus pneumoniae* and*Moraxella catarrhalis, Staphylococcus aureus* and *Pseudomonas aeruginosa* are common pathogens in cultures of ear discharge in children with grommets (van Dongen 2015).

Treatment of this condition with either ototopical or systemic antibiotics aims to eradicate these bacteria and cure the infection. Antibiotic eardrops have the advantage over oral antibiotics of being delivered directly to the site of infection resulting in higher local concentrations of antibiotics. This approach is therefore less likely to cause antimicrobial resistance (Weber 2004), and in addition avoids the side effects of systemic antibiotics, such as gastrointestinal symptoms and skin rash. Ototopical treatment, however, comes with concerns about ototoxicity and may cause local skin irritation and allergy.

Corticosteroids, either ototopical or systemic, given as an adjunct to antibiotic treatment may provide additional benefits by inhibiting the inflammatory cascade evoked in the middle ear as a result of the infection.

Cleaning the ear canal of ear discharge by microsuction or saline rinsing of the ear canal allows eardrops to reach the tube and enter

the middle ear.
Since the middle ear infection that causes ear discharge in children with grommets may be self-limiting and resolve without treatment over time, initial observation is practised as an alternative strategy, in particular in primary care.

Why it is important to do this review

Insertion of grommets is one of the most common surgical procedures in children and episodes of ear discharge are very common in children receiving grommets, occurring in up to 75% (Ah-Tye 2001; Cullen 2009; Kay 2001; van Dongen 2013). Parents generally have high expectations that this operation will solve their child's middle ear problems and are therefore disappointed when their child develops ear discharge. The treatment children with grommets receive for this problem varies widely (Badalyan 2013), due to varying treatment preferences and differences in guidelines. Whilst the American Academy of Otolaryngology - Head and Neck Surgery recommends antibiotic eardrops (Rosenfeld 2013), the UK National Institute for Health and Care Excellence (NICE) recommends taking an ear swab for culture and either treating this condition as an episode of acute otitis media (initial observation for uncomplicated disease and oral antibiotics for complicated or persisting disease) or seeking advice from an ENT surgeon (NICE 2015).
In addition there is uncertainty about the additional benefit of ototopical or oral corticosteroids, whether interventions to clean the ear canal are beneficial and whether or not initial observation is an appropriate treatment strategy.
It is therefore important to review the evidence on the current management options for children with grommets who develop ear discharge, so that informed decisions can be made.

OBJECTIVES

To assess the benefits and harms of current treatment strategies for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Children (aged below 18 years) with grommets (irrespective of type) who developed acute ear discharge outside the immediate postoperative period, that is ear discharge existing for no more than three weeks prior to randomisation and occurring at least two weeks following grommet (ventilation tube) insertion.

Types of interventions

We included all trials comparing the benefits and/or harms of at least two of the following treatments and comparators:

- Oral antibiotics
- Oral corticosteroids
- Antibiotic eardrops
- Antibiotic(s)-corticosteroid eardrops
- Corticosteroid eardrops
- Cleaning the ear canal using microsuction
- Saline rinsing of the ear canal
- Placebo (in the form of eardrops, oral suspension or tablets, depending on the 'active' intervention that is studied) or no treatment

We included all possible comparison pairs in this review, but the main comparison of interest is:

- oral antibiotics *versus* antibiotic eardrops (with or without a corticosteroid).

As such, we analysed the two different types of antibiotic eardrops (with and without a corticosteroid) together as a comparison pair, and performed subgroup analysis to test whether the type of eardrops impacted on the meta-analysis results (see Subgroup analysis and investigation of heterogeneity). In a separate analysis, we compared the effectiveness of antibiotic-only eardrops to eardrops containing antibiotic(s) and a corticosteroid (see How the intervention might work and Subgroup analysis and investigation of heterogeneity).
We included RCTs reporting on combined interventions (e.g. oral antibiotics plus antibiotic eardrops *versus* antibiotic eardrops only) only if they allowed a direct comparison between one of the combined interventions and a control group and if the groups were not treated differently except for the treatment under study.

Types of outcome measures

We analysed the primary and secondary outcomes listed below in this review, but they were not used as a basis for including or excluding studies.

Primary outcomes

- Proportion of children with resolution of ear discharge at short-term follow-up (less than two weeks).
- Adverse events likely to be related to the study medications (ototoxicity, gastrointestinal symptoms, skin rash).

- Serious complications related to middle ear infection, including acute mastoiditis and intracranial complications.

Secondary outcomes

- Proportion of children with resolution of ear discharge at intermediate- (two to four weeks) and long-term (four to 12 weeks) follow-up.
- Proportion of children without other signs of a middle ear infection (ear pain and fever) at short-term follow-up.
- Duration of ear discharge (after randomisation).
- Proportion of children with chronic ear discharge (longer than four weeks).
- Number of recurrent ear discharge episodes during follow-up.
- Proportion of children with tube extrusion.
- Proportion of children with tube blockage.
- Health-related quality of life using a validated instrument; either disease-specific (e.g. Otitis Media-6) or generic (e.g. EQ-5D; Infant Toddler Quality of Life Questionnaire; Child Heath Questionnaire).
- Hearing levels as determined by audiometry.

Search methods for identification of studies

The Cochrane ENT Information Specialist conducted systematic searches for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions. The date of the search was 23 June 2016.

Electronic searches

The Information Specialist searched:

- the ENT Trials Register (searched 23 June 2016);
- the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 5);
- Ovid MEDLINE (1946 to May Week 3 2016);
    - Ovid MEDLINE (In-Process & Other Non-Indexed Citations 24 June 2016);
    - PubMed (as a top-up to searches in Ovid MEDLINE 23 June 2016);
- Ovid EMBASE (1974 to 2016 week 25);
- Ovid CAB Abstracts (1910 to 2016 week 23);
- EBSCO CINAHL (1982 to 23 June 2016);
- LILACS, lilacs.bvsalud.org (searched 24 June 2016);
- KoreaMed (searched via Google Scholar 24 June 2016);
- IndMed, www.indmed.nic.in (searched 24 June 2016);
- PakMediNet, www.pakmedinet.com (searched 24 June 2016);
- Web of Knowledge, Web of Science (1945 to 23 June 2016);
- CNKI, www.cnki.com.cn (searched via Google Scholar 24 June 2016);
- ClinicalTrials.gov, (searched via the Cochrane Register of Studies 23 June 2016);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), www.who.int/ictrp (searched 23 June 2016);
- ISRCTN, www.isrctn.com (searched 24 June 2016);
- Google Scholar, scholar.google.co.uk (searched 24 June 2016);
- Google, www.google.com (searched 24 June 2016).

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

Searching other resources

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

Data collection and analysis

This review is based on a published protocol (Javed 2015). Any differences between the published protocol and the review have been listed in the Differences between protocol and review section.

Selection of studies

Two review authors independently screened the titles and abstracts found by the searches and scanned the reference lists of relevant studies and systematic reviews to assess potential relevance for full review. The same review authors independently reviewed the full text of potentially relevant studies against the pre-defined inclusion and exclusion criteria. Any disagreements were resolved by discussion with a third review author.

Data extraction and management

Two review authors independently extracted data from the included trials using a standardised data extraction form. We extracted the following information from each trial:

- Study characteristics: setting, design, method of data analysis.

- Participants: study population, number of participants in each group, patient characteristics including age, gender, ethnicity, duration of ear discharge prior to enrollment, number of discharging ears at baseline and main indication for tube insertion.
- Interventions: type of intervention and comparison used including dosage, duration and route of administration.
- Outcomes: primary and secondary outcomes recorded, adverse events including adverse effects likely to be related to the use of study medications and serious complications of middle ear infection.

If a study provided more than one data point within the same time period (e.g. data on the proportion of patients with resolution of ear discharge at 5 and 10 days of follow-up), we used the data point with the shortest duration of follow-up. If a study reported both parental and otoscopic observations, we used the latter as this is considered the most objective method of diagnosing resolution or persistence of middle ear infection (ear discharge) in children. Any disagreements in data extraction were resolved by discussion with a third review author.

Assessment of risk of bias in included studies

Two review authors independently assessed the methodological quality of the included trials and any disagreements were resolved by discussion with a third review author. We performed 'Risk of bias' assessment by using the 'Risk of bias' tool described in Chapter 8 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). Cochrane has moved away from high/low-quality trials to high/low/uncertain risk of bias. We therefore judged the following domains as high, low or unclear risk of bias:

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective outcome reporting (reporting bias);
- other sources of bias.

We presented the results of the 'Risk of bias' assessment in a 'Risk of bias' graph and a 'Risk of bias' summary.

Measures of treatment effect

We expressed dichotomous outcomes as risk ratios (RRs) with accompanying 95% confidence intervals (CIs) and calculated the number needed to treat to benefit (NNTB). We proposed to express continuous outcome variables either as mean differences (MDs), if reported on the same scale, or as standardised mean differences (SMD), if different continuous scales were used, with accompanying 95% CIs.

Unit of analysis issues

In the case of cluster-randomised trials, we proposed to use analysis techniques that take into account the effect of clustering, as described in Chapter 16 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

Dealing with missing data

One trial author contacted the corresponding trial authors of the included trials to try to obtain additional information in case of missing data. For continuous outcomes, we calculated missing statistics, such as standard deviations (SDs), from other available statistics (e.g. P values) according the methods described in Chapter 7 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

Assessment of heterogeneity

We assessed the level of clinical diversity by reviewing the included trials for potential differences in study populations, interventions or comparisons used and outcomes measured. We assessed statistical heterogeneity for each outcome with visual inspection of the forest plots using the Chi^2 test, with a significance level set at $P < 0.10$, and the I^2 statistic, with I^2 values of 50% or more suggesting substantial statistical heterogeneity (Handbook 2011).
Where substantial statistical heterogeneity was present, we carried out pre-specified subgroup analyses and conducted sensitivity analyses based on the risk of bias (see Subgroup analysis and investigation of heterogeneity; Sensitivity analysis). We based assessments of differences in effect sizes between subgroups on the Chi^2 tests for heterogeneity statistics between subgroups. If none of these analyses completely resolved statistical heterogeneity then we employed a random-effects (DerSimonian and Laird) model to provide amore conservative effect estimate.

Assessment of reporting biases

We searched the internet and ClinicalTrials.gov (http://clinicaltrials.gov) for available study protocols to determine whether outcomes reported in the included trials were pre-defined and whether all outcomes listed in the study protocol were reported in the publication. If there were sufficient trials, we proposed to assess reporting bias by using funnel plots.

Data synthesis

We performed available case analyses, so using data for every participant for whom the outcome was obtained, according to the intention-to-treat (ITT) principle (i.e. analysing participants in the groups to which they were originally allocated).
We proposed to pool data for the interventions that are listed as a separate category under the Types of interventions heading but we intended to analyse the two different interventions of antibiotic

eardrops (with and without a corticosteroid) together as a comparison pair in our main comparison of interest (oral antibiotics *versus* antibiotic eardrops (with or without a corticosteroid)).
For dichotomous data, we calculated the RR with 95% CI using the Mantel-Haenszel method with a fixed-effect (I^2 values < 50%) or random-effects (DerSimonian and Laird) model. In addition, we calculated the number needed to treat to benefit (NNTB) or number needed to treat to harm (NNTH) based on the average risks of the control groups in the included studies ('study population') (Handbook 2011).

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analysis for the following categories if sufficient data were available:

- duration of ear discharge prior to randomisation (four weeks or less versus more than four weeks);
- number of discharging ears at baseline (unilateral versus bilateral discharge);
- main indication for tube insertion (recurrent acute otitis media versus persistent otitis media with effusion);
- type of eardrops (antibiotic-only eardrops versus eardrops containing antibiotic(s) and a corticosteroid); eardrops containing antibiotic(s) and a corticosteroid may be more effective than antibiotic-only eardrops.

Sensitivity analysis

We proposed to perform a sensitivity analysis in which only trials judged as low risk of bias (based on a low risk in the key domains affecting bias including allocation concealment and incomplete outcome data) were included.

GRADE approach and 'Summary of findings'

We used the GRADE approach to rate the overall quality of evidence for each outcome. Two review authors (RPV and FJ) independently rated the quality of evidence as high, moderate, low or very low. Any disagreements were resolved by discussion. We rated evidence from RCTs that did not have serious limitations as high quality. However, the following factors could lead to downgrading of the quality of evidence to moderate, low or very low:

- study limitations (risk of bias);
- indirectness of evidence (directness of evidence);
- imprecision (precision of results);
- inconsistency (consistency of results);
- publication bias (existence of publication bias).

We included a 'Summary of findings' table for the main comparison of interest (oral antibiotics versus antibiotic eardrops with or without a corticosteroid), which contains what we felt to be the seven most important outcomes: resolution of ear discharge at short-term follow-up (one week); adverse events; serious complications; resolution of ear discharge at intermediate-term follow-up (two weeks); duration of ear discharge; tube blockage; health-related quality of life.

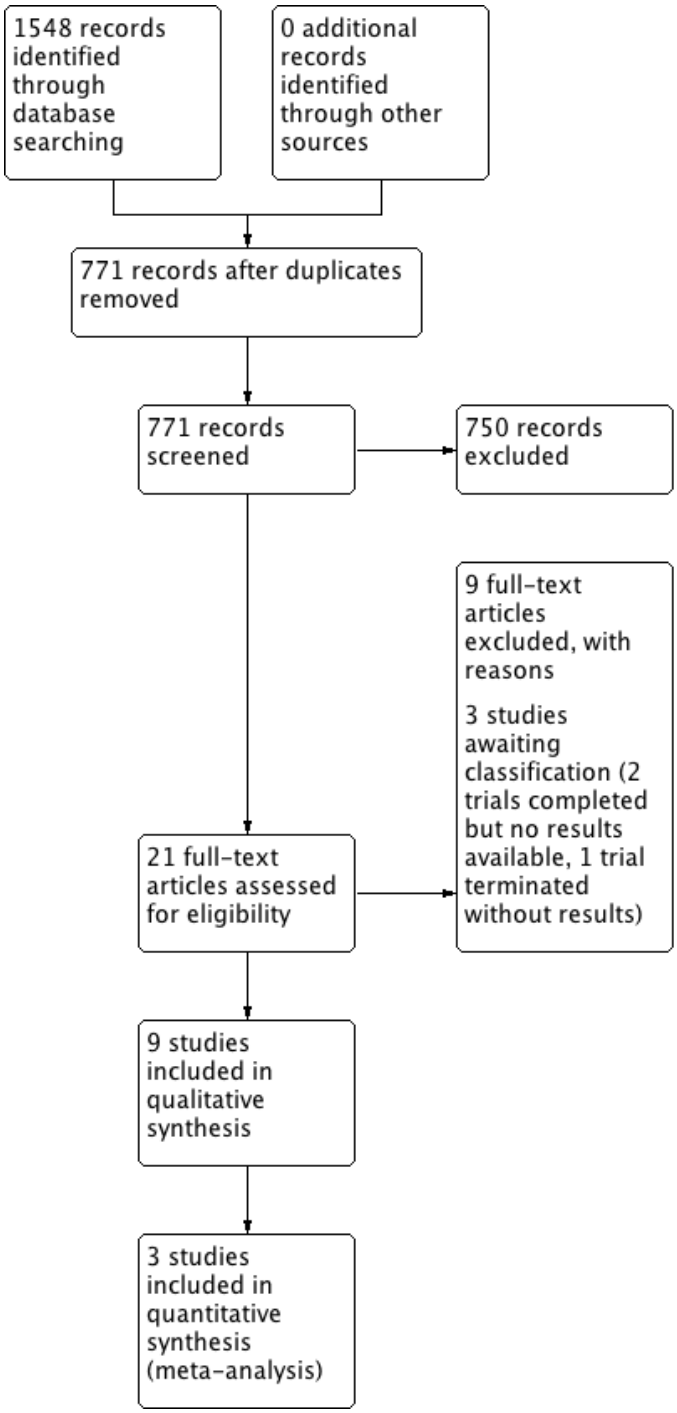
RESULTS

Description of studies

Results of the search

The searches retrieved a total of 1548 records. Removing duplicates left 771 unique records. After screening titles and abstracts we identified 21 potentially eligible references. We excluded nine studies (see Excluded studies). Nine studies are included in the review. Three studies are awaiting assessment, two of which are listed as completed but no results are available and one of which has been terminated for unknown reasons (see Studies awaiting classification). We did not identify any ongoing studies. Figure 1 shows the flow chart of study retrieval and selection.

Figure 1. Process for sifting search results and selecting studies for inclusion



Included studies

For details of the included studies see the Characteristics of included studies table.

Design

All included studies were randomised trials. Three (33%) were double-blind, five (56%) were single-blind and one (11%) was an open-label trial.

Sample sizes

Sample sizes of the included studies ranged from 68 to 599 children.

Setting

Most studies were conducted in a secondary or tertiary care setting in a range of countries, mainly the USA and Northern Europe (Scandinavia and the Netherlands).

Participants

The participants in all studies were children ranging in age from 0 to 12 years. The percentage of participants who were boys in the included studies ranged from 52% to 67%. Most studies included children with uncomplicated ear discharge of less than three weeks duration; duration of ear discharge was less than 48 hours in two trials.

Interventions

In the nine included studies a wide range of interventions were studied. Six trials compared two interventions and three compared three different interventions. Table 1 provides an overview of interventions and the eight comparison pairs included in this review. Details of the specific interventions (formulae, dosage, duration) can be found in the Characteristics of included studies table.

Outcomes

Table 2 summarises whether the included studies did (or did not) report on our pre-specified outcomes. All outcomes were reported in at least one study except for the secondary outcome "proportion of children without other signs of a middle ear infection (ear pain and fever) at short-term follow-up".

Funding and conflict of interest

Five studies were either directly funded or financially supported by pharmaceutical companies (Alcon (three trials), Daiichi, Salvat); the pharmaceutical companies provided the study medication in two studies. One study received non-commercial (governmental) funding; one study was performed without funding.

Excluded studies

We excluded nine articles after reviewing the full text. Reasons for exclusion are provided in the Characteristics of excluded studies table.

Risk of bias in included studies

Summaries of the 'Risk of bias' assessment of the included studies are presented in Figure 2 and Figure 3.

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

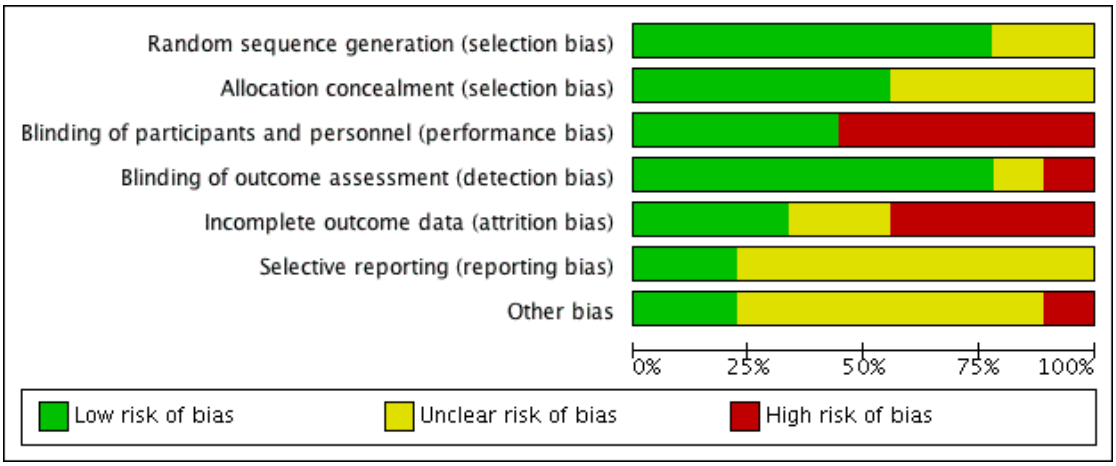
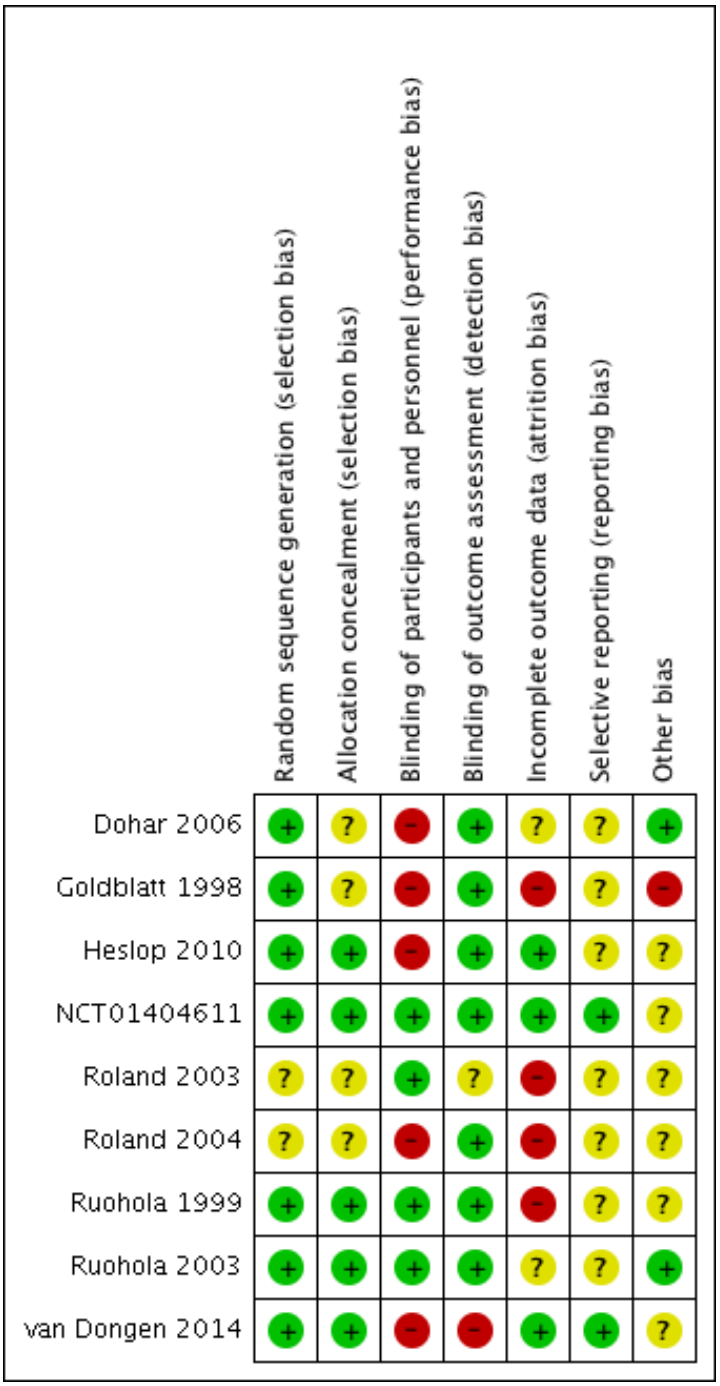


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

The method of random sequence generation was adequately described in seven studies (78%) and unclear in two studies (22%).

Allocation concealment

Concealment of allocation was adequately described in five studies (56%) and unclear in four studies (44%).

Blinding

We judged the risk of bias for blinding of participants and personnel (performance bias) as low in four studies (44%) and high in five studies (56%). We judged the risk of bias for blinding of outcome assessment (detection bias) as low in seven studies (78%), unclear in one study (11%) and high in one study (11%).

Incomplete outcome data

We judged the risk of bias for incomplete outcome data as low in three studies (33%), unclear in two studies (22%) and high in four studies (44%).

Selective reporting

We judged the risk of bias for selective reporting as low in two studies (22%). We could not retrieve trial protocols for the remaining seven studies (78%) and could therefore not determine the risk of selective outcome reporting bias for these studies.

Other potential sources of bias

We judged the risk of other potential sources of bias as low in two studies (22%), unclear in six studies (67%) and high in one study (11%).

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics in children with grommets (ventilation tubes) who develop ear discharge beyond the immediate postoperative period

We have reported all available outcome data for all comparisons (those not listed were not available).

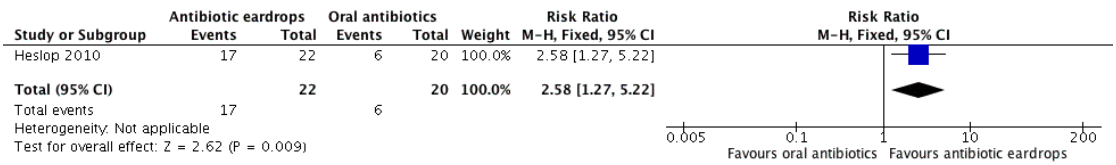
1. Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics

Primary outcomes

Proportion of patients with resolution of ear discharge at short-term follow-up

For this outcome, we could use data from only one study (Heslop 2010) (42 randomised children; 42 (100%) included in analysis). Children treated with antibiotic eardrops (ciprofloxacin) were more likely to have resolution of ear discharge at one week than those treated with oral antibiotics (amoxicillin) (ciprofloxacin eardrops versus amoxicillin: 77% versus 30%; risk ratio (RR) 2.58, 95% confidence interval (CI) 1.27 to 5.22, number needed to treat to benefit (NNTB) 3) (Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics, outcome: 1.1 Resolution of ear discharge at one week.



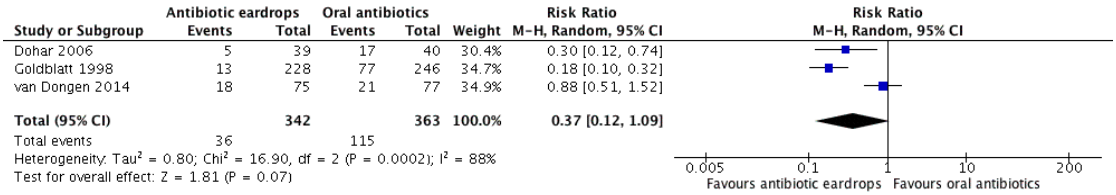
Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to imprecise effect estimates (small sample size).

Adverse events likely to be related to study medications

We combined data from three studies (Dohar 2006; Goldblatt 1998; van Dongen 2014) (707 randomised children; 705 (99.6%) included in analysis). The frequency of adverse events did not significantly differ between children treated with antibiotic eardrops with or without corticosteroids and those treated with oral antibiotics (RR 0.37, 95% CI 0.12 to 1.09; I^2 = 88%, random-effects model) (Analysis 1.2; Figure 5). We also did not find evidence that the effects differed among subgroups for this outcome.

Figure 5. Forest plot of comparison: 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics, outcome: 1.2 Adverse events likely to be related to the use of study medications.



In the sensitivity analysis including only studies judged as low risk of bias for allocation concealment and incomplete outcome data, only one study could be included (van Dongen 2014). In this study, adverse events did not differ between children treated with antibiotic-corticosteroid eardrops (bacitracin-colistin-hydrocortisone) and those treated with oral antibiotics (RR 0.88, 95% CI 0.51 to 1.52) (Analysis 2.1). It should be noted that 89% of adverse events associated with antibiotic-corticosteroid eardrops related to ear pain or discomfort during administration of the drops whereas 86% of adverse events associated with oral antibiotics were gastrointestinal symptoms.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and inconsistency of effect estimates across individual studies.

Serious complications related to middle ear infection

For this outcome, we could use data from one study only (153 randomised children; 153 (100%) included in analysis) (van Dongen 2014). Serious complications related to middle ear infection were not reported in this study.

Quality of the evidence

The evidence for this outcome was of very low quality; we downgraded it from high to very low quality due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of outcome).

Secondary outcomes

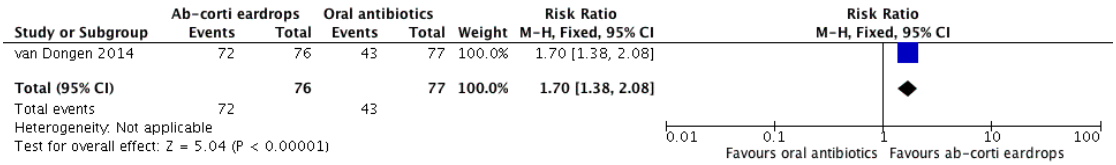
Proportion of patients with resolution of ear discharge at intermediate-term follow-up

For this outcome, we could use data from three studies (Dohar 2006; Goldblatt 1998; van Dongen 2014) (707 randomised children; 465 (66%) included in analysis). In this analysis, one of the subgroup analyses showed a significant subgroup difference: children treated with antibiotic(s)-corticosteroid eardrops were more likely to have resolution of ear discharge at two to four weeks than those treated with oral antibiotics and those treated with antibiotic-only eardrops (RR 1.59, 95% CI 1.35 to 1.88, I^2 = 5%, fixed-effect model; NNTB 8 versus RR 1.00, 95% CI 0.91 to 1.09, respectively) (Analysis 1.3).

In the sensitivity analysis including only studies judged as low risk of bias for allocation concealment and incomplete outcome data, one study was included (van Dongen 2014). Children treated with antibiotic-corticosteroid eardrops (bacitracin-colistin-hydrocortisone) were more likely to have resolution of ear discharge at two weeks than those treated with oral antibiotics (bacitracin-colistin-

hydrocortisone eardrops versus amoxicillin-clavulanate: 95% versus 56%; RR 1.70, 95% CI 1.38 to 2.08, NNTB 3) (Analysis 2.2; Figure 6).

Figure 6. Forest plot of comparison: 2 Sensitivity analysis - Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics, outcome: 2.2 Resolution of ear discharge at two weeks.



Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to study limitations.

Duration of ear discharge

For this outcome, we could use data from two studies (Dohar 2006; van Dongen 2014) (233 randomised children; 232 (99.6%) included in analysis). Children treated with antibiotic-corticosteroid eardrops had a shorter duration of ear discharge than those treated with oral antibiotics; median 4 days (range 1 to 28) versus 5 days (range 1 to 36) (van Dongen 2014) and median 4 days (range not reported) versus 7 days (range not reported) (Dohar 2006), respectively. We did not deem sensitivity analysis to be useful because of the low number of studies.

Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to study limitations.

Proportion of patients with chronic ear discharge

For this outcome, we could use data from one study only (153 randomised children; 148 (97%) included in analysis) (van Dongen 2014). The proportion of children with chronic ear discharge did not differ significantly between children treated with antibiotic-corticosteroid eardrops (bacitracin-colistin- hydrocortisone) and those treated with oral antibiotics (RR 0.20, 95% CI 0.02 to 1.67) (Analysis 1.4).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to due to study limitations and imprecise effect estimate (infrequent occurrence of outcome).

Ear discharge recurrences

For this outcome, we could use data from one study only (153 randomised children; 148 (97%) included in analysis) (van Dongen 2014). Children treated with antibiotic-corticosteroid eardrops had fewer recurrences of ear discharge during six months follow-up than those treated with oral antibiotics: median 0 episodes (range 0 to 9) versus 1 episode (range 0 to 6) (median difference -1, P = 0.03).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to due to study limitations and imprecise effect estimate (small sample size).

Proportion of patients with tube blockage

We combined data from two studies (122 randomised children; 121 (99%) included in analysis) (Dohar 2006; Heslop 2010). The proportion of children with tube blockage did not differ significantly between those treated with antibiotic eardrops with or without corticosteroids and oral antibiotics (RR 1.20, 95% CI 0.33 to 4.45; I^2 = 0%, fixed-effect model) (Analysis 1.5). We did not deem subgroup and sensitivity analyses to be useful because of the low number of studies and included children.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of outcome).

Health-related quality of life

For this outcome, we could use data from one study only (153 randomised children; 153 (100%) included in analysis) (van Dongen 2014). This study measured generic quality of life with the Child Heath Questionnaire and disease-specific quality of life with the Otitis Media-6 questionnaire. At two weeks, the change in generic health-related quality of life scores did not differ significantly between those treated with antibiotic-corticosteroid eardrops and those treated with oral antibiotics. The changes in Otitis Media-6 total score (range 6 to 42) at two weeks were small, but favoured the antibiotic-corticosteroid eardrops group (difference in median change between treatment groups: -2, $P < 0.01$).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimate (small sample size).

Hearing levels

Two studies provided information on this outcome. Dohar 2006 (79 children) compared antibiotic-corticosteroid eardrops (ciprofloxacin-dexamethasone) with oral antibiotics (amoxicillin-clavulanic acid) and stated that "neither treatment group had any negative effect on patient audiometry". Goldblatt 1998 (474 randomised children) performed audiometry in only a small subset of randomised children (56, i.e. 12%) and reported improvement in detecting air-conducted sound in 19/28 (68%) children treated with antibiotic eardrops (ofloxacin) versus 9/26 (35%) of those treated with oral antibiotics (amoxicillin-clavulanic acid).

Quality of the evidence

The evidence for this outcome was of very low quality; we downgraded it from high to very low quality due to study limitations, imprecise effect estimate (small sample size) and inconsistency of effect estimates across studies.

2. Antibiotic eardrops (with or without a corticosteroid) versus corticosteroid eardrops

Primary outcomes

Adverse events likely to be related to study medications

For this outcome, we could use data from only one study (331 randomised children; 331 (100%) included in analysis) (NCT01404611). Frequency of adverse events did not significantly differ between children treated with antibiotic-corticosteroid eardrops (ciprofloxacin-fluocinolone acetonide), antibiotic eardrops (ciprofloxacin) and corticosteroid eardrops (fluocinolone acetonide): 0/111 (0%) versus 1/112 (1%) versus 2/108 (2%), respectively.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to moderate quality due to imprecise effect estimate (small sample size and infrequent occurrence of outcome).

Serious complications related to middle ear infection

For this outcome, we could use data from only one study (331 randomised children; 331 (100%) included in analysis) (NCT01404611). Serious complications related to middle ear infection were reported infrequently and did not significantly differ between children treated with antibiotic-corticosteroid eardrops (ciprofloxacin-fluocinolone acetonide), antibiotic eardrops (ciprofloxacin) and corticosteroid eardrops (fluocinolone acetonide): 0/111 (0%) versus 1/112 (1%; acute mastoiditis) versus 0/108 (0%), respectively.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to imprecise effect estimate (small sample size and infrequent occurrence of outcome).

Secondary outcomes

Duration of ear discharge

For this outcome, we could use data from only one study (331 randomised children; 331 (100%) included in analysis) (NCT01404611). Children treated with corticosteroid eardrops (fluocinolone acetonide) had a longer duration of ear discharge than those treated with antibiotic-corticosteroid eardrops (ciprofloxacin-fluocinolone acetonide) and antibiotic eardrops (ciprofloxacin): median 22 days (95% CI 14 to 22) versus 5 days (95% CI 4 to 6) versus 7 days (95% CI 6 to 8), respectively.

Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to imprecise effect estimate (small sample size).

3. Antibiotic eardrops (with or without a corticosteroid) versus saline rinsing of the ear canal

Primary outcomes

Proportion of patients with resolution of ear discharge at short-term follow-up

For this outcome, we could use data from only one study (48 randomised children; 48 (100%) included in analysis) (Heslop 2010). Children treated with antibiotic eardrops (ciprofloxacin) were more likely to have resolution of ear discharge at one week than those treated with saline rinsing of the ear canal (ciprofloxacin eardrops versus saline rinsing: 77% versus 46%; RR 1.67, 95% CI 1.04 to 2.69, NNTB 4) (Analysis 3.1).

Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to imprecise effect estimate (small sample size).

Secondary outcomes

Proportion of patients with tube blockage

For this outcome, we could use data from only one study (48 randomised children; 48 (100%) included in analysis) (Heslop 2010). The proportion of children with tube blockage did not differ significantly between those treated with antibiotic eardrops (ciprofloxacin) and saline rinsing of the ear canal (RR 1.77, 95% CI 0.32 to 9.67) (Analysis 3.2).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to imprecise effect estimate (small sample size and infrequent occurrence of outcome).

4. Antibiotic eardrops (with or without a corticosteroid) versus no treatment

Primary outcomes

Serious complications related to middle ear infection

For this outcome, we could use data from only one study (153 randomised children; 153 (100%) included in analysis) (van Dongen 2014). Serious complications related to the middle ear infection did not occur in this study.

Quality of the evidence

The evidence for this outcome was of very low quality; we downgraded it from high to very low quality due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of outcome).

Secondary outcomes

Proportion of patients with resolution of ear discharge at intermediate-term follow-up

For this outcome, we could use data from only one study (153 randomised children; 151 (99%) included in analysis) (van Dongen 2014). Children treated with antibiotic-corticosteroid eardrops (hydrocortisone-bacitracin-colistin) were more likely to have resolution of ear discharge at two weeks than those who did not receive treatment (bacitracin-colistin-hydrocortisone eardrops versus no treatment: 95% versus 45%; RR 2.09, 95% CI 1.62 to 2.69, NNTB 2) (Analysis 4.1).

Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to study limitations.

Duration of ear discharge

For this outcome, we could use data from only one study (153 randomised children; 147 (96%) included in analysis) (van Dongen 2014). Children treated with antibiotic-corticosteroid eardrops (hydrocortisone-bacitracin-colistin) had a shorter duration of ear discharge than those who did not receive treatment: median 4 days (range 1 to 28) versus 12 days (range 1 to 159), respectively.

Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to study limitations.

Proportion of patients with chronic ear discharge

For this outcome, we could use data from only one study (153 randomised children; 147 (96%) included in analysis) (van Dongen 2014). Children treated with antibiotic-corticosteroid eardrops (hydrocortisone-bacitracin-colistin) were less likely to have chronic ear discharge than those who did not receive treatment (RR 0.08, 95% CI 0.01 to 0.62, NNTB 7) (Analysis 4.2).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to due to study limitations and imprecise effect estimate (infrequent occurrence of outcome).

Ear discharge recurrences

For this outcome, we could use data from only one study (153 randomised children; 147 (96%) included in analysis) (van Dongen 2014). The median number of recurrent ear discharge episodes during six months follow-up did not differ significantly between children treated with antibiotic-corticosteroid eardrops (hydrocortisone-bacitracin-colistin) and those who did not receive treatment: median 0 episodes (range 0 to 9) versus 1 episode (range 0 to 5) (median difference -1, P = 0.26).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimate (small sample size).

Health-related quality of life

For this outcome, we could use data from only one study (153 randomised children; 153 (100%) included in analysis) (van Dongen 2014). This study measured generic quality of life with the Child Heath Questionnaire and disease-specific quality of life with the Otitis Media-6 questionnaire. At two weeks, the change in generic health-related quality of life scores did not differ significantly between children treated with antibiotic-corticosteroid eardrops (hydrocortisone-bacitracin-colistin) and those who did not receive treatment. The changes in Otitis Media-6 total score (range 6 to 42) at two weeks were small but favoured antibiotic-corticosteroid eardrops (difference in median difference between treatment groups: -1.5, P < 0.01).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimate (small sample size).

5. Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops

Primary outcomes

Proportion of patients with resolution of ear discharge at short-term follow-up

We combined data from two studies (800 randomised children; 590 (74%) included in analysis) (Roland 2003; Roland 2004). Children treated with antibiotic-corticosteroid eardrops were more likely to have resolution of ear discharge at less than two weeks than those treated with antibiotic eardrops (35% versus 20%; RR 1.76, 95% CI 1.33 to 2.31, I^2 = 0%, fixed-effect model; NNTB 12) (Analysis 5.1). We did not deem sensitivity analysis to be useful because of the low number of studies.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and risk of publication bias (two studies were completed but the results were not available, one study was terminated for unknown reasons, see Characteristics of studies awaiting classification).

Adverse events likely to be related to study medications

We combined data from three studies (1023 randomised children; 1023 (100%) included in analysis) (NCT01404611; Roland 2003; Roland 2004). Adverse events did not differ significantly between children treated with antibiotic-corticosteroid eardrops and those treated with antibiotic eardrops (RR 0.86, 95% CI 0.55 to 1.32; I^2 = 0%, fixed-effect model) (Analysis 5.2). The data did not allow us to perform subgroup analyses.

In the sensitivity analysis, where we only included studies judged as low risk of bias for allocation concealment and incomplete outcome data, data from one study could be used (NCT01404611). The results from sensitivity analysis were comparable with the effect estimate observed in our main analysis (Analysis 6.1).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to imprecise effect estimate (small sample size) and risk of publication bias (two studies were

completed but results were not available, one study was terminated for unknown reasons, see Characteristics of studies awaiting classification).

Serious complications related to middle ear infection

For this outcome, we could use data from two studies (822 randomised children; 822 (100%) included in analysis) (NCT01404611; Roland 2004). Serious complications related to middle ear infection were reported infrequently and did not differ significantly between children treated with antibiotic-corticosteroid eardrops and those treated with antibiotic eardrops: 0/408 versus 1/414 (mastoiditis), respectively. We did not deem sensitivity analysis to be useful because of the low number of studies and events.

Quality of the evidence

The evidence for this outcome was of very low quality; we downgraded it from high to very low quality due to imprecise effect estimate (small sample size and infrequent occurrence of outcome) and risk of publication bias (two studies were completed but results were not available, one study was terminated for unknown reasons, see Characteristics of studies awaiting classification).

Secondary outcomes

Proportion of patients with resolution of ear discharge at intermediate-term follow-up

We combined data from two studies (800 randomised children; 590 (74%) included in analysis) (Roland 2003; Roland 2004). The proportion of children with resolution of ear discharge at two to four weeks did not differ significantly between children with antibiotic-corticosteroid eardrops and those treated with antibiotic eardrops (RR 1.09, 95% CI 0.90 to 1.31; I^2 = 84%, random-effects model) (Analysis 5.3). We did not deem sensitivity analysis to be useful because of the low number of studies.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and risk of publication bias (two studies were completed but results were not available, one study was terminated for unknown reasons, see Characteristics of studies awaiting classification).

Duration of ear discharge

For this outcome, we could use data from three studies (1023 randomised children; 813 (79%) included in analysis) (NCT01404611; Roland 2003; Roland 2004). The data did not allow pooling, but study results showed a small but consistent difference in the number of days with ear discharge in favour of antibiotic-corticosteroid eardrops (mean duration 4.22 versus 5.31 days; 4 versus 6 days and 5 versus 7 days, respectively).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and risk of publication bias (two studies were completed but results were not available, one study was terminated for unknown reasons, see Characteristics of studies awaiting classification).

Proportion of patients with tube blockage

For this outcome, we could use data from two studies (800 randomised children; 766 (96%) included in analysis) (Roland 2003; Roland 2004). The proportion of children with tube blockage did not differ significantly between those treated with antibiotic eardrops with or without a corticosteroid; one study (201 randomised children; 167 (83%) included in analyses) reported that "there were no significant differences between the two treatments in continued tympanostomy tube patency (> 97% in both groups)" (Roland 2003), whereas the proportions of children with tube blockage in the other study were 1/297 and 0/302, respectively (Roland 2004).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and risk of publication bias (two studies were completed but results were not available, one study was terminated for unknown reasons, see Characteristics of studies awaiting classification).

Hearing levels

Two studies provided information on this outcome. In one study (201 randomised children; number of children analysed unknown) it was stated that "audiometric examinations performed on patients exiting from the study revealed no clinically meaningful or statistically significant (P = 0.3038) worsening of the speech reception threshold in any patient" (Roland 2003), whereas in the other study (599 randomised children; number of children analysed unknown) it was stated that "no clinically relevant or statistically significant differences in mean change of speech recognition threshold from baseline or decrease in hearing from baseline were observed after treatment with either ciprofloxacin/dexamethasone or ofloxacin, based on bone and air conduction audiometry" (Roland 2004).

Quality of the evidence

The evidence for this outcome was of very low quality; we downgraded it from high to very low quality due to due to study limitations, imprecise effect estimate and risk of publication bias (two studies were completed but results were not available, one study was terminated for unknown reasons, see Characteristics of studies awaiting classification).

6. Oral antibiotics versus saline rinsing of the ear canal

Primary outcomes

Proportion of patients with resolution of ear discharge at short-term follow-up

For this outcome, we could use data from only one study (46 randomised children; 46 (100%) included in analysis) (Heslop 2010). The proportion of children with resolution of ear discharge at one week did not differ significantly between children treated with oral antibiotics and those treated with saline rinsing of the ear canal (RR 0.65, 95% CI 0.30 to 1.43) (Analysis 7.1).

Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to imprecise effect estimate (small sample size).

Secondary outcomes

Proportion of patients with tube blockage

For this outcome, we could use data from only one study (46 randomised children; 46 (100%) included in analysis) (Heslop 2010). The proportion of children with tube blockage did not differ significantly differ between children treated with oral antibiotics and those treated with saline rinsing of the ear canal (RR 1.95, 95% CI 0.36 to 10.58) (Analysis 7.2).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to imprecise effect estimate (small sample size and infrequent occurrence of outcome).

7. Oral antibiotics versus placebo or no treatment

Primary outcomes

Proportion of patients with resolution of ear discharge at short-term follow-up

For this outcome, we could use data from only one study (79 randomised children; 79 (100%) included in analysis) (Ruohola 2003). Children treated with oral antibiotics (amoxicillin-clavulanate) were more likely to have resolution of ear discharge at less than two weeks than those treated with placebo (amoxicillin-clavulanate versus placebo: 72% versus 33%; RR 2.21, 95% CI 1.36 to 3.60, NNTB 3) (Analysis 8.1).

Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to imprecise effect estimate (small sample size).

Adverse events likely to be related to study medications

For this outcome, we could use data from only one study (Ruohola 2003) (79 randomised children; 79 (100%) included in analysis). Adverse events did not differ significantly between children treated with oral antibiotics and those treated with placebo (RR 1.71, 95% CI 0.69 to 4.25) (Analysis 8.2).

Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to imprecise effect estimate (small sample size).

Serious complications related to middle ear infection

For this outcome, we could use data from two studies (233 randomised children; 233 (100%) included in analysis) (Ruohola 2003; van Dongen 2014). In both studies no serious adverse events related to middle ear infection occurred.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to imprecise effect estimate (small sample size and infrequent occurrence of outcome).

Secondary outcomes

Proportion of patients with resolution of ear discharge at intermediate-term follow-up

For this outcome, we could use data from only one study (154 randomised children; 152 (99%) included in analysis) (van Dongen 2014). The proportion of children with resolution of ear discharge at two weeks did not differ significantly differ between children treated with oral antibiotics and those who did not receive treatment (RR 1.23, 95% CI 0.90 to 1.69) (Analysis 8.3).

Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to study limitations.

Duration of ear discharge

For this outcome, we could use data from two studies (233 randomised children; 226 (97%) included in analysis) (Ruohola 2003; van Dongen 2014). The data did not allow pooling, but study results showed a significant difference in the number of days with ear discharge in favour of oral antibiotics (median duration 3 versus 8 days and median duration 5 versus 12 days).

Quality of the evidence

The evidence for this outcome was of moderate quality; we downgraded it from high to moderate quality due to imprecise effect estimate (small sample size).

Proportion of patients with chronic ear discharge

For this outcome, we could use data from only one study (154 randomised children; 147 (95%) included in analysis) (van Dongen 2014). The proportion of children with chronic ear discharge did not differ significantly differ between children treated with oral antibiotics and those who did not receive treatment (RR 0.41, 95% CI 0.15 to 1.11) (Analysis 8.4).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to due to study limitations and imprecise effect estimate (infrequent occurrence of outcome).

Ear discharge recurrences

For this outcome, we could use data from only one study (154 randomised children; 147 (95%) included in analysis) (van Dongen 2014). The median number of ear discharge recurrences during six months follow-up did not differ significantly between children treated with oral antibiotics and those who did not receive treatment: median 1 episode (range 0 to 6) versus 1 episode (range 0 to 5) (median difference 0, P = 0.21).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimate (small sample size).

Proportion of patients with tube extrusion

For this outcome, we could use data from one study (79 randomised children; 79 (100%) included in analysis) (Ruohola 2003). The proportion of children with tube extrusion did not differ significantly between children treated with oral antibiotics and those treated with placebo (RR 0.51, 95% CI 0.05 to 5.43) (Analysis 8.5).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to imprecise effect estimate (small sample size and infrequent occurrence of outcome).

Health-related quality of life

For this outcome, we could use data from only one study (154 randomised children; 154 (100%) included in analysis) (van Dongen 2014). This study measured generic quality of life with the Child Heath Questionnaire and disease-specific quality of life with the Otitis Media-6 questionnaire. At two weeks, the change in generic health-related quality of life scores and Otitis Media-6 total score did not differ significantly between children treated with oral antibiotics and those who did not receive treatment.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimate (small sample size).

8. Oral corticosteroids versus placebo

Primary outcomes

Proportion of patients with resolution of ear discharge at short-term follow-up

For this outcome, we could use data from only one study (70 randomised children; 50 (71%) included in analysis) (Ruohola 1999). The proportion of children with resolution of ear discharge within two weeks did not differ significantly between children treated with oral corticosteroids and those treated with placebo as adjunctive therapy to oral antibiotics (RR 1.08, 95% CI 0.92 to 1.26) (Analysis 9.1).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to moderate quality due to study limitations and imprecise effect estimate (small sample size).

Adverse events likely to be related to the use of study medications

For this outcome, we could use data from only one study (70 randomised children; 50 (71%) included in analysis) (Ruohola 1999). Adverse events did not differ significantly between children treated with oral corticosteroids and those treated with placebo as adjunctive therapy to oral antibiotics (RR 0.23, 95% CI 0.01 to 4.63) (Analysis 9.2).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to moderate quality due to study limitations and imprecise effect estimate (small sample size).

Serious complications related to middle ear infection

For this outcome, we could use data from only one study (70 randomised children; 50 (71%) included in analysis) (Ruohola 1999). In this study serious adverse events related to middle ear infection did not occur.

Quality of the evidence

The evidence for this outcome was of very low quality; we downgraded it from high to very low quality due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of outcome).

Secondary outcomes

Duration of ear discharge

For this outcome, we could use data from only one study (70 randomised children; 50 (71%) included in analysis) (Ruohola 1999). In this study, a small but statistically significant difference in the median number of days with ear discharge in favour of oral corticosteroids (prednisolone) was observed: median duration 1 versus 3 days.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to moderate quality due to study limitations and imprecise effect estimate (small sample size).

Ear discharge recurrences

For this outcome, we could use data from only one study (70 randomised children; 50 (71%) included in analysis) (Ruohola 1999). The number of recurrences of ear discharge did not differ significantly between children treated with oral corticosteroids and those treated with placebo as adjunctive therapy to oral antibiotics: 1/23 versus 3/27, respectively.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to moderate quality due to study limitations and imprecise effect estimate (small sample size).

DISCUSSION

Summary of main results

Nine studies (2132 children) were included in this review, evaluating a range of interventions for children aged under 12 years with grommets who developed acute ear discharge beyond the immediate postoperative period. We judged the risk of bias to be low to moderate in most studies.

Current evidence indicates that **antibiotic eardrops (with or without a corticosteroid)** are *more effective* than the following:

- **Oral antibiotics** in terms of resolution of ear discharge at one week and two weeks (*moderate-quality evidence*), duration of ear discharge (*moderate-quality evidence*), ear discharge recurrences (*low-quality evidence*) and disease-specific quality of life (*low-quality evidence*), but not in terms chronic ear discharge (*low-quality evidence*), tube blockage (*low-quality evidence*),

generic quality of life (*low-quality evidence*) or hearing (*low-quality evidence*). Frequency of adverse events did not significantly differ between children treated antibiotic eardrops and those treated with oral antibiotics (*low-quality evidence*).

- **Corticosteroid eardrops** in terms of duration of ear discharge (*moderate-quality evidence*). Frequency of adverse events did not significantly differ between children treated with topical antibiotics and those treated with topical corticosteroids (*low-quality evidence*).

- **No treatment** in terms of resolution of ear discharge at two weeks (*moderate-quality evidence*), duration of ear discharge (*moderate-quality evidence*), chronic ear discharge (*low-quality evidence*) and disease-specific quality of life (*low-quality evidence*), but not in terms of ear discharge recurrences (*low-quality evidence*) and generic quality of life (*low-quality evidence*).

There is also some evidence that **antibiotic eardrops** are more effective than **saline rinsing of the ear canal** in terms of resolution of ear discharge at one week (*moderate-quality evidence*), but not in terms of tube blockage (*low-quality evidence*). These findings should, however, be interpreted with caution since a trivial or clinically irrelevant difference between antibiotic eardrops and saline rinsing of the ear canal cannot be excluded.

We found low-quality evidence that eardrops containing a combination of an antibiotic and a corticosteroid are more effective than antibiotic eardrops in terms of resolution of ear discharge at short-term follow-up and duration of ear discharge, but not in terms of resolution of ear discharge at intermediate-term follow-up and tube blockage. These findings should, however, be interpreted with caution because of a substantial risk of publication bias.

Overall completeness and applicability of evidence

The children participating in the nine studies included in this review represent those most commonly encountered in clinical practice, that is children below 12 years of age with grommets who developed uncomplicated ear discharge of less than three weeks duration. The studies evaluate the full range of interventions that are most commonly used in day-to-day practice, including antibiotic eardrops with or without a corticosteroid, oral antibiotics, saline rinsing of thee ar canal and initial observation. As such, the overall degree of completeness is high.

Quality of the evidence

The quality of the evidence for the primary outcomes looking at effectiveness in the studies comparing antibiotic eardrops versus other interventions was moderate. The quality of evidence for the safety outcomes and secondary outcomes looking at effectiveness in the studies comparing antibiotic eardrops versus other interventions was mostly low or very low. The facts that all studies favoured antibiotic eardrops over other interventions and that the difference between treatments was large (in favour of eardrops) increase our confidence in the review findings; it is therefore unlikely that further research will change our confidence in the effects observed.

Potential biases in the review process

We used an extensive search strategy without language or publication restrictions; it is therefore unlikely that we have missed relevant studies. For the comparison antibiotic-corticosteroid eardrops versus antibiotic-only eardrops three studies are, however, awaiting classification (see Characteristics of studies awaiting classification). This may impact the findings substantially and the results of this comparison should therefore be interpreted with caution.

Two authors independently undertook data extraction and 'Risk of bias' assessment and we strictly adhered to the instructions in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). Three review authors are, however, authors of the included study comparing antibiotic-corticosteroid eardrops with oral antibiotics and no treatment (van Dongen 2014). To avoid potential conflict of interest, the two other review authors reviewed the eligibility and performed the 'Risk of bias' assessment and data extraction for this study.

In this review, we have assigned a unitary weight for each adverse event. Although we followed our published protocol when analysing adverse events, categorising these by severity may have been more appropriate. We encourage researchers to report adverse events by severity in future trials in this field and we will consider this approach when updating the current review.

Finally, downgrading of the quality of evidence according to sample/effect size, i.e. the determination of 'imprecise effect estimate', was not based on a predetermined criterion but rather based on a post hoc subjective interpretation of the review authors.

Agreements and disagreements with other studies or reviews

Since the 2006 Cochrane Review on this topic (Vaile 2006), four new studies have been published and included in this new review. This provides a robust evidence base for the treatment of children with grommets who develop ear discharge beyond the immediate postoperative period. Our main findings are in agreement with a recently published review on this topic (Chee 2016), and with the clinical practice guideline 'Tympanostomy tubes in children' issued by the American Academy of Otolaryngology - Head and Neck Surgery (Rosenfeld 2013), but they are not in line with current National Institute for Health and Care Excellence (NICE) recommendations to treat this condition as an episode of acute

otitis media (initial observation for uncomplicated disease and oral antibiotics for complicated or persisting disease) (NICE 2015).

AUTHORS' CONCLUSIONS

Implications for practice

This review provides robust evidence that antibiotic eardrops are more effective than oral antibiotics, corticosteroid eardrops and no treatment in children with grommets who develop acute ear discharge beyond the immediate postoperative period. We hope that this review will help a consensus to be reached across countries regarding first-line treatment for children with uncomplicated ear discharge occurring at least two weeks following grommet (ventilation tube) insertion.

This review provides no evidence to suggest that effectiveness varies across different types or formulations of antibiotic eardrops. Antibiotic eardrops covering the otopathogens that most commonly cause ear discharge in children with grommets (i.e. non-typeable*Haemophilus influenzae*,*Staphylococcus aureus*, *Pseudomonas aeruginosa*,*Streptococcus pneumoniae* and*Moraxella catarrhalis*) are likely to be equally effective.

Quinolones are considered non-ototoxic (Pappas 2006) and are currently the recommended ototopical agent in the USA (Rosenfeld 2013). However, these eardrops are not widely available in many countries (in contrast to ophthalmic formulations) and widespread use of quinolones has been suggested to induce antimicrobial resistance and fungal overgrowth, especially when used for a prolonged duration.

Animal studies have shown that aminoglycoside-containing eardrops are potentially ototoxic. The evidence in humans with an infected middle ear is, however, debated. Consensus statements by various ENT professional organisations have therefore suggested that "in patients with a discharging ear in the presence of a perforation or patent grommet, if a topical aminoglycoside is used, this should only be in the presence of obvious infection...[and] for no longer than two weeks" (Mylanus 2004; Phillips 2007).

Implications for research

We feel that this review answers the most important questions around the best management of children with grommets who develop ear discharge beyond the immediate postoperative period. Current evidence comparing antibiotic eardrops and saline rinsing of the ear canal is, however, limited and inconclusive. Future trials comparing these treatment strategies may therefore have an impact on the current review findings. Also, there is a need for well-designed trials comparing antibiotic-corticosteroid eardrops and eardrops containing antibiotics only because the current evidence is of low quality and carries a substantial risk of publication bias.

A further unresolved issue is that of the safety of both quinolone and non-quinolone antibiotic eardrops; implementation of the findings of this review will likely increase the use of antibiotic eardrops in children with grommets. We therefore emphasise the importance of continuous active surveillance of adverse effects including antimicrobial resistance, fungal overgrowth and sensorineural hearing loss associated with antibiotic eardrops.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Dohar 2006

Methods	**Allocation:** randomised **Design:** parallel, outcome-assessor blinded
Participants	**Number:** 80 (79 included in analyses) **Age:** 6 months to 8 years; mean age 1.9 years (SD 1.7 years) **Gender:** 42 boys (53%), 38 girls (47%) **Setting:** secondary care, 6 ENT surgeons located in the USA participated as investigators **Eligibility criteria:** children aged 6 months to 12 years with patent grommets and a clinical diagnosis of uncomplicated AOM with ear discharge (drainage visible to parent/guardian) of ≤ 3 weeks duration in one or both ears **Exclusion criteria:** ear discharge of ≥ 3 weeks duration; acute or malignant otitis externa; known or suspected fungal or mycobacterial ear infections; history of or active viral infections of the tympanic membrane; mastoiditis; infections requiring systemic antibiotics; otologic surgery in the previous year (except that confined to tympanic membrane); children with diabetes, immunosuppressive disorders, acute/chronic renal disease, active hepatitis, chronic nasal obstruction and/or persistent rhinorrhoea, complicating structural anomalies, known/suspected quinolone hypersensitivity, menarche (girls); previous history of chronic diarrhoea or pseudomembranous colitis; current or previous history of cholestatic jaundice or hepatic dysfunction; current diagnosis of mononucleosis; use of topical (otic or ophthalmic) corticosteroids or antibiotics concurrently or within the preceding 3 days, systemic corticosteroids within the preceding 7 days, inhaled corticosteroids at doses of 800 g/day, topical antibiotics for skin infections within the preceding 7 days, topical otic analgesics/anaesthetics or antiseptic washes, or nonsteroidal anti-inflammatory drugs, with the exception of oral acetaminophen for relief of pain; concurrent administration of allopurinol or probenecid
Interventions	**Intervention group:** antibiotic-corticosteroid eardrops; ciprofloxacin (0.3%)/dexamethasone (0.1%) otic suspension, 4 drops twice daily for 7 days in the affected ear(s) **Comparator group:** oral antibiotics; amoxicillin/clavulanic acid oral suspension; 90 mg/kg per day divided into 2 doses for 10 days **Use of additional interventions:** in both treatment groups, the ear canal was cleaned of all fluid and debris via suction (aural toilet) at baseline (and possibly during follow-up visits)
Outcomes	**Primary outcomes:** 1. time to cessation of ear discharge (parent-reported); 2. clinical cure (defined as absence of ear discharge as assessed by investigator) at TOC visit (18 to 21 days) **Secondary outcomes:** adverse events (assessed during follow-up visits and by parental report), audiometry at TOC visit, microbiologic response
Funding sources	This study was supported by a grant from Alcon Research Ltd (Fort Worth, TX)

Declarations of interest	Dr Dohar, Giles, Bikhazi, Carroll, Moe and Reese are independent physicians who received compensation from the sponsor for the study expenses but received no other financial incentives. Dr Roland is an independent physician who is paid by the sponsor for services as a medical monitor and consultant
Notes	**Participants lost to follow-up total:** 1/80 (1%) **Participants lost to follow-up intervention group:** 0/40 (0%); 1 child discontinued the study because of tube obstruction in the study ear but was included in ITT analysis **Participants lost to follow-up comparator group:** 1/41 (2%); 1 child discontinued the study because of dermatitis and diarrhoea

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were sequentially assigned to treatment according to a randomization code provided by the Alcon Biostatistics department. The randomization was blocked within center to ensure balanced treatment groups within each center."
Allocation concealment (selection bias)	Unclear risk	Method not described The randomisation was blocked within a centre to ensure balanced treatment groups within each centre. It is, however, unclear how large these blocks were, i.e. it is unclear if the person performing the randomisation procedure could predict treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome assessor-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor-blinded; those conducting the clinical observations were unaware of the treatment assignments. However, time to cessation of otorrhoea and adverse events were recorded from parental diaries
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1/80 (1%) children were excluded from analyses; antibiotic-corticosteroid eardrops group: 0/39 (0%), oral antibiotics group: 1/41 (2%) Children with pre-therapy culture of pure yeast, *P. aeruginosa* or group A streptococci were 'discontinued' from study and started on alternative therapy. It is unclear how

Dohar 2006 (*Continued*)

		many children were excluded from analysis
Selective reporting (reporting bias)	Unclear risk	Protocol was not available; insufficient information to permit a judgement of low or high risk
Other bias	Low risk	Baseline characteristics: balanced ITT analysis: performed Sample size calculations: performed Use of co-interventions: similar across groups (aural toilet)

Goldblatt 1998

Methods	**Allocation:** randomised **Design:** parallel, outcome-assessor blinded
Participants	**Number:** 474 (286 included in analyses) **Age:** 1 to 12 years; mean age 3.6 years **Gender:** 166 boys (58%), 120 girls (42%) **Setting:** secondary care, 36 centres in the USA and 1 centre in Chile **Eligibility criteria:** children aged 1 to 12 years with patent grommets and mucopurulent or purulent ear discharge of presumed bacterial origin for less than 3 weeks **Exclusion criteria:** positive culture for *P. aeruginosa* and fungus as sole pathogen in final otorrhoea culture and positive culture for group A beta-haemolytic streptococcus, menarche (girls)
Interventions	**Intervention group:** antibiotic eardrops; ofloxacin (0.3%) otic suspension, 0.25 ml twice daily for 10 days in the affected ear(s) **Comparator group:** oral antibiotics; amoxicillin/clavulanic acid oral suspension; 40 mg/kg per day (25 mg/kg/day in children under 2 years of age if they developed diarrhoea) divided into 3 doses for 10 days **Use of additional interventions:** not described
Outcomes	**Primary outcome:** clinical response (cure defined as absence of ear discharge as assessed by investigator at follow-up visits at 4 to 6 days, 11 to 13 days, 17 to 20 days) **Secondary outcomes:** adverse events (assessed during follow-up visits), audiometry at 17 to 20 days visit, microbiologic response
Funding sources	The study was sponsored by the Daiichi Pharmaceutical Corporation
Declarations of interest	None stated
Notes	**Participants lost to follow-up total:** 188/474 (40%) excluded from analyses **Participants lost to follow-up intervention group:** 88/228 (39%) excluded from analyses **Participants lost to follow-up comparator group:** 100/246 (41%) excluded from analyses

Goldblatt 1998 (*Continued*)

	Main reason for exclusion was positive culture for *P. aeruginosa* as a sole pathogen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome assessor-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor-blinded; those conducting the clinical observations were unaware of the treatment assignments
Incomplete outcome data (attrition bias) All outcomes	High risk	188/474 (40%) children excluded from analyses; antibiotic eardrops group: 88/228 (39%), oral antibiotics group: 100/246 (41%) Main reason for exclusion was positive culture for *P. aeruginosa* as a sole pathogen
Selective reporting (reporting bias)	Unclear risk	Protocol was not available; insufficient information to permit a judgement of low or high risk
Other bias	High risk	Baseline characteristics: balanced ITT analysis: not performed Sample size calculations: not performed Use of co-interventions: not described

Heslop 2010

Methods	**Allocation:** randomised **Design:** parallel, outcome-assessor blinded
Participants	**Number:** 68 (68 included in analyses) **Age:** aged below 10 years; mean age 22 months **Gender:** 40 boys (59%), 28 girls (41%) **Setting:** secondary care, ENT outpatient clinic, Denmark **Eligibility criteria:** Caucasian children aged below 10 years with grommets in situ and a first episode of ear discharge after grommets insertion **Exclusion criteria:** otorrhoea due to other ear diseases such as chronic suppurative otitis media or cholesteatoma, presence of other diseases or handicaps, treatment with systemic

	or local antibiotics during the preceding 3 weeks, patients taking topical or systemic steroids or non-steroidal anti-inflammatory drugs
Interventions	**Intervention group 1:** Antibiotic eardrops; ciprofloxacin (0.3%) otic suspension, 4 drops twice daily for 7 days in the affected ear(s) accompanied by massage of the tragus **Intervention group 2:** Saline rinsing; rinsing the ear canal with 2 x 5 ml normal saline through a syringe by the parents 3 times daily for 7 days **Comparator group:** Oral antibiotics; amoxicillin oral suspension, 25 to 50 mg/kg/day divided into 3 daily doses for 7 days (in case of penicillin allergy, erythromycin, 40 mg/kg/day divided into 3 doses daily for 7 days was chosen) **Use of additional interventions:** at baseline cleansing and suction of the ear canal was performed in all children. No co-medication was allowed except for mild analgesics
Outcomes	**Primary outcome:** treatment failure at 7 days (defined as presence of ear discharge as assessed by investigator) **Secondary outcomes:** adverse events (otitis externa and tube blockage or extrusion)
Funding sources	No funding
Declarations of interest	None
Notes	**Participants lost to follow-up total:** 0/68 (0%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Only in the presence of a nurse in the clinic, the parents chose a sealed envelope containing a slip of paper describing the specific treatment. Each envelope was marked with a random number from a list of random sequences constructed by the first author, who was not in contact with the patients."
Allocation concealment (selection bias)	Low risk	Quote: "Only in the presence of a nurse in the clinic, the parents chose a sealed envelope containing a slip of paper describing the specific treatment. Each envelope was marked with a random number from a list of random sequences constructed by the first author, who was not in contact with the patients."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome assessor-blinded

Heslop 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised children were included in analyses
Selective reporting (reporting bias)	Unclear risk	Protocol was not available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: not balanced for gender and slight imbalance for age ITT analysis: performed Sample size calculations: performed Use of co-interventions: at baseline cleansing and suction of the ear canal was performed in all children. No co-medication was allowed except for mild analgesics

NCT01404611

Methods	**Allocation:** randomised **Design:** parallel, double-blind
Participants	**Number:** 331 (331 included in analyses) **Age:** 6 months to 12 years; mean age 3.2 years (SD 2.4) **Gender:** 193 boys (58%), 138 girls (42%) **Setting:** unclear, study centres in Europe (Czech Republic, Denmark, Finland, Spain and Sweden), South Africa, Canada and USA **Eligibility criteria:** children aged 6 months to 12 years with moderate or severe, purulent ear discharge through a grommet of $\leq$ 3 weeks duration in one or both ears **Exclusion criteria:** other ear diseases
Interventions	**Intervention group 1:** antibiotic-corticosteroid eardrops; ciprofloxacin 0.3% plus fluocinolone acetonide 0.025% otic solution twice a day for 7 days in the affected ear(s) **Intervention group 2:** antibiotic eardrops; ciprofloxacin 0.3% otic solution twice a day for 7 days in the affected ear(s) **Comparator group:** corticosteroid eardrops; fluocinolone acetonide 0.025% otic solution twice a day for 7 days in the affected ear(s) **Use of additional interventions:** not described
Outcomes	**Primary outcome:** duration of ear discharge (time to cessation of ear discharge) **Secondary outcomes:** adverse events
Funding sources	This study was sponsored by Laboratorios SALVAT S.A.
Declarations of interest	Not described

NCT01404611 (*Continued*)

Notes	**Participants lost to follow-up total:** 0/331 (0%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patient was randomized using IWRS (Interactive Web Response System) "
Allocation concealment (selection bias)	Low risk	Double-blind. Quote: "The central laboratory was blinded to the treatment assignment of the patient from whom the sample was collected."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "All study medication products (test and comparators) had the same packaging and labels, and the boxes in which the study medication was packaged, shipped, and dispensed were identical in appearance."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised children were included in the primary analysis
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered at ClinicalTrials.gov (NCT01404611) and in the EU Clinical Trials Register (2010-023239-40). Results were presented for all pre-specified outcome measures
Other bias	Unclear risk	Baseline characteristics: balanced ITT analysis: unclear Sample size calculations: unclear Use of co-interventions: not described

Roland 2003

Methods	**Allocation:** randomised **Design:** parallel, patient-blinded
Participants	**Number:** 201 (167 included in analyses) **Age:** 6 months to 12 years; mean age 2.4 years **Gender:** 87 boys (52%), 80 girls (48%)

	Setting: secondary care, 18 clinical centres in the USA **Eligibility criteria:** children aged 6 months to 12 years with patent grommets and a clinical diagnosis of AOM with visible ear discharge of ≤ 3 weeks duration in one or both ears **Exclusion criteria:** fungal or mycobacterial ear infections, active herpes simplex, vaccinia, varicella or overt viral infections of the tympanic membrane, mastoiditis or other suppurative non-infectious ear infections, chronic nasal obstruction or persistent rhinorrhoea, a prior or current history of immunosuppressive disorders or immunosuppressive therapy, acute renal disorders, active hepatitis, diabetes or conditions that may predispose to neurosensory hearing loss; short-term antibiotics use in prior 2 days and long-term antibiotics use in prior 7 to 14 days
Interventions	**Intervention group:** antibiotic-corticosteroid eardrops; ciprofloxacin (0.3%)/dexamethasone (0.1%) otic suspension, 3 drops twice daily for 7 days in the affected ear(s) **Comparator group:** antibiotic eardrops; ciprofloxacin (0.3%) otic suspension, 3 drops twice daily for 7 days in the affected ear(s) **Use of additional interventions:** In both treatment groups, the ear canal was cleaned of all fluid and debris via suction (aural toilet) at baseline Analgesic use was restricted to paracetamol (acetaminophen) Any other topical or systemic antimicrobial treatment or anti-inflammatory agents were not allowed. Any dermatologic, nasal or inhaled corticosteroids (> 800 µg/day) or corticosteroid-antibiotic combinations were discontinued prior to study entry
Outcomes	**Primary outcome:** time to cessation of ear discharge (parent-reported) **Secondary outcomes:** investigator assessment of clinical response (presence or absence of ear discharge), reduction of granulation tissue, microbiologic response; adverse events, continued tube patency, audiometric evaluation at baseline and at end of study period
Funding sources	This study was supported by a grant from Alcon Research Ltd (Fort Worth, TX)
Declarations of interest	None stated
Notes	**Participants lost to follow-up total:** 34/201 (17%); insufficient information to calculate the number of children excluded from the intervention and comparator groups 34 culture-negative children were excluded from analyses; 17/34 were subsequently excluded due to failure to conform to inclusion/exclusion criteria. The remaining 17 patients were clinically cured at end of treatment (8 children treated with ciprofloxacin/dexamethasone, and 9 children treated with ciprofloxacin only)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described Quote: "The patients were assigned equally (1:1) via a randomization code to receive ototopical treatment with either ciprofloxacin 0.3% plus dexamethasone 0.1% otic

Roland 2003 (*Continued*)

		suspension or ciprofloxacin 0.3% ophthalmic solution."
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patient-blinded Quote: "Both medications were provided in opaque white plastic dropper bottles [...] Because of the physical distinction between the suspension and solution formulations, the study is best described as patient-masked (i.e., patients had no knowledge of their treatment assignment) rather than double-masked. However, all reasonable efforts were made to maintain masking of the clinical investigators. The study coordinator, not the clinical investigator, performed the initial dosing and subsequent dispensing of the medication."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Patient-blinded. Time to cessation of otorrhoea and adverse events were recorded from parental diaries. Efforts were made to maintain masking of the clinical investigators (see above)
Incomplete outcome data (attrition bias) All outcomes	High risk	34/201 (17%); 34 culture-negative children were excluded from analyses Insufficient information to calculate the number of children excluded from the intervention and comparator groups
Selective reporting (reporting bias)	Unclear risk	Protocol was not available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced ITT analysis: not performed Sample size calculations: not performed Use of co-interventions: similar across groups (aural toilet at baseline)

Roland 2004

Methods	**Allocation:** randomised **Design:** parallel, outcome assessor-blinded
Participants	**Number:** 599 (423 included in analyses) **Age:** 6 months to 12 years; mean age 2.45 years (SD 2.37 years) **Gender:** 373 boys (62%), 226 girls (32%) **Setting:** secondary care, 39 clinical centres in the USA and Canada **Eligibility criteria:** children aged 6 months to 12 years with patent grommets and a clinical diagnosis of uncomplicated AOM with ear discharge (drainage visible to parent/guardian) of $\leq$ 3 weeks duration in one or both ears **Exclusion criteria:** acute or malignant otitis externa; known or suspected fungal or mycobacterial ear infections; history of or active viral infections of the tympanic membrane; mastoiditis; infections requiring systemic antibiotics; otologic surgery in the previous year (except that confined to tympanic membrane); patients with diabetes, immunosuppressive disorders, acute/chronic renal disease, active hepatitis, chronic nasal obstruction and/or persistent rhinorrhoea, complicating structural anomalies, known/suspected quinolone hypersensitivity; menarche (girls); use of topical (otic or ophthalmic) corticosteroids or antibiotics concurrently or within the preceding 3 days, systemic corticosteroids within the preceding 7 days, inhaled corticosteroids at doses of 800 g/day, topical antibiotics for skin infections within the preceding 7 days
Interventions	**Intervention group:** antibiotic-corticosteroid eardrops; ciprofloxacin (0.3%)/dexamethasone (0.1%) otic suspension, 4 drops twice daily for 7 days in the affected ear(s) **Comparator group:** antibiotic eardrops; ofloxacin (0.3%) otic solution, 5 drops twice daily for 10 days in the affected ear(s) **Use of additional interventions:** In both treatment groups, the ear canal was cleaned of all fluid and debris via suction (aural toilet) at baseline. Use of topical otic analgesics/anaesthetics or antiseptic washes, or non-steroidal anti-inflammatory drugs was not allowed, except for oral paracetamol (acetaminophen) for relief of pain
Outcomes	**Primary outcome:** at 18 + 3 days: investigator assessment of clinical response (presence or absence of ear discharge), microbiologic response, treatment failure rate based on the number of children who were discontinued from the study because they did not respond to the assigned therapy **Secondary outcomes:** time to cessation of ear discharge (parent-reported and as assessed by the investigator during each study visit, adverse events (parent-reported), audiometric evaluations
Funding sources	This study was supported by a grant from Alcon Research Ltd (Fort Worth, TX)
Declarations of interest	Dr Roland is an independent physician who was paid by the sponsor for services as a medical monitor and consultant. Drs Kreisler, Reese, Fornelli and Lanier are independent physicians who received compensation from the sponsor for study expenses but received no other financial incentives
Notes	**Participants lost to follow-up total:** 176/599 (29%); 423 children were included in the modified intention-to-treat analyses (received treatment, met inclusion and exclusion criteria, had positive culture for bacteria at day 1) **Participants lost to follow-up intervention group:** 90/297 (30%)

Roland 2004 (*Continued*)

	Participants lost to follow-up comparator group: 86/302 (28%)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Outcome assessor-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor-blinded; those conducting the clinical observations were unaware of the treatment assignments. However, time to cessation of otorrhoea and adverse events were recorded from parental diaries
Incomplete outcome data (attrition bias) All outcomes	High risk	176/599 (29%) excluded from analyses; 423 children were included in the modified intention-to-treat analyses (received treatment, met inclusion and exclusion criteria, had positive culture for bacteria at day 1)
Selective reporting (reporting bias)	Unclear risk	Protocol was not available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced ITT analysis: not performed Sample size calculations: not performed Use of co-interventions: similar across groups (aural toilet at baseline)

Ruohola 1999

Methods	**Allocation:** randomised **Design:** parallel, double-blind
Participants	**Number:** 70 (50 included in analyses) **Age:** 6 months to 12 years; median age 1.9 years **Gender:** 28 boys (56%), 22 girls (44%) **Setting:** tertiary care, Department of Pediatrics, Turku and Department of Otorhinolaryngology, Helsinki, Finland **Eligibility criteria:** children aged 6 months to 12 years with ear discharge through a

	grommet of ≤ 48 hours duration in one or both ears **Exclusion criteria:** grommet placement or any antimicrobial treatment during the preceding 2 weeks; ear discharge during the preceding 4 weeks; use of systemic, inhaled or intranasal corticosteroids; allergy to penicillin or amoxicillin; known immunodeficiency; Down syndrome, cleft palate, diabetes mellitus, varicella or recent exposure to a patient with varicella; and middle ear granulomatous tissue or polyp
Interventions	**Intervention group:** oral corticosteroids; oral prednisolone 2 mg/kg/day divided into 3 equal doses for 3 days **Comparator group:** placebo for 3 days **Use of additional interventions:** all children received co-treatment with amoxicillin-clavulanate 40 to 10 mg/kg/day divided into 2 doses for 7 days and their ear canals were cleaned by suction daily. The use of eardrops was not permitted
Outcomes	**Primary outcome:** duration of ear discharge as assessed daily by a study physician and defined as ceased at the visit when no more discharge could be obtained by suction **Secondary outcomes:** adverse events, recurrence of ear discharge
Funding sources	This study was supported by grants from the Academy of Finland, the Foundation for Pediatric Research, Finland and Emil Aaltonen Foundation, Finland. The study drugs were provided by Leiras Oy and SmithKline Beecham
Declarations of interest	None stated
Notes	**Participants lost to follow-up total:** 20/70 (29%) excluded from final analyses. Insufficient information to calculate the number of children excluded from the intervention and comparator groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomization was done according to a computer-based scheme by Leiras Oy, which also performed the packing and labeling of the study drugs"
Allocation concealment (selection bias)	Low risk	Double-blind. Packing and labelling of prednisolone and placebo was "matched". In addition, randomisation was done according to a computer-based scheme and the participants were given the next available (i.e. the lowest number) bottle of medication
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Ruohola 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	20/70 (29%) excluded from final analyses. Insufficient information to calculate the number of children excluded from the intervention and comparator groups
Selective reporting (reporting bias)	Unclear risk	Protocol was not available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced ITT analysis: not performed Sample size calculations: performed Use of co-interventions: similar across groups (daily suction of ear canal)

Ruohola 2003

Methods	**Allocation:** randomised **Design:** parallel, double-blind
Participants	**Number:** 79 (66 excluded from analyses; 79 children included in analyses according to a worst-case scenario) **Age:** 6 months to 6 years; median age 24 months **Gender:** 44 boys (67%), 22 girls (33%) **Setting:** primary care, Finland **Eligibility criteria:** children aged 6 months to 6 years with ear discharge through a grommet of $\leq$ 48 hours duration in one or both ears **Exclusion criteria:** grommet placement or any antimicrobial treatment during the preceding 2 weeks; ear discharge during the preceding 4 weeks; use of systemic, inhaled or intranasal corticosteroids during the preceding 2 weeks; allergy to penicillin or amoxicillin; known immunodeficiency; Down syndrome, cleft palate, diabetes mellitus, granulation or polyp in the tympanic membrane
Interventions	**Intervention group:** oral antibiotics; amoxicillin-clavulanate 45 mg/kg/day divided into 2 doses for 7 days **Comparator group:** placebo for 7 days **Use of additional interventions:** ear canals were cleaned by suction daily. The use of eardrops or any other medications was not permitted, except for paracetamol (acetaminophen)
Outcomes	**Primary outcome:** duration of ear discharge as assessed daily by a study physician and defined as ceased at the visit when no more discharge could be obtained by suction **Secondary outcomes:** duration of bacterial growth in middle-ear fluid, adverse events

Ruohola 2003 (*Continued*)

Funding sources	This study was supported by the Foundation of Pediatric Research, the Jenny and Antti Wihuri Foundation, and the Academy of Finland. The study drugs were provided by SmithKline Beecham Pharmaceuticals, Bristol, TN
Declarations of interest	None stated
Notes	**Participants lost to follow-up total:** 13/79 (16%); however, the authors did perform ITT analyses in which all randomised children were analysed according to the worst-case scenario (if the actual duration of ear discharge was unknown, it was determined as 8 days) **Participants lost to follow-up intervention group:** 5/39 (13%) **Participants lost to follow-up comparator group:** 7/40 (18%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The random allocation sequence was done in blocks of 4 according to a computerized scheme by the Department of Biostatistics, University of Turku, and the medication bottles were labeled and provided for us by the pharmacy of Turku University Hospital."
Allocation concealment (selection bias)	Low risk	Double-blind. Quote: " The randomization list included numbers from 1 to 100, and the study physicians allocated each enrolled individual in consecutive order of the study entry to receive the medication bottles with the text ie, the lowest number in the list"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. The masking of the study drugs was ensured by the identical appearance, smell and taste of the syrups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13/79 (16%) excluded from final analyses; however, the authors did perform ITT analyses in which all randomised children were analysed according to the worst-case scenario (if the actual duration of ear discharge was unknown, it was determined as 8 days)

Ruohola 2003 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Protocol was not available; insufficient information to permit a judgement of low or high risk
Other bias	Low risk	Baseline characteristics: balanced ITT analysis: modified ITT analysis performed (worst-case scenario) Sample size calculations: performed Use of co-interventions: similar across groups (daily suction of ear canal)

van Dongen 2014

Methods	**Allocation:** randomised **Design:** parallel, open-label
Participants	**Number:** 230 (228 included in analyses) **Age:** 1 to 10 years; mean age 4.5 years (SD 2.0 years) **Gender:** 133 boys (58%), 97 girls (52%) **Setting:** primary and secondary care, the Netherlands **Eligibility criteria:** children aged 1 to 10 years with a clinical diagnosis of uncomplicated ear discharge through a grommet of ≤ 7 days duration in one or both ears **Exclusion criteria:** body temperature of more than 38.5 °C, antibiotics during the previous 2 weeks, grommets placed within the previous 2 weeks, episode of ear discharge in the previous 4 weeks, 3 or more episodes in the previous 6 months or 4 or more episodes in the previous year, Down syndrome, craniofacial anomaly, known immunodeficiency, allergy to the medications used in this study
Interventions	**Intervention group:** antibiotic-corticosteroid eardrops; hydrocortisone-bacitracin-colistin otic suspension, 5 drops 3 times daily for 7 days in the affected ear(s) **Intervention group 2:** oral antibiotics; amoxicillin/clavulanic acid oral suspension; 30/7.5 mg/kg per day divided into 3 doses for 7 days **Comparator group:** initial observation; initial observation (no assigned medication prescription to fill) for 2 weeks **Use of additional interventions:** parents of children assigned to treatment with antibiotic eardrops were instructed to clean the outer ear of any discharge that could easily be removed with a tissue before applying the drops. After 2 weeks, further management of ear discharge was left to the discretion of the child's physician
Outcomes	**Primary outcome:** treatment failure defined as the presence of ear discharge in one or both ears, as observed otoscopically by the study physician 2 weeks after study group assignment **Secondary outcomes:** duration of the initial ear discharge episode (from study group assignment up to the first day of ear discharge that was followed by 7 or more days without ear discharge), total number of days with ear discharge during 6 months of follow-up, number of recurrent ear discharge episodes (> 1 day with ear discharge after 7 days without ear discharge) during 6 months of follow-up, complications and treatment-related adverse events in the first 2 weeks, generic and disease-specific health-related

van Dongen 2014 (*Continued*)

	quality of life at 2 weeks of follow-up
Funding sources	This study was supported by a grant from Netherlands Organization for Health Research and Development
Declarations of interest	None declared
Notes	**Participants lost to follow-up total:** 2/230 (1%) **Participants lost to follow-up intervention group:** 0/76 (0%) **Participants lost to follow-up intervention group 2:** 0/77 (0%) **Participants lost to follow-up comparator group:** 2/77 (2%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "An independent data manager generated a randomization sequence (with the use of block sizes of six), with stratification according to age (<4 years vs > 4 yrs). "
Allocation concealment (selection bias)	Low risk	Quote: "The study physician accessed the trial randomization website at the conclusion of the home visit to obtain the study group assignment. The randomization assignment was concealed and could not be predicted in advance of or during enrollment."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/230 (1%) children excluded from analyses
Selective reporting (reporting bias)	Low risk	Trial registered before start of trial; Netherlands Trial Register number, NTR1481 Full protocol available on NEJM.org; outcomes listed at NTR and protocol reported in paper
Other bias	Unclear risk	Baseline characteristics: balanced ITT analysis: performed

van Dongen 2014 (*Continued*)

		Sample size calculations: performed Use of co-interventions: parents of children assigned to treatment with antibiotic eardrops were instructed to clean the outer ear of any discharge that could easily be removed with a tissue before applying the drops. After 2 weeks, further management of ear discharge was left to the discretion of the child's physician

AOM: acute otitis media
ENT: ear, nose and throat
ITT: intention-to-treat
SD: standard deviation
TOC: test of cure

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

Study	Reason for exclusion
Chee 2016	STUDY TYPE Review article
Dohar 1999	ALLOCATION Not a randomised trial
Giles 2007	INTERVENTIONS Treatment to prevent ear discharge after insertion of grommets
Goldblatt 2001	STUDY TYPE Review article
Granath 2008	PARTICIPANTS 14/50 randomised children (24%) did not have ear discharge during the study period and 2/41 ear discharge episodes occurred within the first 2 weeks after tube placement
Manolidis 2004	STUDY TYPE Review article
NCT01908803	INTERVENTIONS Trial comparing 2 types of antibiotic-corticosteroid eardrops combinations
NCT01994642	INTERVENTIONS Trial comparing 2 types of antibiotic-corticosteroid eardrops combinations

(*Continued*)

Strachan 2000	INTERVENTIONS Trial comparing 2 types of antibiotic-corticosteroid eardrops combinations

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00578474

Methods	**Allocation:** randomised **Design:** parallel, stated to be double-blind
Participants	**Number:** 911 **Eligibility criteria:** children aged 6 months to 12 years with ear discharge (visible by parent/guardian) through a grommet of ≤ 12 days duration in one or both ears **Exclusion criteria:** silver oxide, silver salt, t-type or long-shafted grommet, ear surgery other than grommets in prior year, menarche, diabetes mellitus, any disease that would negatively affect the conduct of the study, pre-disposition to neurosensory hearing loss **Use of additional interventions:** analgesics other than paracetamol (acetaminophen), systemic antibiotics are not allowed during the study
Interventions	**Intervention group:** antibiotic-corticosteroid eardrops; Moxidex otic solution 4 drops twice daily for 7 days in the affected ear(s) **Comparator group:** antibiotic eardrops; ofloxacin otic solution 5 drops twice daily for 10 days in the affected ear(s)
Outcomes	**Primary outcome:** clinical cure rate at the test of cure visit as determined by the investigator **Secondary outcomes:** time to cessation of otorrhoea, treatment failures, microbiological outcome
Notes	https://clinicaltrials.gov/show/NCT00578474 (accessed 18 April 2016) **Official title:** 'Safety and efficacy of a topical otic formulation in the treatment of acute otitis media with otorrhea through tympanostomy tubes (AOMT)' **Sponsor:** Alcon Research **Status:** study has been completed, but trial results are not available (study start date: December 2005; study completion date: August 2008)

NCT00579189

Methods	**Allocation:** randomised **Design:** parallel, stated to be double-blind
Participants	**Number:** 776 **Eligibility criteria:** children aged 6 months to 12 years with ear discharge (visible by parent/guardian) through a grommet of ≤ 12 days duration in one or both ears **Exclusion criteria:** silver oxide, silver salt, t-type or long-shafted grommet, ear surgery other than grommets in prior year, menarche, diabetes mellitus, any disease that would negatively affect the conduct of the study, pre-disposition to neurosensory hearing loss **Use of additional interventions:** analgesics other than paracetamol (acetaminophen), systemic antibiotics are not allowed during the study

NCT00579189 (*Continued*)

Interventions	**Intervention group:** antibiotic-corticosteroid eardrops; Moxidex otic solution 4 drops twice daily for 7 days in the affected ear(s) **Comparator group:** antibiotic eardrops; moxifloxacin otic solution 4 drops twice daily for 7 days in the affected ear (s)
Outcomes	**Primary outcome:** clinical cure rate at the test of cure visit as determined by the investigator **Secondary outcomes:** time to cessation of otorrhoea, treatment failures, microbiological outcome
Notes	https://clinicaltrials.gov/show/NCT00579189 (accessed 18 April 2016) **Official title:** 'Safety and efficacy of a topical otic formulation in the treatment of acute otitis media with otorrhea through tympanostomy tubes (AOMT)' **Sponsor:** Alcon Research **Status:** study has been completed, but trial results are not available (study start date: January 2006; study completion date: January 2009)

NCT01071902

Methods	**Allocation:** randomised **Design:** parallel, double-blind, placebo-controlled
Participants	**Number:** 400 **Eligibility criteria:** children aged 6 months to 12 years with ear discharge (visible by parent/guardian) through a grommet of ≤ 12 days duration in one or both ears **Exclusion criteria:** children not free from ear discharge for 7 days or less following grommet insertion, grommets with antimicrobial activity and/or longer than 2.5 mm, ear surgery other than grommets in prior year, menarche, diabetes mellitus, any disease that would negatively affect the conduct of the study, pre-disposition to neurosensory hearing loss **Use of additional interventions:** analgesics other than paracetamol (acetaminophen), systemic antibiotics are not allowed during the study
Interventions	**Intervention group 1:** antibiotic-corticosteroid eardrops; Moxidex otic solution 4 drops twice daily for 7 days in the affected ear(s) **Intervention group 2:** antibiotic eardrops; moxifloxacin otic solution 4 drops twice daily for 7 days in the affected ear(s) **Comparator group:** placebo; vehicle 4 drops twice daily for 7 days in the affected ear(s)
Outcomes	**Primary outcome:** clinical cure at end of treatment (day 8) **Secondary outcomes:** time to cessation of otorrhoea, microbiological success at end of treatment (day 8)
Notes	https://clinicaltrials.gov/show/NCT01071902 (accessed 18 April 2016) **Official title:** 'Safety and efficacy evaluation of topical Moxidex otic solution in the treatment of acute otitis media with otorrhea in tympanostomy tubes' **Sponsor:** Alcon Research **Status:** study has been terminated ('management decision', no further details available; study start date: February 2010; study stop date: October 2011)

DATA AND ANALYSES

Comparison 1. Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge at one week	1	42	Risk Ratio (M-H, Fixed, 95% CI)	2.58 [1.27, 5.22]
2 Adverse events likely to be related to the use of study medications	3	705	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.12, 1.09]
3 Resolution of ear discharge at two to four weeks	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Antibiotic-corticosteroid eardrops versus oral antibiotics	2	232	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.35, 1.88]
3.2 Antibiotic-only eardrops versus oral antibiotics	1	233	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.09]
4 Proportion of patients with chronic ear discharge	1	148	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.02, 1.67]
5 Proportion of patients with tube blockage	2	121	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.33, 4.45]

Comparison 2. Sensitivity analysis - Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events likely to be related to the use of study medications	1	152	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.51, 1.52]
2 Resolution of ear discharge at two weeks	1	153	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.38, 2.08]

Comparison 3. Antibiotic eardrops (with or without a corticosteroid) versus saline rinsing of the ear canal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge at one week	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.04, 2.69]
2 Proportion of patients with tube blockage	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [0.32, 9.67]

Comparison 4. Antibiotic eardrops (with or without a corticosteroid) versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge at two weeks	1	151	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.62, 2.69]
2 Proportion of patients with chronic ear discharge	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.01, 0.62]

Comparison 5. Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge at less than two weeks	2	590	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.33, 2.31]
2 Adverse events likely to be related to the use of study medications	3	1023	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.55, 1.32]
3 Resolution of ear discharge at two to four weeks	2	590	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.90, 1.31]

Comparison 6. Sensitivity analysis - Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events likely to be related to the use of study medications	1	223	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.17]

Comparison 7. Oral antibiotics versus saline rinsing of the ear canal

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge at one week	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.30, 1.43]
2 Proportion of patients with tube blockage	1	46	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.36, 10.58]

Comparison 8. Oral antibiotics versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge within two weeks	1	79	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [1.36, 3.60]
2 Adverse events likely to be related to the use of study medications	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.69, 4.25]
3 Resolution of ear discharge at two weeks	1	152	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.90, 1.69]
4 Proportion of patients with chronic ear discharge	1	147	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.15, 1.11]
5 Proportion of patients with tube extrusion	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.43]

Comparison 9. Oral corticosteroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge within two weeks	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.26]
2 Adverse events likely to be related to the use of study medications	1	50	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.01, 4.63]

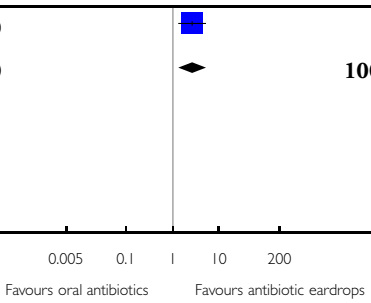
Analysis 1.1. Comparison 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics, Outcome 1 Resolution of ear discharge at one week.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics

Outcome: 1 Resolution of ear discharge at one week

Study or subgroup	Antibiotic eardrops n/N	Oral antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heslop 2010	17/22	6/20		100.0 %	2.58 [1.27, 5.22]
Total (95% CI)	**22**	**20**		**100.0 %**	**2.58 [1.27, 5.22]**
Total events: 17 (Antibiotic eardrops), 6 (Oral antibiotics)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.62 (P = 0.0087)					
Test for subgroup differences: Not applicable					



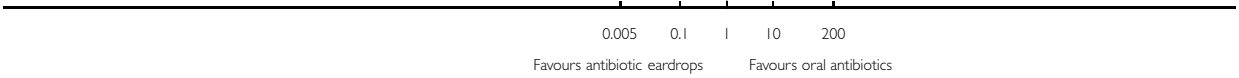
Analysis 1.2. Comparison 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics, Outcome 2 Adverse events likely to be related to the use of study medications.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics

Outcome: 2 Adverse events likely to be related to the use of study medications

Study or subgroup	Antibiotic eardrops n/N	Oral antibiotics n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Dohar 2006	5/39	17/40		30.4 %	0.30 [0.12, 0.74]
Goldblatt 1998	13/228	77/246		34.7 %	0.18 [0.10, 0.32]
van Dongen 2014	18/75	21/77		34.9 %	0.88 [0.51, 1.52]
Total (95% CI)	**342**	**363**		**100.0 %**	**0.37 [0.12, 1.09]**
Total events: 36 (Antibiotic eardrops), 115 (Oral antibiotics)					
Heterogeneity: $Tau^2 = 0.80$; $Chi^2 = 16.90$, df = 2 (P = 0.00021); $I^2 = 88\%$					
Test for overall effect: Z = 1.81 (P = 0.070)					
Test for subgroup differences: Not applicable					

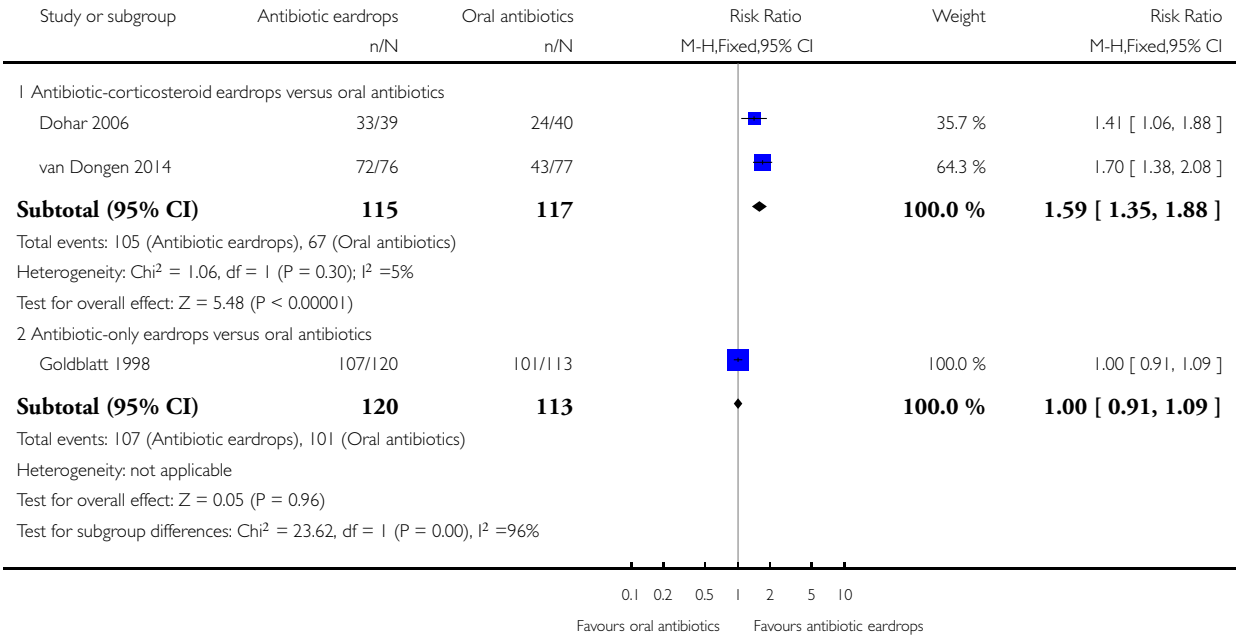


Analysis 1.3. Comparison 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics, Outcome 3 Resolution of ear discharge at two to four weeks.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics

Outcome: 3 Resolution of ear discharge at two to four weeks



Analysis 1.4. Comparison 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics, Outcome 4 Proportion of patients with chronic ear discharge.

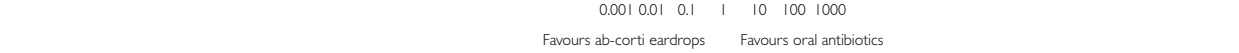
Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics

Outcome: 4 Proportion of patients with chronic ear discharge

Study or subgroup	Ab-corti eardrops n/N	Oral antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
van Dongen 2014	1/74	5/74		100.0 %	0.20 [0.02, 1.67]
Total (95% CI)	**74**	**74**		**100.0 %**	**0.20 [0.02, 1.67]**

Total events: 1 (Ab-corti eardrops), 5 (Oral antibiotics)
Heterogeneity: not applicable
Test for overall effect: Z = 1.49 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics, Outcome 5 Proportion of patients with tube blockage.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 1 Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics

Outcome: 5 Proportion of patients with tube blockage

Study or subgroup	Antibiotic eardrops n/N	Oral antibiotics n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dohar 2006	1/39	0/40		13.6 %	3.08 [0.13, 73.27]
Heslop 2010	3/22	3/20		86.4 %	0.91 [0.21, 4.00]
Total (95% CI)	**61**	**60**		**100.0 %**	**1.20 [0.33, 4.45]**

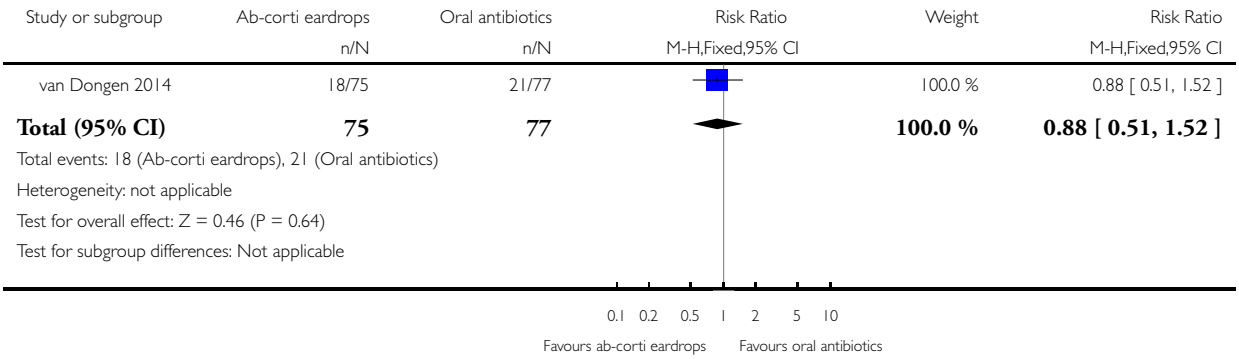
Total events: 4 (Antibiotic eardrops), 3 (Oral antibiotics)
Heterogeneity: Chi^2 = 0.47, df = 1 (P = 0.49); I^2 =0.0%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Sensitivity analysis - Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics, Outcome 1 Adverse events likely to be related to the use of study medications.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 2 Sensitivity analysis - Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics

Outcome: 1 Adverse events likely to be related to the use of study medications

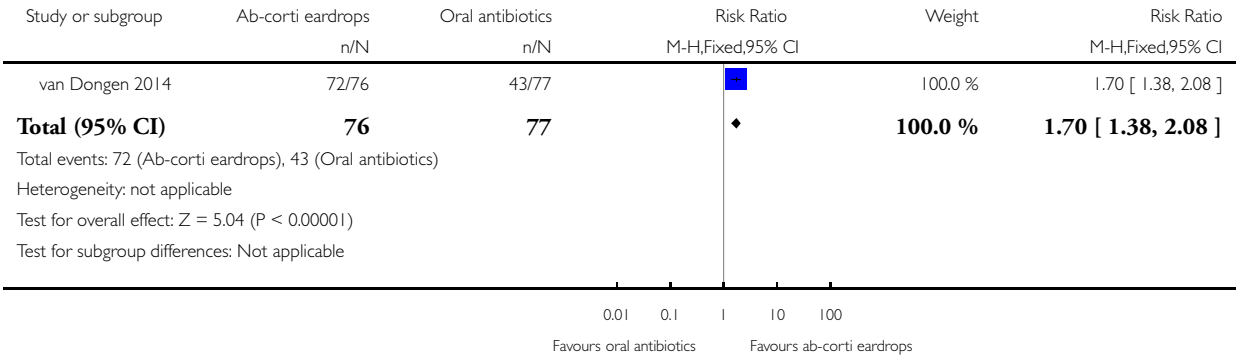


Analysis 2.2. Comparison 2 Sensitivity analysis - Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics, Outcome 2 Resolution of ear discharge at two weeks.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 2 Sensitivity analysis - Antibiotic eardrops (with or without a corticosteroid) versus oral antibiotics

Outcome: 2 Resolution of ear discharge at two weeks

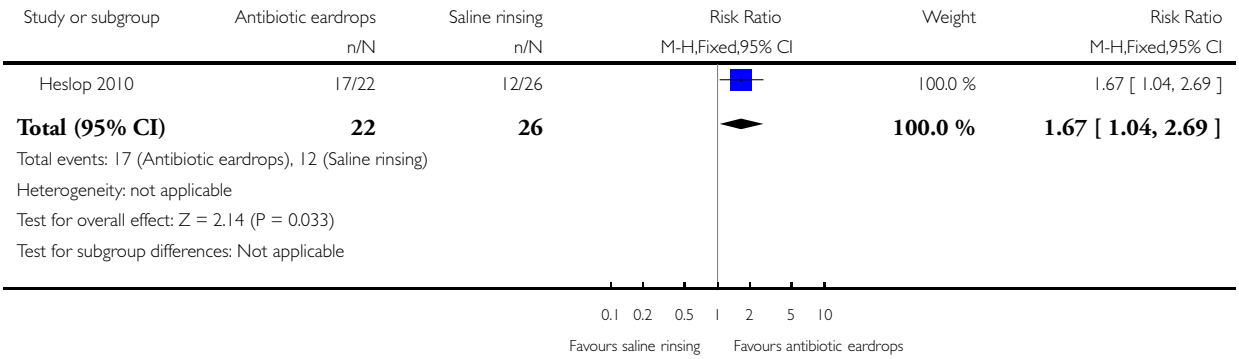


Analysis 3.1. Comparison 3 Antibiotic eardrops (with or without a corticosteroid) versus saline rinsing of the ear canal, Outcome 1 Resolution of ear discharge at one week.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 3 Antibiotic eardrops (with or without a corticosteroid) versus saline rinsing of the ear canal

Outcome: 1 Resolution of ear discharge at one week



Analysis 3.2. Comparison 3 Antibiotic eardrops (with or without a corticosteroid) versus saline rinsing of the ear canal, Outcome 2 Proportion of patients with tube blockage.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 3 Antibiotic eardrops (with or without a corticosteroid) versus saline rinsing of the ear canal

Outcome: 2 Proportion of patients with tube blockage

Study or subgroup	Ab eardrops n/N	Saline rinsing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heslop 2010	3/22	2/26		100.0 %	1.77 [0.32, 9.67]
Total (95% CI)	**22**	**26**		**100.0 %**	**1.77 [0.32, 9.67]**
Total events: 3 (Ab eardrops), 2 (Saline rinsing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
Test for subgroup differences: Not applicable					

Analysis 4.1. Comparison 4 Antibiotic eardrops (with or without a corticosteroid) versus no treatment, Outcome 1 Resolution of ear discharge at two weeks.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 4 Antibiotic eardrops (with or without a corticosteroid) versus no treatment

Outcome: 1 Resolution of ear discharge at two weeks

Study or subgroup	Ab-corti eardrops n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
van Dongen 2014	72/76	34/75		100.0 %	2.09 [1.62, 2.69]
Total (95% CI)	**76**	**75**		**100.0 %**	**2.09 [1.62, 2.69]**
Total events: 72 (Ab-corti eardrops), 34 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.68 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 4.2. Comparison 4 Antibiotic eardrops (with or without a corticosteroid) versus no treatment, Outcome 2 Proportion of patients with chronic ear discharge.

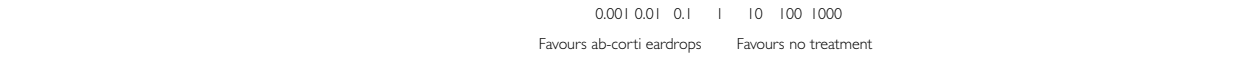
Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 4 Antibiotic eardrops (with or without a corticosteroid) versus no treatment

Outcome: 2 Proportion of patients with chronic ear discharge

Study or subgroup	Ab-corti eardrops n/N	No treatment n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
van Dongen 2014	1/74	12/73		100.0 %	0.08 [0.01, 0.62]
Total (95% CI)	**74**	**73**		**100.0 %**	**0.08 [0.01, 0.62]**

Total events: 1 (Ab-corti eardrops), 12 (No treatment)
Heterogeneity: not applicable
Test for overall effect: Z = 2.43 (P = 0.015)
Test for subgroup differences: Not applicable



Analysis 5.1. Comparison 5 Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops, Outcome 1 Resolution of ear discharge at less than two weeks.

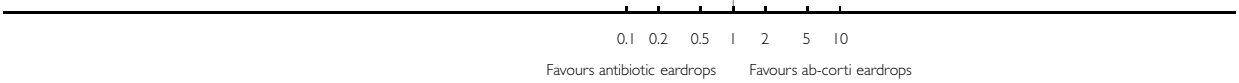
Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 5 Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops

Outcome: 1 Resolution of ear discharge at less than two weeks

Study or subgroup	Ab-corti eardrops n/N	Antibiotic eardrops n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Roland 2003	40/87	21/80		37.0 %	1.75 [1.14, 2.70]
Roland 2004	64/207	38/216		63.0 %	1.76 [1.23, 2.50]
Total (95% CI)	**294**	**296**		**100.0 %**	**1.76 [1.33, 2.31]**

Total events: 104 (Ab-corti eardrops), 59 (Antibiotic eardrops)
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%
Test for overall effect: Z = 4.02 (P = 0.000057)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5 Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops, Outcome 2 Adverse events likely to be related to the use of study medications.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 5 Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops

Outcome: 2 Adverse events likely to be related to the use of study medications

Study or subgroup	Ab-corti eardrops n/N	Antibiotic eardrops n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
NCT01404611	0/111	1/112		3.7 %	0.34 [0.01, 8.17]
Roland 2003	7/103	7/98		17.8 %	0.95 [0.35, 2.61]
Roland 2004	27/297	32/302		78.5 %	0.86 [0.53, 1.40]
Total (95% CI)	**511**	**512**		**100.0 %**	**0.86 [0.55, 1.32]**

Total events: 34 (Ab-corti eardrops), 40 (Antibiotic eardrops)

Heterogeneity: $Chi^2 = 0.37$, df = 2 (P = 0.83); $I^2 = 0.0\%$

Test for overall effect: Z = 0.71 (P = 0.48)

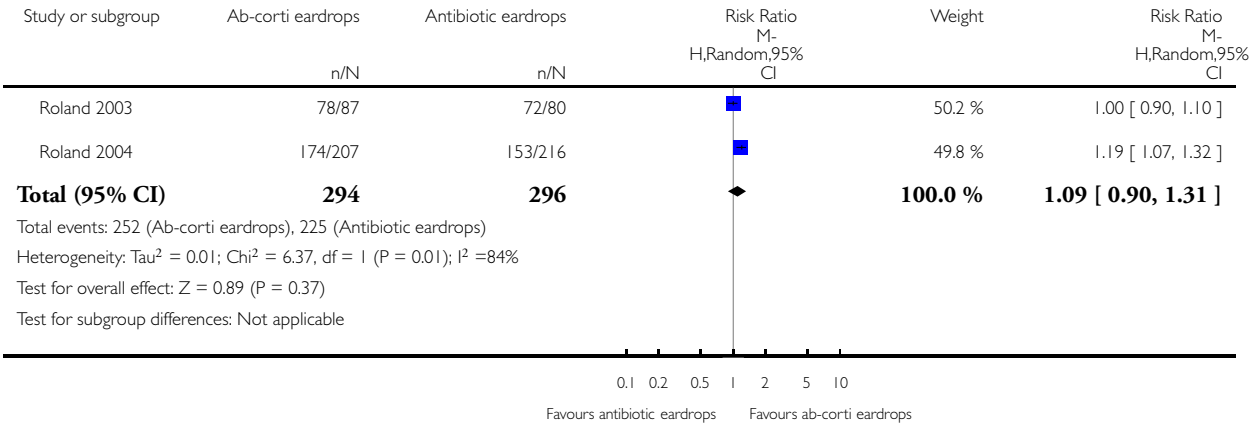
Test for subgroup differences: Not applicable

Analysis 5.3. Comparison 5 Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops, Outcome 3 Resolution of ear discharge at two to four weeks.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 5 Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops

Outcome: 3 Resolution of ear discharge at two to four weeks

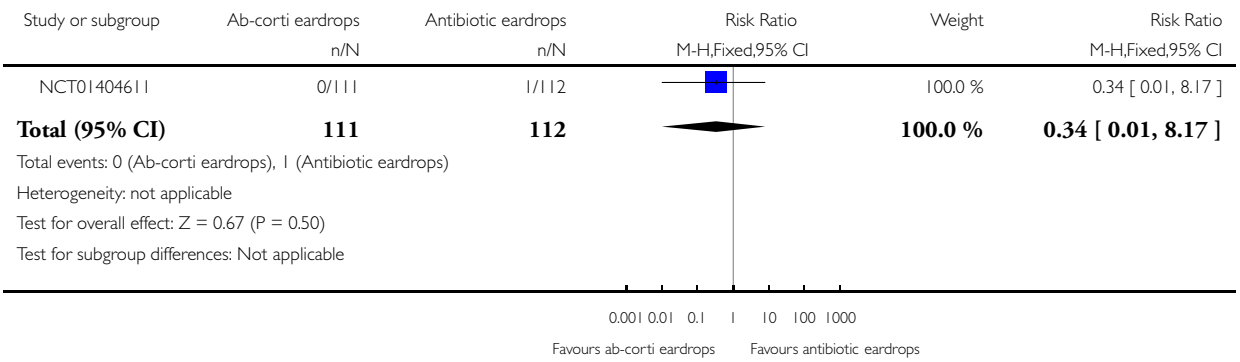


Analysis 6.1. Comparison 6 Sensitivity analysis - Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops, Outcome 1 Adverse events likely to be related to the use of study medications.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 6 Sensitivity analysis - Antibiotic(s)-corticosteroid eardrops versus antibiotic eardrops

Outcome: 1 Adverse events likely to be related to the use of study medications



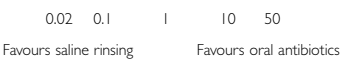
Analysis 7.1. Comparison 7 Oral antibiotics versus saline rinsing of the ear canal, Outcome 1 Resolution of ear discharge at one week.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 7 Oral antibiotics versus saline rinsing of the ear canal

Outcome: 1 Resolution of ear discharge at one week

Study or subgroup	Oral antibiotics n/N	Saline rinsing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heslop 2010	6/20	12/26		100.0 %	0.65 [0.30, 1.43]
Total (95% CI)	**20**	**26**		**100.0 %**	**0.65 [0.30, 1.43]**
Total events: 6 (Oral antibiotics), 12 (Saline rinsing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.28)					
Test for subgroup differences: Not applicable					



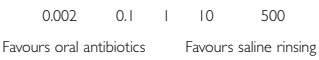
Analysis 7.2. Comparison 7 Oral antibiotics versus saline rinsing of the ear canal, Outcome 2 Proportion of patients with tube blockage.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 7 Oral antibiotics versus saline rinsing of the ear canal

Outcome: 2 Proportion of patients with tube blockage

Study or subgroup	Oral antibiotics n/N	Saline rinsing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heslop 2010	3/20	2/26		100.0 %	1.95 [0.36, 10.58]
Total (95% CI)	**20**	**26**		**100.0 %**	**1.95 [0.36, 10.58]**
Total events: 3 (Oral antibiotics), 2 (Saline rinsing)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.77 (P = 0.44)					
Test for subgroup differences: Not applicable					



Analysis 8.1. Comparison 8 Oral antibiotics versus placebo or no treatment, Outcome 1 Resolution of ear discharge within two weeks.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 8 Oral antibiotics versus placebo or no treatment

Outcome: 1 Resolution of ear discharge within two weeks

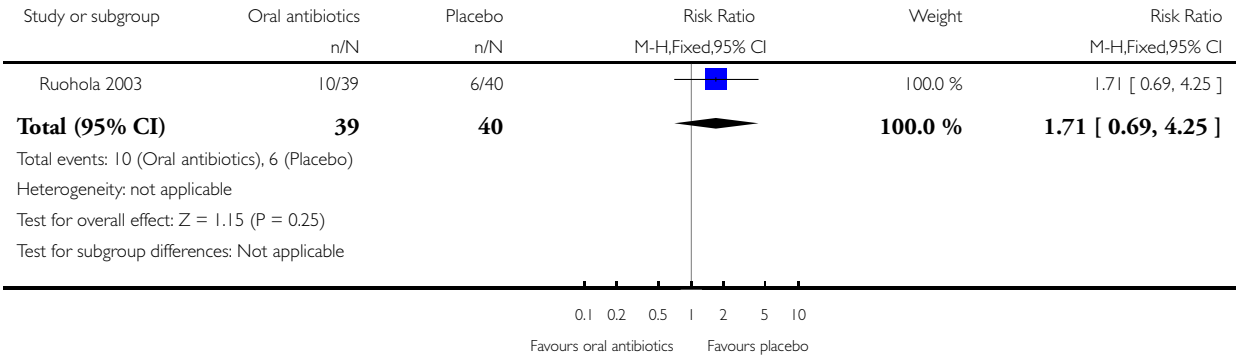
Study or subgroup	Oral antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ruohola 2003	28/39	13/40		100.0 %	2.21 [1.36, 3.60]
Total (95% CI)	**39**	**40**		**100.0 %**	**2.21 [1.36, 3.60]**
Total events: 28 (Oral antibiotics), 13 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.18 (P = 0.0015)					
Test for subgroup differences: Not applicable					

Analysis 8.2. Comparison 8 Oral antibiotics versus placebo or no treatment, Outcome 2 Adverse events likely to be related to the use of study medications.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 8 Oral antibiotics versus placebo or no treatment

Outcome: 2 Adverse events likely to be related to the use of study medications

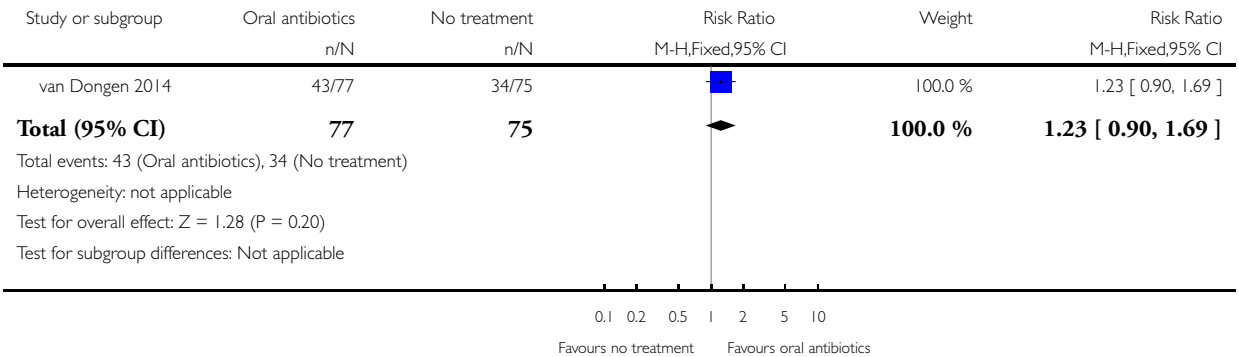


Analysis 8.3. Comparison 8 Oral antibiotics versus placebo or no treatment, Outcome 3 Resolution of ear discharge at two weeks.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 8 Oral antibiotics versus placebo or no treatment

Outcome: 3 Resolution of ear discharge at two weeks

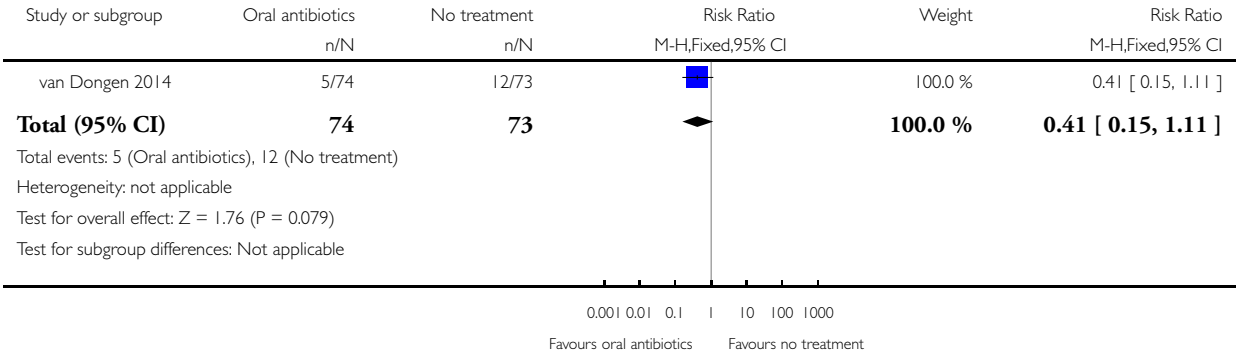


Analysis 8.4. Comparison 8 Oral antibiotics versus placebo or no treatment, Outcome 4 Proportion of patients with chronic ear discharge.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 8 Oral antibiotics versus placebo or no treatment

Outcome: 4 Proportion of patients with chronic ear discharge

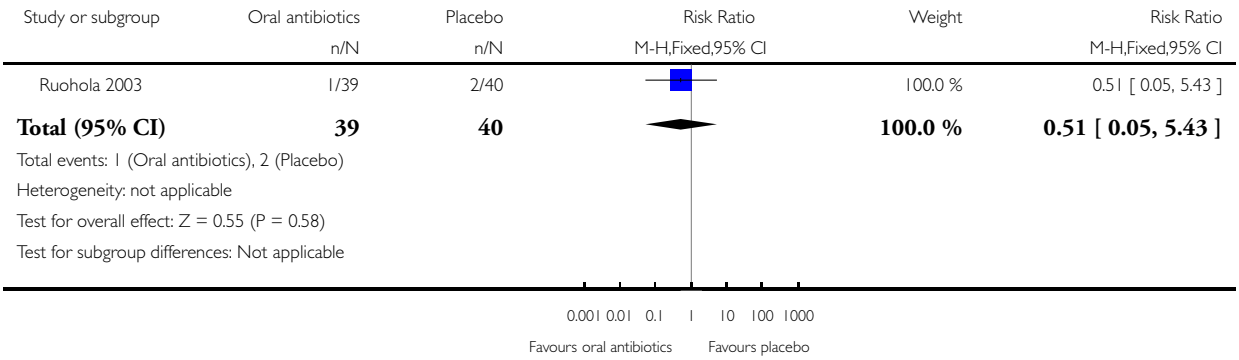


Analysis 8.5. Comparison 8 Oral antibiotics versus placebo or no treatment, Outcome 5 Proportion of patients with tube extrusion.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 8 Oral antibiotics versus placebo or no treatment

Outcome: 5 Proportion of patients with tube extrusion



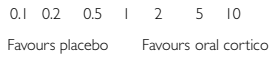
Analysis 9.1. Comparison 9 Oral corticosteroids versus placebo, Outcome 1 Resolution of ear discharge within two weeks.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 9 Oral corticosteroids versus placebo

Outcome: 1 Resolution of ear discharge within two weeks

Study or subgroup	Oral cortico n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ruohola 1999	22/23	24/27		100.0 %	1.08 [0.92, 1.26]
Total (95% CI)	**23**	**27**		**100.0 %**	**1.08 [0.92, 1.26]**
Total events: 22 (Oral cortico), 24 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.90 (P = 0.37)					
Test for subgroup differences: Not applicable					



Analysis 9.2. Comparison 9 Oral corticosteroids versus placebo, Outcome 2 Adverse events likely to be related to the use of study medications.

Review: Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion

Comparison: 9 Oral corticosteroids versus placebo

Outcome: 2 Adverse events likely to be related to the use of study medications

Study or subgroup	Oral cortico n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ruohola 1999	0/23	2/27		100.0 %	0.23 [0.01, 4.63]
Total (95% CI)	**23**	**27**		**100.0 %**	**0.23 [0.01, 4.63]**
Total events: 0 (Oral cortico), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.95 (P = 0.34)					
Test for subgroup differences: Not applicable					

ADDITIONAL TABLES

Table 1. Interventions and comparison pairs included in this review

Study ID	Antibiotic-corticosteroid eardrops	Antibiotic-only eardrops	Corticosteroid-only eardrops	Oral antibiotics	Oral corticosteroids	Saline rinsing	Placebo	No treatment
Dohar 2006	x			x				
Goldblatt 1998		x		x				
Heslop 2010		x		x		x		
NCT0140461	x	x	x					
Roland 2003	x	x						
Roland 2004	x	x						
Ruohola 1999					x		x	
Ruohola 2003				x			x	
van Dongen 2014	x			x				x

Comparison pairs for this review

#	Intervention	Comparator	Number of trials	Study ID
1	Antibiotic eardrops (with or without corticosteroids)	Oral antibiotics	4	Dohar 2006; Goldblatt 1998; Heslop 2010; van Dongen 2014
2	Antibiotic eardrops (with or without corticosteroids)	Corticosteroid-only eardrops	1	NCT01404611

Table 1. Interventions and comparison pairs included in this review (*Continued*)

3	Antibiotic eardrops (with or without corticosteroids)	Saline rinsing	1	Heslop 2010
4	Antibiotic eardrops (with or without corticosteroids)	Placebo or no treatment	1	van Dongen 2014 Note: 1 trial terminated, no results available (NCT01071902)
5	Antibiotic-corticosteroid eardrops	Antibiotic-only eardrops	3	NCT01404611; Roland 2003; Roland 2004 Note: 2 completed trials without results (NCT00578474; NCT00579189) and 1 trial terminated (NCT01071902)
6	Oral antibiotics	Saline rinsing	1	Heslop 2010
7	Oral antibiotics	Placebo or no treatment	2	Ruohola 2003; van Dongen 2014
8	Oral corticosteroids	Placebo	1	Ruohola 1999

Table 2. Overview of the outcomes reported in the included studies

Outcome	Dohar 2006	Goldblatt 1998	Heslop 2010	NCT01404(	Roland 2003	Roland 2004	Ruohola 1999	Ruohola 2003	van Dongen 2014
Primary outcomes									
Proportion of children with resolution of ear discharge at < 2 weeks			x		x	x	x	x	
Adverse events likely to be related to the	x	x		x	x	x	x	x	x

Table 2. Overview of the outcomes reported in the included studies (*Continued*)

study medications									
Serious complications related to middle ear infection				x		x	x	x	x
Secondary outcomes									
Proportion of children with resolution of ear discharge at									
2 to 4 weeks	x	x			x	x			x
4 to 12 weeks									
Proportion of children without ear pain and fever									
Duration of ear discharge	x			x	x	x	x	x	x
Proportion of children with chronic ear discharge (duration < 4 weeks)									x
Number of recurrent ear discharge episodes during follow-up							x		x

Table 2. Overview of the outcomes reported in the included studies (*Continued*)

Proportion of children with tube extrusion								x	
Proportion of children with tube blockage	x		x		x	x			
Health-related quality of life									x
Hearing levels (audiometry)	x	x			x	x			

APPENDICES

Appendix 1. Search strategies

CENTRAL	MEDLINE (Ovid)	EMBASE (Ovid)	Web of Science (Web of Knowledge)
#1 MeSH descriptor: [Middle Ear Ventilation] explode all trees #2 grommet* or tubulation #3 middle next ear near ventilat* #4 (ventilat* near tube*) and ((otitis near media) or OME or ear) #5 (tympanostomy or middle next ear or tympanic) near tube* #6 ear* near insert* near tube* #7 #1 or #2 or #3 or #4 or #5 or #6 #8 MeSH descriptor: [Cere-	1 exp Middle Ear Ventilation/ 2 (grommet* or tubulation).ab,ti. 3 (middle adj5 ear adj5 ventilat*).ab,ti. 4 ((ventilat* adj5 tube*) and ((otitis adj5 media) or OME or ear)).ab,ti 5 ((((tympanostomy or middle) adj5 ear) or tympanic) adj5 tube*).ab,ti 6 (ear* adj5 insert* adj5 tube*) .ab,ti. 7 1 or 2 or 3 or 4 or 5 or 6 8 exp Cerebrospinal Fluid Otorrhea/	1 exp Middle Ear Ventilation/ 2 (grommet* or tubulation).ab,ti. 3 (middle adj5 ear adj5 ventilat*).ab,ti. 4 ((ventilat* adj5 tube*) and ((otitis adj5 media) or OME or ear)).ab,ti 5 ((((tympanostomy or middle) adj5 ear) or tympanic) adj5 tube*).ab,ti 6 (ear* adj5 insert* adj5 tube*) .ab,ti. 7 1 or 2 or 3 or 4 or 5 or 6 8 exp Cerebrospinal Fluid Otorrhea/	#1 TOPIC: (grommet* or tubulation) #2 TOPIC: (middle near/5 ear near/5 ventilat*) #3 TOPIC: ((tympanostomy or (middle near/5 ear) or tympanic) near/5 tube*) #4 TOPIC: (ear* near/5 insert* near/5 tube*) #5 TOPIC: ((ventilat* near/5 tube*) and ((otitis near/5 media) or OME or ear)) #6 #5 OR #4 OR #3 OR #2 OR #1 #7

(*Continued*)

brospinal Fluid Otorrhea] explode all trees #9 liquorrh* or liquorh* or otoliquorrh* or otoliquorh* #10 suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or Mucopurulen* or wet or moist or weep* #11 infect* or obstruct* #12 (acute near otitis near media) or AOM or AOMT #13 #8 or #9 or #10 or #11 or #12 #14 #7 and #13 #15 MeSH descriptor: [Middle Ear Ventilation] explode all trees and with qualifier(s): [Adverse effects - AE] #16 #14 or #15	9 (liquorrh* or liquorh* or otoliquorrh* or otoliquorh*).ab,ti 10 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or Mucopurulen* or wet or moist or weep*).ab,ti 11 (infect* or obstruct*).ab,ti. 12 ((acute adj5 otitis adj5 media) or AOM or AOMT).ab,ti. 13 8 or 9 or 10 or 11 or 12 14 7 and 13 15 exp Middle Ear Ventilation/ae [Adverse Effects] 16 14 or 15	9 (liquorrh* or liquorh* or otoliquorrh* or otoliquorh*).ab,ti 10 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or Mucopurulen* or wet or moist or weep*).ab,ti 11 (infect* or obstruct*).ab,ti. 12 ((acute adj5 otitis adj5 media) or AOM or AOMT).ab,ti. 13 8 or 9 or 10 or 11 or 12 14 7 and 13 15 exp Middle Ear Ventilation/ae [Adverse Effects] 16 14 or 15	TOPIC: (liquorrh* or liquorh* or otoliquorrh* or otoliquorh*) #8 TOPIC: (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or Mucopurulen* or wet or moist or weep*) #9 TOPIC: (infect* or obstruct*) #10 TOPIC: ((acute near/5 otitis near/5 media) or AOM or AOMT) #11 #10 OR #9 OR #8 OR #7 #12 #11 AND #6 #13
CINAHL (EBSCO)	**ICTRP**	**ClinicalTrials.gov**	**LILACS**
S16 S14 OR S15 S15 (MH "Middle Ear Ventilation/AE") S14 S7 AND S13 S13 S8 OR S9 OR S10 OR S11 OR S12 S12 TX (acute N5 otitis N5 media) or AOM or AOMT S11 TX infect* or obstruct* S10 TX suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or Mucopurulen* or wet or moist or weep* S9 TX liquorrh* or liquorh* or otoliquorrh* or otoliquorh* S8 (MH "Cerebrospinal Fluid Otorrhea") S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6 S6 middle N5 ear N5 ventilat* S5 TX ear* N5 insert* N5 tube* S4 TX (tympanostomy or middle N5 ear or tympanic) N5 tube* S3 TX (ventilat* N5 tube*) and	grommet* OR middle AND ear AND venitalat* OR tubulation OR tympanostomy AND tube	grommet* OR (middle AND ear AND venitalat*) OR tubulation OR (tympanostomy AND tube)	(TW:grommet$ OR TW:tubulation OR (TW:Middle AND TW:Ear AND TW:Ventilat$) OR (TW:ventilac$ AND (TW:Oído OR TW:Orelha) AND TW:medi$) OR (TW:tympanostomy AND TW:tube))

(*Continued*)

((otitis N5 media) or OME or ear) S2 TX grommet* or tubulation S1 (MH "Middle Ear Ventilation")			

CONTRIBUTIONS OF AUTHORS

Protocol drafted by: all authors

Screening search results: Faisal Javed (FJ), Thijs MA van Dongen (TMAvD)

Extracting data: FJ, TMAvD, Roderick P Venekamp (RPV)

Assessing risk of bias: FJ, TMAvD, RPV

Entering data into RevMan: FJ, RPV

Carrying out the analysis: FJ, RPV

Interpreting the analysis: all authors

General advice on the review: all authors

DECLARATIONS OF INTEREST

Faisal Javed and Angus Waddell declare no conflicts of interests in the current work.

Anne GM Schilder is joint Co-ordinating Editor for Cochrane ENT, but had no role in the editorial process for this review.

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

Thijs MA van Dongen, Roderick P Venekamp and Anne GM Schilder are authors of an included study (van Dongen 2014). To avoid any potential conflicts of interest, two other review authors (Faisal Javed and Angus Waddell) reviewed the eligibility and performed 'Risk of bias' assessment and data extraction for this study.

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- No sources of support supplied

External sources

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- National Institute for Health Research, UK.

Infrastructure funding for Cochrane ENT

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review has been based on a published protocol (Javed 2015). Any differences between the protocol and the review can be found below.

Title

The title has been changed from 'Pharmacological and conservative interventions for ear discharge associated with grommets (ventilation tubes) outside the postoperative period' to 'Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion'.

Participants

In our review we focused on children only, whereas we stated in the protocol that we would include "patients of any age". Although we did not limit our search strategy to children only, we found no relevant trials focusing on adults. Recognising that the vast majority of patients with grommets who develop ear discharge encountered in clinical practice are children and to reflect the findings of the included studies, we decided to limit our review to children only.

Outcomes

In the protocol, we listed "Proportion of patients with resolution of ear discharge at various time points (up to two weeks, two to four weeks and four to 12 weeks)" as a primary outcome. In this review, we included "Proportion of children with resolution of ear discharge at short-term follow-up (< two weeks)" as a primary outcome and listed "Proportion of children with resolution of ear discharge at intermediate- (two to four weeks) and long-term (four to 12 weeks) follow-up" as important secondary outcomes.

NOTES

This review replaces 'Interventions for ear discharge associated with grommets (ventilation tubes)' (Vaile 2006), which is now out of date.