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Antibiotics versus topical antiseptics for chronic suppurative otitis media (Review)

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[Intervention Review]

Antibiotics versus topical antiseptics for chronic suppurative otitis media

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ABSTRACT

Background

Chronic suppurative otitis media (CSOM), sometimes referred to as chronic otitis media (COM), is a chronic inflammation and infection of the middle ear and mastoid cavity, characterised by ear discharge (otorrhoea) through a perforated tympanic membrane. The predominant symptoms of CSOM are ear discharge and hearing loss.

Antibiotics and antiseptics kill or inhibit the micro-organisms that may be responsible for the infection. Antibiotics can be applied topically or administered systemically via the oral or injection route. Antiseptics are always directly applied to the ear (topically).

Objectives

To assess the effectiveness of antibiotics versus antiseptics for people with chronic suppurative otitis media (CSOM).

Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Register; Central Register of Controlled Trials (CENTRAL; 2019, Issue 4, via the Cochrane Register of Studies); Ovid MEDLINE; Ovid Embase; CINAHL; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 1 April 2019.

Selection criteria

We included randomised controlled trials (RCTs) with at least a one-week follow-up involving patients (adults and children) who had chronic ear discharge of unknown cause or CSOM, where ear discharge had continued for more than two weeks.

The intervention was any single, or combination of, antibiotic agent, whether applied topically (without steroids) or systemically. The comparison was any single, or combination of, topical antiseptic agent, applied as ear drops, powders or irrigations, or as part of an aural toileting procedure.

Two comparisons were topical antiseptics compared to: a) topical antibiotics or b) systemic antibiotics. Within each comparison we separated where both groups of patients had received topical antibiotic a) alone or with aural toilet and b) on top of background treatment (such as systemic antibiotics).

Data collection and analysis

We used the standard Cochrane methodological procedures. We used GRADE to assess the certainty of the evidence for each outcome.

Our primary outcomes were: resolution of ear discharge or 'dry ear' (whether otoscopically confirmed or not), measured at between one week and up to two weeks, two weeks to up to four weeks, and after four weeks; health-related quality of life using a validated instrument; and ear pain (otalgia) or discomfort or local irritation. Secondary outcomes included hearing, serious complications and ototoxicity measured in several ways.

Main results

We identified seven studies (935 participants) across four comparisons with antibiotics compared against acetic acid, aluminium acetate, boric acid and povidone-iodine.

None of the included studies reported the outcomes of quality of life or serious complications.

A. Topical antiseptic (acetic acid) versus topical antibiotics (quinolones or aminoglycosides)

It is very uncertain if there is a difference in resolution of ear discharge with acetic acid compared with aminoglycosides at one to two weeks (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.72 to 1.08; 1 study; 100 participants; very low-certainty evidence). No study reported results for ear discharge after four weeks. It was very uncertain if there was more ear pain, discomfort or local irritation with acetic acid or topical antibiotics due to the low numbers of participants reporting events (RR 0.16, 95% CI 0.02 to 1.34; 2 RCTs; 189 participants; very low-certainty evidence). No differences between groups were reported narratively for hearing (quinolones) or suspected ototoxicity (aminoglycosides) (very low-certainty evidence).

B. Topical antiseptic (aluminium acetate) versus topical antibiotics

No results for the one study comparing topical antibiotics with aluminium acetate could be used in the review.

C. Topical antiseptic (boric acid) versus topical antibiotics (quinolones)

One study reported more participants with resolution of ear discharge when using topical antibiotics (quinolones) compared with boric acid ear drops at between one to two weeks (risk ratio (RR) 1.86, 95% confidence interval (CI) 1.48 to 2.35; 1 study; 411 participants; moderate-certainty evidence). This means that one additional person will have resolution of ear discharge for every four people receiving topical antibiotics (compared with boric acid) at two weeks. No study reported results for ear discharge after four weeks. There was a bigger improvement in hearing in the topical antibiotic group compared to the topical antiseptic group (mean difference (MD) 2.79 decibels (dB), 95% CI 0.48 to 5.10; 1 study; 390 participants; low-certainty evidence) but this difference may not be clinically significant.

There may be more ear pain, discomfort or irritation with boric acid compared with quinolones (RR 0.56, 95% CI 0.32 to 0.98; 2 studies; 510 participants; low-certainty evidence). Suspected ototoxicity was not reported.

D. Topical antiseptic (povidone-iodine) versus topical antibiotics (quinolones)

It is uncertain if there is a difference between quinolones and povidone-iodine with respect to resolution of ear discharge at one to two weeks (RR 1.02, 95% CI 0.82 to 1.26; 1 RCT, 39 participants; very low-certainty evidence). The study reported qualitatively that there were no differences between the groups for hearing and no patients developed ototoxic effects (very low-certainty evidence). No results for resolution of ear discharge beyond four weeks, or ear pain, discomfort or irritation, were reported.

E. Topical antiseptic (acetic acid) + aural toileting versus topical + systemic antibiotics (quinolones)

One study reported that participants receiving topical and oral antibiotics had less resolution of ear discharge compared with acetic acid ear drops and aural toileting (suction clearance every two days) at one month (RR 0.69, 95% CI 0.53 to 0.90; 100 participants). The study did not report results for resolution of ear discharge at between one to two weeks, ear pain, discomfort or irritation, hearing or suspected ototoxicity.

Authors' conclusions

Treatment of CSOM with topical antibiotics (quinolones) probably results in an increase in resolution of ear discharge compared with boric acid at up to two weeks. There was limited evidence for the efficacy of other topical antibiotics or topical antiseptics and so we are unable to draw conclusions. Adverse events were not well reported.

PLAIN LANGUAGE SUMMARY

Topical antiseptics compared with antibiotics for people with chronic suppurative otitis media

What is the aim of this review?

The aim of this Cochrane Review is to find out whether topical antiseptics are more effective than antibiotics in treating chronic suppurative otitis media. The review authors collected and analysed all relevant studies to answer this question.

Key messages

There is not much evidence comparing topical antiseptics with topical antibiotics. The evidence is very uncertain as to whether antibiotics or topical antiseptics are more effective for reducing ear discharge, except that topical antibiotics are likely to be more effective than boric acid.

What was studied in the review?

Chronic suppurative otitis media (CSOM) is a long-term (chronic) swelling and infection of the middle ear, with ear discharge (otorrhoea) through a perforated tympanic membrane (eardrum). The main symptoms of CSOM are ear discharge and hearing loss.

Antibiotics are the most commonly used treatment for CSOM. Antibiotics can either be 'topical' (put into the ear canal as ear drops, ointments, sprays or creams) or 'systemic' (taken either by mouth or by an injection into a muscle or vein). Topical antiseptics (antiseptics put directly into the ear as ear drops or as a powder) are a possible treatment for CSOM. Both antibiotics and topical antiseptics kill or stop the growth of the micro-organisms that may be responsible for the infection.

Antibiotics and topical antiseptics can be used on their own or added to other treatments for CSOM, such as antibiotics or ear cleaning (aural toileting). It was important in this review to examine whether there were any adverse effects from using antibiotics and antiseptics. Possible adverse events could include irritation of the skin within the outer ear, which may cause discomfort, pain or itching. Some antibiotics and antiseptics (such as alcohol) can also be toxic to the inner ear (ototoxicity), which means that they may cause irreparable hearing loss (sensorineural), dizziness or ringing in the ear (tinnitus).

What are the main results of the review?

We found seven studies, which included 935 participants. We found evidence for four different types of topical antiseptics: acetic acid, aluminium acetate, boric acid and povidone-iodine.

Comparison of antibiotics to acetic acid, aluminium acetate or povidone-iodine

Compared to acetic acid, aluminium acetate and povidone-iodine it is very uncertain whether topical antibiotics or systemic antibiotics improve the resolution of ear discharge in patients with CSOM because the certainty of the evidence is very low. It is not possible to know whether there is a difference between the groups for any other outcome.

Comparison of antibiotics to boric acid

We included two studies (532 participants), which showed evidence that topical antibiotics (quinolones) are likely to be better than boric acid at resolving ear discharge at one to two weeks. There also may be less ear discomfort (pain, irritation and bleeding) and a bigger improvement in hearing with topical antibiotics compared with boric acid.

How up to date is this review?

The evidence is up to date to April 2019.

Summary of findings 1. Topical antibiotics compared to acetic acid for chronic suppurative otitis media

Topical antibiotics compared to acetic acid for chronic suppurative otitis media

Patient or population: chronic suppurative otitis media
Setting: secondary care (India, South Africa)
Intervention: topical antibiotics
Comparison: acetic acid

Outcomes	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Without topical antibiotics	With topical antibiotics	Difference		
Resolution of ear discharge (1 to 2 weeks) Aminoglycosides assessed with: 'clinical cure' Follow-up: 14 days	100 (1 RCT)	RR 0.88 (0.72 to 1.08)	Study population			⊕⊖⊖⊖ **very low** [1]	It is very uncertain whether acetic acid is more effective at resolving ear discharge compared with topical aminoglycoside antibiotics at 14 days
			84.0%	73.9% (60.5 to 90.7)	10.1% fewer (23.5 fewer to 6.7 more)		
Resolution of ear discharge (after 4 weeks) - not measured	—	—	—	—	—	—	No study reported this outcome
Quality of life - not measured	—	—	—	—	—	—	No study reported this outcome
Ear pain, discomfort, irritation Follow-up: range 14 days to 43 days	189 (2 RCTs)	RR 0.16 (0.02 to 1.34)	Study population			⊕⊖⊖⊖ **very low** [2]	Acetic acid may cause more ear pain, discomfort and/or irritation than topical antibiotics (aminoglycosides and quinolones) but we are very uncertain about the results
			5.3%	0.9% (0.1 to 7.1)	4.5% fewer (5.2 fewer to 1.8 more)		
Hearing assessed with: audiometric testing Follow-up: mean 8 weeks	107 (1 RCT)	One study reports that "audiometric tests showed no detectable overall, isolated not idiosyncratic hearing loss from any treatment". No numeric results were provided.				**very low** [3]	It is uncertain whether there is a difference in hearing between topical quinolones and topical acetic acid

Serious complications - not measured	—	—	—	—	—	—	No study reported that any participant died or had any intracranial or extracranial complications
Suspected ototoxicity Follow-up: 14 days	100 (1 RCT)	One study (100 participants) reported: "… none of the patients had any kind of ear damage or toxicity"				**very low[4]**	It is uncertain if there is a difference in ototoxicity between topical aminoglycosides and topical acetic acid

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

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

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

[1]Downgraded to very low-certainty evidence: downgraded by one level due to study limitations (risk of bias) as the study had unclear randomisation, allocation concealment and blinding. Downgraded by one level due to indirectness as the outcome used was 'clinical cure' rather than resolution of ear discharge. Downgraded by one level due to suspected publication bias as one 'unpublished' study was identified indicating the possibility of unreported trials.
[2]Downgraded to very low-certainty evidence: downgraded by one level due to study limitations (risk of bias) as one study had unclear randomisation and allocation concealment and both studies had unclear blinding. Downgraded by two levels due to imprecision as the result had large confidence intervals, which include the possibility of no effect and crossed both lines of minimally important difference. Downgraded by one level due to suspected publication bias as one 'unpublished' study was identified indicating the possibility of unreported trials.
[3]Downgraded to very low-certainty evidence: downgraded by two levels due to imprecision as no numeric results were provided and the result came from a small study (107 participants). Downgraded by one level due to suspected publication bias as one 'unpublished' study was identified indicating the possibility of unreported trials.
[4]Downgraded to very low-certainty evidence: downgraded by one level due to study limitations (risk of bias) as the study had unclear randomisation, allocation concealment and blinding. Downgraded by one level due to imprecision as the result came from a small study (100 participants). Downgraded by one level due to suspected publication bias (one 'unpublished' study identified indicating the possibility of unreported trials).

Summary of findings 2. Topical antibiotics (quinolones) compared to boric acid for chronic suppurative otitis media

Topical quinolones compared to boric acid for chronic suppurative otitis media

Patient or population: chronic suppurative otitis media
Setting: secondary care (one study, South Africa), community care (one study, Kenya)
Intervention: topical antibiotics (quinolones)
Comparison: boric acid

Outcomes	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Without topical quinolones	With topical quinolones	Difference		
Resolution of ear discharge (1 to 2 weeks) Quinolones assessed with: resolution of ear discharge (both ears) Follow-up: mean 2 weeks	411 (1 RCT)	RR 1.86 (1.48 to 2.35)	Study population			⊕⊕⊕⊖ **moderate** [1]	Topical quinolones are likely to increase the number of people with resolution of ear discharge at 2 weeks compared with topical boric acid
			31.9%	59.3% (47.2 to 74.9)	27.4% more (15.3 more to 43 more)		
Resolution of ear discharge (after 4 weeks) - not measured	—	—	—	—	—	—	No study measured resolution of ear discharge at 4 weeks
Quality of life - not measured	—	—	—	—	—	—	No study measured quality of life
Ear pain, discomfort, irritation Assessed with: pain, irritation and bleeding Follow-up: mean 4 weeks	510 (2 RCTs)	RR 0.56 (0.32 to 0.98)	Study population			⊕⊕⊖⊖ **low** [2]	Topical quinolones may result in less ear pain, discomfort or irritation at 4 weeks compared to topical boric acid
			11.8%	6.6% (3.8 to 11.5)	5.2% fewer (8 fewer to 0.2 fewer)		
Average change in hearing from baseline Assessed with: pure-tone average of air conduction over 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz Follow-up: mean 4 weeks	390 (1 RCT)	—	The mean average change in hearing from baseline without topical quinolones was 2.69 dB	The mean average change in hearing from baseline with topical quinolones was 5.42 dB	MD 2.79 dB higher (0.48 higher to 5.1 higher)	⊕⊕⊖⊖ **low** [3]	Topical quinolones may result in greater improvement in mean hearing from baseline compared with topical boric acid; however this effect size may not be clinically important
Serious complications - not measured	—	—	—	—	—	—	No study reported that any participant died or had any intracranial or extracranial complications
Suspected ototoxicity - not measured	—	—	—	—	—	—	No study measured this outcome

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **dB**: decibels; **RCT:** randomised controlled trial; **RR:** risk ratio

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

[1]Downgraded by one level to moderate-certainty evidence due to suspected publication bias. We identified two unpublished studies comparing antibiotics and antiseptics, which indicates that there may be more unpublished studies.
[2]Downgraded to low-certainty evidence. Downgraded by one level due to imprecision: there was a low number of events resulting in wide confidence intervals, which include no clinically important benefit. Downgraded by one level due to suspected publication bias: we identified two unpublished studies comparing antibiotics and antiseptics, which indicates that there may be more unpublished studies.
[3]Downgraded to low-certainty evidence. Downgraded by one level due to imprecision. Downgraded by one level due to suspected publication bias: we identified two unpublished studies comparing antibiotics and antiseptics, which indicates that there may be more unpublished studies.

Summary of findings 3. Topical antibiotics (quinolones) compared to povidone-iodine for chronic suppurative otitis media

Topical antibiotics compared to povidone-iodine for chronic suppurative otitis media

Patient or population: chronic suppurative otitis media
Setting: secondary care (India)
Intervention: topical antibiotics (quinolones)
Comparison: povidone-iodine

Outcomes	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Without topical antibiotics	With topical antibiotics	Difference		
Resolution of ear discharge (1 to 2 weeks) Follow-up: mean 2 weeks	39 (1 RCT)	RR 1.02 (0.82 to 1.26)	Study population			⊕⊖⊖⊖ **very low** [1]	It is uncertain whether there is a difference in the resolution of ear discharge at 2 weeks between topical antibiotics and topical povidone-iodine
			88.9%	90.7% (72.9 to 100)	1.8% more (16 fewer to 23.1 more)		
Resolution of ear discharge (after 4 weeks) - not measured	—	—	—	—	—	—	No study measured this outcome
Quality of life - not measured	—	—	—	—	—	—	No study measured this outcome

Ear pain, discomfort, irritation - not measured	—	—	—	—	—	—	No study measured this outcome
Hearing Follow-up: mean 4 weeks	40 (1 RCT)	"There was no deterioration of hearing as assessed by pure tone audiometry"				**very low** [2]	—
Serious complications - not measured	—	—	—	—	—	—	No study reported that any participant died or had any intracranial or extracranial complications
Suspected ototoxicity	40 (1 RCT)	"No patient developed allergic manifestations or ototoxic effects"				**very low** [3]	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

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

[1]Downgraded to very low-certainty evidence. Downgraded by one level due to risk of bias (uncertain randomisation, allocation concealment and possibility of selective reporting). Downgraded by one level due to imprecision (small study size: 39 participants, confidence interval crosses the line of minimally clinical important difference). Downgraded by one level due to suspected publication bias (one study referred to long-term results that appear to be unpublished and we identified one abstract that appeared to be relevant to this comparison but for which no paper was obtainable).
[2]Downgraded to very low-certainty evidence. Downgraded by one level due to risk of bias (uncertain randomisation, allocation concealment and possibility of selective reporting). Downgraded by two levels due to imprecision (no numeric results were presented and very small study size (39 participants)). Downgraded by one level due to suspected publication bias (one study referred to long-term results, which appear to be unpublished, and we identified one abstract that appeared to be relevant to this comparison but for which no paper was obtainable).
[3]Downgraded to very low-certainty evidence. Downgraded by two levels due to risk of bias (uncertain randomisation, allocation concealment and possibility of selective reporting as it is unclear how the outcome was defined). Downgraded by two levels due to imprecision (no numeric results were presented and very small study size (39 participants). Downgraded by one level due to suspected publication bias (one study referred to long-term results that appear to be unpublished and we identified one abstract that appeared to be relevant to this comparison but for which no paper was obtainable).

BACKGROUND

This is one of a suite of Cochrane Reviews evaluating the comparative effectiveness of non-surgical interventions for chronic suppurative otitis media (CSOM) using topical antibiotics, topical antibiotics with corticosteroids, systemic antibiotics, topical antiseptics and aural toileting (ear cleaning) methods (Table 1).

This review compares the effectiveness of topical antibiotics (without steroids), or systemic antibiotics, against topical antiseptics for CSOM.

Description of the condition

Chronic suppurative otitis media (CSOM), which is also often referred to as chronic otitis media (COM), is a chronic inflammation and infection of the middle ear and mastoid cavity, characterised by ear discharge (otorrhoea) through a perforated tympanic membrane.

The predominant symptoms of CSOM are ear discharge and hearing loss. Ear discharge can be persistent or intermittent, and many sufferers find it socially embarrassing (Orji 2013). Some patients also experience discomfort or earache. Most patients with CSOM experience temporary or permanent hearing loss with average hearing levels typically between 10 and 40 decibels (Jensen 2013). The hearing loss can be disabling, and it can have an impact on speech and language skills, employment prospects, and on children's psychosocial and cognitive development, including academic performance (Elemraid 2010; Olatoke 2008; WHO 2004). Consequently, quality of life can be affected. CSOM can also progress to serious complications in rare cases (and more often when cholesteatoma is present): both extracranial complications (such as mastoid abscess, postauricular fistula and facial palsy) and intracranial complications (such as otitic meningitis, lateral sinus thrombosis and cerebellar abscess) have been reported (Dubey 2007; Yorgancılar 2013).

CSOM is estimated to have a global incidence of 31 million episodes per year, or 4.8 new episodes per 1000 people (all ages), with 22% of cases affecting children under five years of age (Monasta 2012; Schilder 2016). The prevalence of CSOM varies widely between countries, but it disproportionately affects people at socio-economic disadvantage. It is rare in high-income countries, but common in many low- and middle-income countries (Mahadevan 2012; Monasta 2012; Schilder 2016; WHO 2004).

Definition of disease

There is no universally accepted definition of CSOM. Some define CSOM in patients with a duration of otorrhoea of more than two weeks but others may consider this an insufficient duration, preferring a minimum duration of six weeks or more than three months (Verhoeff 2006). Some include diseases of the tympanic membrane within the definition of CSOM, such as tympanic perforation without a history of recent ear discharge, or the disease cholesteatoma (a growth of the squamous epithelium of the tympanic membrane).

In accordance with a consensus statement, here we use CSOM only to refer to tympanic membrane perforation, with intermittent or continuous ear discharge (Gates 2002). We have used a duration of otorrhoea of two weeks as an inclusion criterion, in accordance with the definition used by the World Health Organization, but we have used subgroup analyses to explore whether this is a factor that affects observed treatment effectiveness (WHO 2004).

Many people affected by CSOM do not have good access to modern primary healthcare, let alone specialised ear and hearing care, and in such settings health workers may be unable to view the tympanic membrane to definitively diagnose CSOM. It can also be difficult to view the tympanic membrane when the ear discharge is profuse. Therefore we have also included, as a subset for analysis, studies where participants have had chronic ear discharge for at least two weeks, but where the diagnosis is unknown.

At-risk populations

Some populations are considered to be at high risk of CSOM. There is a high prevalence of disease among Indigenous people such as the Aboriginal and Torres Strait Islander Australian, Native American and Inuit populations. This is likely due to an interplay of factors, including socio-economic deprivation and possibly differences resulting from population genetics (Bhutta 2016). Those with primary or secondary immunodeficiency are also susceptible to CSOM. Children with craniofacial malformation (including cleft palate) or chromosomal mutations such as Down syndrome are prone to chronic non-suppurative otitis media ('glue ear'), and by extrapolation may also be at greater risk of suppurative otitis media. The reasons for this association with craniofacial malformation are not well understood, but may include altered function of the Eustachian tube, coexistent immunodeficiency, or both. These populations may be less responsive to treatment and more likely to develop CSOM, recurrence or complications.

Children who have a grommet (ventilation tube) in the tympanic membrane to treat glue ear or recurrent acute otitis media may be more prone to develop CSOM; however, their pathway to CSOM may differ and therefore they may respond differently to treatment. Children with grommets who have chronic ear discharge meeting the CSOM criteria are therefore considered to be a separate high-risk subgroup (van der Veen 2006).

Treatment

Treatments for CSOM may include topical antibiotics (administered into the ear) with or without steroids, systemic antibiotics (given either by mouth or by injection), topical antiseptics and ear cleaning (aural toileting), all of which can be used on their own or in various combinations. Whereas primary healthcare workers or patients themselves can deliver some treatments (for example, some aural toileting and antiseptic washouts), in most countries antibiotic therapy requires prescription by a doctor. Surgical interventions are an option in cases where complications arise or in patients who have not responded to pharmacological treatment; however, there is a range of practice in terms of the type of surgical intervention that should be considered and the timing of the intervention. In addition, access to or availability of surgical interventions is setting-dependent. This series of Cochrane Reviews therefore focuses on non-surgical interventions. In addition, most clinicians consider cholesteatoma to be a variant of CSOM, but acknowledge that it will not respond to non-surgical treatment (or will only respond temporarily) (Bhutta 2011). Therefore, studies in which more than half of the participants were identified as having cholesteatoma are not included in these reviews.

Description of the intervention

Antibiotics are the most commonly used treatment for CSOM. They can be administered topically (as drops, ointments, sprays or creams to the affected area) or systemically (either by mouth or by injection into a vein (intravenous) or muscles (intramuscular)).

Topical application of antibiotics has the advantage of potentially delivering high concentrations of antibiotic to the affected area, whereas systemic antibiotics are absorbed and distributed throughout the body. However, the penetration of topical antibiotics into the middle ear may be compromised if the perforation in the tympanic membrane is small or there is copious mucopurulent discharge in the ear canal that cannot be cleaned. It may also be difficult to achieve compliance with topical dosing in young children. In these cases, systemic antibiotics may have an advantage.

Antiseptics are substances that kill or inhibit the growth and development of micro-organisms. Agents that have been used for treating CSOM include povidone-iodine, aluminium acetate, boric acid, chlorhexidine, alcohol, acetic acid and hydrogen peroxide. Antiseptics can be delivered as drops or as washes using a syringe. The frequency of administration and duration of treatment can vary. Syringing may bring additional benefit by flushing out debris or pus, thus reducing the overall bacterial load. Antiseptics can be used alone or in addition to other treatments for CSOM, such as antibiotics or aural toileting.

How the intervention might work

CSOM is a chronic and often polymicrobial (involving more than one micro-organism) infection of the middle ear. Broad-spectrum antibiotics such as second-generation quinolones and aminoglycosides, which are often active against the most frequently cultured micro-organisms (*Pseudomonas aeruginosa* and *Staphylococcus aureus*), are therefore commonly used (Mittal 2015) (Table 2). It is possible that antibiotics for CSOM that target *Pseudomonas aeruginosa* may have an advantage over antibiotics that do not. Dose and duration of treatment are also important factors but are less likely to affect relative effectiveness if given within the therapeutic range. Generally, treatment for at least five days is necessary and a duration of one to two weeks is sufficient to resolve uncomplicated infections. However, in some cases it may take more than two weeks for the ear to become dry and therefore longer follow-up (more than four weeks) may be needed to monitor for recurrence of discharge.

Topical antiseptics are administered to the ear to inhibit the micro-organisms that may be responsible for the condition. Although the mechanism of action of most antiseptics is thought to relate to disruption of the bacterial cell wall followed by penetration into the cell and action at the target site(s), different groups of antiseptics have different properties (e.g. iodines, alcohols, acids) (Table 3). We therefore analysed these groups separately and pooling only occurred where there was no evidence of a difference in effect.

Some antibiotics (such as aminoglycosides) and antiseptics (such as chlorhexidine or alcohol) can be toxic to the inner ear (ototoxicity), which might be experienced as sensorineural hearing loss, dizziness or tinnitus. For antibiotics, ototoxicity is less likely to be a risk when applied topically in patients with CSOM (Phillips 2007).

For both topical antibiotics and antiseptics, local discomfort, ear pain or itching may occur through the action of putting ear drops into the ear or because the topical antibiotics/antiseptics or their excipients cause chemical or allergic irritation of the skin of the outer ear.

Systemic antibiotics can have off-target side effects, for example diarrhoea or nausea. However, the risk or incidence of these events is not expected to be different from other common infections since the doses and duration of treatment used are similar in CSOM. A broader concern is the association of the overuse of antibiotics with increasing resistance among community- and hospital-acquired pathogens.

Why it is important to do this review

Although antibiotics are widely recommended as first-line treatment for CSOM, topical antiseptic agents generally cost less. They are also more readily available, do not require prescription by a doctor and do not need refrigerated transport. These factors make them an attractive option in resource-constrained environments. Evidence-based knowledge of the relative effectiveness of antibiotics and topical antiseptics could help to optimise their use.

OBJECTIVES

To assess the effectiveness of antibiotics versus antiseptics for people with chronic suppurative otitis media (CSOM).

METHODS

Criteria for considering studies for this review

Types of studies

We included studies with the following design characteristics:

- Randomised controlled trials (including cluster-randomised trials where the unit of randomisation is the setting or operator) and quasi-randomised trials.
- Patients were followed up for at least one week.

We excluded studies with the following design characteristics:

- Cross-over trials, because CSOM is not expected to be a stable chronic condition. Unless data from the first phase were available, we excluded such studies.
- Studies that randomised participants by ear (within-patient controlled) because, by definition, the effects of systemic treatments are not localised. This applies to studies that compared systemic antibiotics versus topical antiseptics. Note: we did not exclude studies comparing topical antibiotics with topical antiseptics that randomised participants by ear but we analysed these using the methods outlined in Unit of analysis issues.

Types of participants

We included studies with patients (adults and children) who had:

- chronic ear discharge of unknown cause; or
- chronic suppurative otitis media.

We defined patients with **chronic ear discharge** as patients with at least two weeks of ear discharge, where the cause of the discharge was unknown.

We defined patients with **chronic suppurative otitis media** (CSOM) as patients with:

- chronic or persistent ear discharge for at least two weeks; and
- a perforated tympanic membrane.

We did **not exclude** any populations based on age, risk factors (cleft palate, Down syndrome), ethnicity (e.g. Australian Aboriginal or Torres Strait Islanders) or the presence of ventilation tubes (grommets). Where available, we recorded these factors in the patient characteristics section during data extraction from the studies. If any of the included studies recruited these patients as a majority (80% or more), we analysed them in a subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

We **excluded** studies where the majority (more than 50%) of participants:

- had an alternative diagnosis to CSOM (e.g. otitis externa);
- had underlying cholesteatoma;
- had ear surgery within the last six weeks.

We did not include studies designed to evaluate interventions in the immediate peri-surgical period, which were focused on assessing the impact of the intervention on the surgical procedure or outcomes.

Types of interventions

Antibiotics

We included all topical and systemic antibiotics. Topical antibiotics were applied directly into the ear canal. The most common formulations are ear drops but other formulations such as sprays have also been included.

Systemic antibiotics are administered orally or parenterally (intramuscular or intravenous).

We excluded studies that conducted swabs and tests for antimicrobial sensitivity and then based the choice of antibiotics for each participant on the results of the laboratory test.

Duration

At least five days of treatment with antibiotics was required, except for antibiotics where a shorter duration has been suggested as equivalent (e.g. azithromycin for systemic antibiotics).

Dose

There was no limitation on the dose or frequency of administration.

Topical antiseptics

Any single, or combination of, topical antiseptic agent of any class including (but not limited to) povidone-iodine, aluminium acetate, boric acid, chlorhexidine, alcohol and hydrogen peroxide. The topical antiseptics could be applied directly into the ear canal as ear drops, powders or irrigations, or as part of an aural toileting procedure.

Dose/duration

There was no limitation on the dose, duration or frequency of application.

Comparisons

We analysed topical antibiotics and systemic antibiotics as separate comparisons:

- Topical antibiotics versus topical antiseptics.
- Systemic antibiotics versus topical antiseptics.

We analysed these as three main scenarios depending on which common therapy was applied in the background:

- **Topical or systemic antibiotics versus topical antiseptics as a single treatment (main therapy):** this included studies where all participants in both treatment groups either received no other treatment or only received aural toileting. This also included situations where antiseptics were applied only once (e.g. as part of microsuction at the start of treatment).
- **Topical or systemic antibiotics versus topical antiseptics as an add-on therapy to antiseptics:** this included studies where all participants in both treatment groups also used a daily antiseptic, which was a different type to the antiseptic under investigation, with or without aural toileting.
- **Topical or systemic antibiotics versus topical antiseptics as an add-on therapy to other systemic or topical antibiotics:** this included studies where all participants in both treatment groups also received a systemic or topical antibiotic, which was a different type to the antibiotic under investigation, with or without aural toileting or antiseptics.

Many comparison pairs were possible in this review. The main comparisons of interest that we have summarised and presented in the 'Summary of findings' tables are:

- topical antibiotics versus topical antiseptics as single therapies (main treatments); and
- systemic antibiotics versus topical antiseptics as single therapies (main treatments).

Types of outcome measures

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

We extracted and reported data from the longest available follow-up for all outcomes.

Primary outcomes

- Resolution of ear discharge or 'dry ear' (whether otoscopically confirmed or not), measured at:
  - between one week and up to two weeks;
  - two weeks to up to four weeks; and
  - after four weeks.
- Health-related quality of life using a validated instrument for CSOM (e.g. Chronic Otitis Media Questionnaire (COMQ)-12 (Phillips 2014a; Phillips 2014b; van Dinther 2015), Chronic Otitis Media Outcome Test (COMOT)-15 (Baumann 2011), Chronic Ear Survey (CES) (Nadol 2000)).
- Ear pain (otalgia) or discomfort or local irritation.

Secondary outcomes

- Hearing, measured as the pure-tone average of air conduction thresholds across four frequencies tested (500 Hz, 1000 Hz, 2000 Hz and 4000 Hz) of the affected ear. If this was not available, we reported the pure-tone average of the thresholds measured.
- Serious complications, including intracranial complications (such as otitic meningitis, lateral sinus thrombosis and cerebellar abscess) and extracranial complications (such as mastoid abscess, postauricular fistula and facial palsy), and death.
- Ototoxicity; this was measured as 'suspected ototoxicity' as reported by the studies where available, and as the number of people with the following symptoms that may be suggestive of ototoxicity:
  * sensorineural hearing loss;
  * balance problems/dizziness/vertigo;
  * tinnitus.

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 1 April 2019.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Register (searched via the Cochrane Register of Studies to 1 April 2019);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 4) (searched via the Cochrane Register of Studies Web to 1 April 2019);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 1 April 2019);
- Ovid EMBASE (1974 to 1 April 2019);
- EBSCO CINAHL (1982 to 1 April 2019);
- LILACS (Latin American and Caribbean Health Science Information database), lilacs.bvsalud.org (search to 1 April 2019);
- Web of Knowledge, Web of Science (1945 to 1 April 2019);
- ClinicalTrials.gov, www.clinicaltrials.gov (search via the Cochrane Register of Studies to 1 April 2019);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search to 1 April 2019).

We also searched:

- IndMed (search to 22 March 2018);
- African Index Medicus (search to 22 March 2018).

The search strategies for major databases are detailed in Appendix 1. The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. The strategies were designed to identify all relevant studies for a suite of reviews on various interventions for chronic suppurative otitis media (Bhutta 2018; Brennan-Jones 2018a; Brennan-Jones 2018b; Chong 2018a; Chong 2018b; Head 2018a; Head 2018b). 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).

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 to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Information Specialist also ran non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

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

We contacted original authors for clarification and further data if trial reports were unclear and we arranged translations of papers where necessary.

Data collection and analysis

Selection of studies

At least two review authors (KH/LYC) independently screened all titles and abstracts of the references obtained from the database searches to identify potentially relevant studies. At least two review authors (KH/LYC) evaluated the full text of each potentially relevant study to determine whether it met the inclusion and exclusion criteria for this review.

We resolved any differences by discussion and consensus, with the involvement of a third author for clinical and methodological input where necessary.

Data extraction and management

At least two review authors (KH/LYC/CBJ/MB) independently extracted data from each study using a standardised data collection form (see Appendix 2). Whenever a study had more than one publication, we retrieved all publications to ensure complete extraction of data. Where there were discrepancies in the data extracted by different review authors, we checked these against the original reports and resolved any differences by discussion and consensus, with the involvement of a third author or a methodologist where appropriate. We contacted the original study authors for clarification or for missing data whenever possible. If differences were found between publications of a study, we contacted the original authors for clarification. We used data from the main paper(s) if no further information was found.

We included key characteristics of the included studies, such as study design, setting (including location), year of study, sample size, age and sex of participants, and how outcomes were defined or collected in the studies. In addition, we also collected baseline information on prognostic factors or effect modifiers (see Appendix 2). For this review, this included the following information whenever available:

- duration of ear discharge at entry to the study;
- diagnosis of ear discharge (where known);

- number people who may have been at higher risk of CSOM, including those with cleft palate or Down syndrome;
- ethnicity of participants including the number who were from Indigenous populations;
- number who had previously had ventilation tubes (grommets) inserted (and, where known, the number who had tubes still in place);
- number who had previous ear surgery;
- number who had previous treatments for CSOM (non-responders, recurrent versus new cases).

We recorded concurrent treatments alongside the details of the interventions used. See the 'Data extraction form' in Appendix 2 for more details.

For the outcomes of interest to the review, we extracted the findings of the studies on an available case analysis basis, i.e. we included data from all patients available at the time points based on the treatment randomised whenever possible, irrespective of compliance or whether patients had received the treatment as planned.

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

- For continuous data: the mean values, standard deviations and number of patients for each treatment group. Where endpoint data were not available, we extracted the values for change from baseline. We analysed data from disease-specific quality of life scales such as COMQ-12, COMOT-15 and CES as continuous data.
- For binary data: the number of participants who experienced an event and the number of patients assessed at the time point.
- For ordinal scale data: if the data appeared to be approximately normally distributed or if the analysis that the investigators performed suggested parametric tests were appropriate, then we treated the outcome measures as continuous data. Alternatively, if data were available, we converted it into binary data.
- Time-to-event outcomes: we were not expecting any outcomes to be measured as time-to-event data. However, if outcomes such as resolution of ear discharge were measured in this way, we would have reported the hazard ratios.

For resolution of ear discharge, we extracted the longest available data within the time frame of interest, defined as from one week up to (and including) two weeks (7 days to 14 days), from two weeks up to (and including) four weeks (15 to 28 days), and after four weeks (28 days or one month).

For other outcomes, we reported the results from the longest available follow-up period.

Extracting data for pain/discomfort and adverse effects

For these outcomes, there were variations in how studies had reported the outcomes. For example, some studies reported both 'pain' and 'discomfort' separately whereas others did not. Prior to the commencement of data extraction, we agreed and specified a data extraction algorithm for how data should be extracted.

We extracted data for serious complications as a composite outcome. If a study reported more than one complication and we could not distinguish whether these occurred in one or more patients, we extracted the data with the highest incidence to prevent double counting.

Extracting data from figures

Where values for primary or secondary outcomes were shown as figures within the paper, we attempted to contact the study authors to try to obtain the raw values. When the raw values were not provided, we extracted information from the graphs using an online data extraction tool, using the best quality version of the relevant figures available.

Assessment of risk of bias in included studies

At least two review authors (KH/LYC/CBJ/MB) independently assessed the risk of bias of each included study. We followed the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011), using the Cochrane 'Risk of bias' tool. With this tool we assessed the risk of bias as 'low', 'high' or 'unclear' for each of the following six domains:

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

Measures of treatment effect

We summarised the effects of dichotomous outcomes (e.g. proportion of patients with complete resolution of ear discharge) as risk ratios (RR) with confidence intervals (CIs). For the key outcomes that are presented in the 'Summary of findings' table, we expressed the results as absolute numbers based on the pooled results and compared to the assumed risk. We also calculated the number needed to treat to benefit (NNTB) using the pooled results. The assumed baseline risk was typically either (a) the median of the risks of the control groups in the included studies, this being used to represent a 'medium-risk population' or, alternatively, (b) the average risk of the control groups in the included studies, which is used as the 'study population' (Handbook 2011). If a large number of studies were available, and where appropriate, we would have also attempted to present additional data based on the assumed baseline risk in (c) a low-risk population and (d) a high-risk population.

For continuous outcomes, we expressed treatment effects as a mean difference (MD) with standard deviation (SD). If different scales were used to measure the same outcome, we used the standardised mean difference (SMD) and provided a clinical interpretation of the SMD values.

Unit of analysis issues

Cross-over studies

This review did not use data from phase II of cross-over studies.

The ear as the unit of randomisation: within-patient randomisation in patients with bilateral ear disease

For data from studies where 'within-patient' randomisation was used (i.e. studies where both ears (right versus left) were randomised) we adjusted the analyses for the paired nature of the data (Elbourne 2002; Stedman 2011), as outlined in section 16.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

The ear as the unit of randomisation: non-paired randomisation in patients with bilateral ear disease

Some patients with bilateral disease may have received the same treatment in both ears, whereas others received a different treatment in each ear. We did not exclude these studies, but we only reported the data if specific pairwise adjustments were completed or if sufficient data were obtained to be able to make the adjustments.

The patient as the unit of randomisation

Some studies randomised by patient and those with bilateral CSOM received the same intervention for both ears. In some studies the results may be reported as a separate outcome for each ear (the total number of ears is used as the denominator in the analysis). The correlation of response between the left ear and right ear when given the same treatment was expected to be very high, and if both ears were counted in the analysis this was effectively a form of double counting, which may be especially problematic in smaller studies if the number of people with bilateral CSOM was unequal. We did not exclude these studies, but we only reported the results if the paper presented the data in such a way that we could include the data from each participant only once (one data point per participant) or if we had enough information to reliably estimate the effective sample size or inflated standard errors as presented in chapter 16.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). If this was not possible, we attempted to contact the authors for more information. If there was no response from the authors, then we did not include data from these studies in the analysis.

If we found cluster-randomised trials by setting or operator, we analysed these according to the methods in section 16.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

Dealing with missing data

We attempted to contact the study authors via email whenever the outcome of interest was not reported but the methods of the study had suggested that the outcome had been measured. We did the same if not all of the data required for the meta-analysis were reported, unless the missing data were standard deviations. If standard deviation data were not available, we approximated these using the standard estimation methods from P values, standard errors or 95% CIs if these were reported, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). Where it was impossible to estimate these, we contacted the study authors.

Apart from imputations for missing standard deviations, we did not conduct any other imputations. We extracted and analysed data for all outcomes using the available case analysis method.

Assessment of heterogeneity

We assessed clinical heterogeneity (which may be present even in the absence of statistical heterogeneity) by examining the included studies for potential differences in the types of participants recruited, interventions or controls used, and the outcomes measured. We did not pool studies where the clinical heterogeneity made it unreasonable to do so.

We assessed statistical heterogeneity by visually inspecting the forest plots and by considering the Chi^2 test (with a significance level set at P value < 0.10) and the I^2 statistic, which calculated the percentage of variability that is due to heterogeneity rather than chance, with I^2 values over 50% suggesting substantial heterogeneity (Handbook 2011).

Assessment of reporting biases

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

Outcome reporting bias (within-study reporting bias)

We assessed within-study reporting bias by comparing the outcomes reported in the published report against the study protocol, whenever this could be obtained. If the protocol was not available, we compared the outcomes reported to those listed in the methods section. If results were mentioned but not reported adequately in a way that allowed analysis (e.g. the report only mentioned whether the results were statistically significant or not), bias in a meta-analysis was likely to occur. We tried to find further information from the study authors, but if no further information could be obtained, we noted this as being a high risk of bias. Where there was insufficient information to judge the risk of bias, we noted this as an unclear risk of bias (Handbook 2011).

Publication bias (between-study reporting bias)

We intended to create funnel plots if sufficient studies (more than 10) were available for an outcome. If we had observed asymmetry of the funnel plot, we would have conducted a more formal investigation using the methods proposed by Egger 1997.

Data synthesis

We conducted all meta-analyses using Review Manager 5.3 (RevMan 2014). For dichotomous data, we analysed treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel methods. We analysed time-to-event data using the generic inverse variance method.

For continuous outcomes, if all the data were from the same scale, we pooled mean values obtained at follow-up with change outcomes and reported this as a MD. However, if the SMD had to be used as an effect measurement, we did not pool change and endpoint data.

When statistical heterogeneity is low, random-effects versus fixed-effect methods yield trivial differences in treatment effects. However, when statistical heterogeneity is high, the random-effects method provides a more conservative estimate of the difference.

Subgroup analysis and investigation of heterogeneity

We subgrouped studies where most participants (80% or more) met the criteria stated below in order to determine whether

the effect of the intervention was different compared to other patients. Due to the risks of reporting and publication bias with unplanned subgroup analyses of trials, we only analysed subgroups reported in studies if these were prespecified and stratified at randomisation.

We planned to conduct subgroup analyses regardless of whether statistical heterogeneity was observed for studies that included **patients identified as high-risk** (i.e. thought to be less responsive to treatment and more likely to develop CSOM, recurrence or complications) and patients with ventilation tubes (grommets). 'High-risk' patients include Indigenous populations (e.g. Australian Aboriginal and Torres Strait Islanders, Native Americans and Inuit populations of Alaska, Canada and Greenland), people with craniofacial malformation (e.g. cleft palate), Down syndrome and people with known immunodeficiency.

We planned to present the main analyses of this review in the form of forest plots based on this main subgroup analysis.

- For the **high-risk** group, this applied to the outcomes resolution of ear discharge (dry ear), quality of life, pain/discomfort, development of complications and hearing loss.

For **patients with ventilation tubes**, this applied to the outcome resolution of ear discharge (dry ear) for the time point of four weeks or more because this group was perceived to be at lower risk of treatment failure and recurrence than other patient groups. If statistical heterogeneity was observed, we also conducted subgroup analysis for the effect modifiers below. If there were statistically significant subgroup effects, we presented these subgroup analysis results as forest plots.

For this review, effect modifiers included:

- **Diagnosis of CSOM:** it was likely that some studies would include patients with chronic ear discharge but who had not had a diagnosis of CSOM. Therefore, we subgrouped studies where most patients (80% or more) met the criteria for CSOM diagnosis in order to determine whether the effect of the intervention was different compared to patients where the precise diagnosis was unknown and inclusion into the study was based purely on chronic ear discharge symptoms.
- **Duration of ear discharge:** there is uncertainty about whether the duration of ear discharge prior to treatment has an impact on the effectiveness of treatment and whether more established disease (i.e. discharge for more than six weeks) is more refractory to treatment compared with discharge of a shorter duration (i.e. less than six weeks).
- **Patient age:** patients who were younger than two years old versus patients up to six years old versus adults. Patients under two years are widely considered to be more difficult to treat.

We presented the results as subgroups regardless of the presence of statistical heterogeneity based on these three factors:

- Class of antibiotics. We grouped by pharmacological class, e.g. quinolones, aminoglycosides, penicillins etc. The rationale for this was that different classes may have had different effectiveness and side effect profiles.
- Spectrum of activity against *Pseudomonas aeruginosa* (groups with known activity against *Pseudomonas aeruginosa* versus groups without activity against *Pseudomonas aeruginosa*. This is the most commonly found bacteria in patients with CSOM and its presence is associated with tissue damage.
- Type of antiseptic used in the comparison arm (e.g. iodines, alcohols, acids). This is because different types of antiseptic have different mechanisms of action and therefore the treatment effects and adverse effect profiles are likely to be different.

When other antibiotics were also used as a common treatment in both the intervention and comparison group, we investigated the class and antipseudomonal activity when statistical heterogeneity was present and could not be explained by the other subgroup analyses.

No other subgroups based on the pharmacological properties of antibiotics were planned, but we considered the method and frequency of aural toileting if there was remaining unexplained heterogeneity despite conducting the other subgroup analyses.

Sensitivity analysis

We planned to carry out sensitivity analyses to determine whether the findings were robust to the decisions made in the course of identifying, screening and analysing the trials. We planned to conduct sensitivity analysis for the following factors, whenever possible:

- Impact of model chosen: fixed-effect versus random-effects model.
- Risk of bias of included studies: excluding studies with high risk of bias (we defined these as studies that have a high risk of allocation concealment bias and a high risk of attrition bias (overall loss to follow-up of 20%, differential follow-up observed)).
- Where there was statistical heterogeneity, studies that only recruited patients who had previously not responded to one of the treatments under investigation in the RCT. Studies that specifically recruited patients who did not respond to a treatment could potentially have reduced the relative effectiveness of an agent.

If any of these investigations found a difference in the size of the effect or heterogeneity, we mentioned this in the Effects of interventions section and/or presented the findings in a table.

GRADE and 'Summary of findings' table

Using the GRADE approach, at least two review authors (KH/LYC) independently rated the overall certainty of evidence using the GDT tool (http://www.guidelinedevelopment.org/) for the main comparison pairs listed in the Types of interventions section. The certainty of evidence reflects the extent to which we were confident that an estimate of effect was correct and we applied this in the interpretation of results. There were four possible ratings: 'high', 'moderate', 'low' and 'very low' (Handbook 2011). A rating of 'high' certainty evidence implies that we were confident in our estimate of effect and that further research was very unlikely to change our confidence in the estimate of effect. A rating of 'very low' certainty implies that any estimate of effect obtained was very uncertain.

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

low. The degree of downgrading was determined by the seriousness of these factors:

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

The 'Summary of findings' tables present the following outcomes:

- resolution of ear discharge or 'dry ear':
  - at between one week and up to two weeks;
  - after four weeks;
- health-related quality of life;
- ear pain (otalgia) or discomfort or local irritation;
- hearing;
- serious complications;
- suspected ototoxicity.

RESULTS

Description of studies

Results of the search

The searches retrieved a total of 7256 references and we identified five additional references from other sources. This reduced to 3147 after removal of duplicates. We screened the titles and abstracts and subsequently removed 2935 references. We assessed 212 full texts for eligibility of which we discarded 199 references; we excluded 78 of these references (52 studies) with reasons recorded in the review (see Excluded studies).

We included seven studies (11 references) (Fradis 1997; Gupta 2015; Jaya 2003; Loock 2012; Macfadyen 2005; van Hasselt 1997; Vishwakarma 2015). The Characteristics of included studies table and Table 4 provide further details of the included studies.

We identified one ongoing study (I-HEAR-BETAa; see Characteristics of ongoing studies). One reference is awaiting classification (Abdul 2005; see Characteristics of studies awaiting classification).

A flow chart of study retrieval and selection is provided in Figure 1.

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

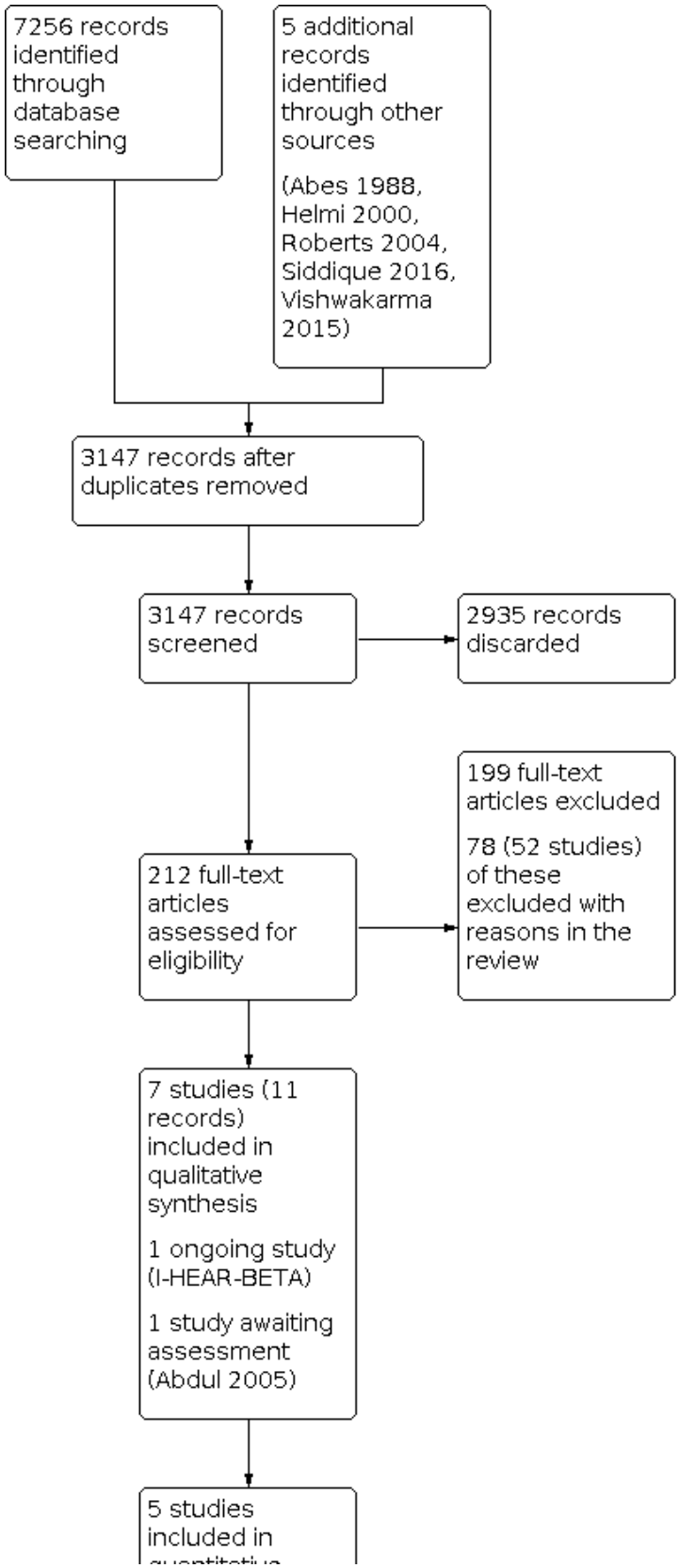
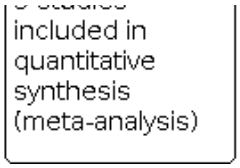


Figure 1. (Continued)



Included studies

We included seven studies (11 references) (Fradis 1997; Gupta 2015; Jaya 2003; Loock 2012; Macfadyen 2005; van Hasselt 1997; Vishwakarma 2015). The Characteristics of included studies table and Table 4 provide a further details of the included studies.

Study design

Three studies were three-arm trials (Fradis 1997; Loock 2012; van Hasselt 1997). In each case, all three study arms were included in the comparison. Details of the other study arms can be found in the Characteristics of included studies table.

One study was presented as a non-peer reviewed report where no mention of randomisation was made (van Hasselt 1997). However, the same study author refers to the study as "randomised" in the introduction of a later publication. The remaining six studies indicated that they were "randomised".

Unit of randomisation

There were no cluster-randomised trials identified. Fradis 1997 randomised participants by ear, rather than by person, meaning that the 9 (of 51) included participants with bilateral disease may have been given different topical antibiotics for each ear. It is not possible to separate out these participants and so the results cannot be used.

Sample size

A total of 935 participants were included in the seven studies. The number of participants in the studies ranged from 40 to 427.

Location

Three studies were conducted in India (Gupta 2015; Jaya 2003; Vishwakarma 2015) and three studies were conducted in different African countries: Malawi (van Hasselt 1997), Kenya (Macfadyen 2005), and South Africa (Loock 2012). The final study was conducted in Israel (Fradis 1997).

Setting

Five studies were based in secondary care in the ENT departments of hospitals (Fradis 1997; Gupta 2015; Jaya 2003; Loock 2012; Vishwakarma 2015). Macfadyen 2005 was completed in primary schools and van Hasselt 1997 was a community study.

Population

Age and sex

The ages of participants are reported in Table 4. One study recruited only children (van Hasselt 1997) and six studies included both adults and children although randomisation did not appear to be stratified by age in any study (Gupta 2015; Jaya 2003; Loock 2012; Macfadyen 2005; Vishwakarma 2015). Six studies reported that they included both males and females. The percentage of females in the studies ranged from 39% to 65%.

Diagnosis

Main diagnosis

Chronic suppurative otitis media (CSOM) was the main diagnosis in all studies (Table 4). None of the studies reported any of the participants having an alternative cause of ear discharge.

Duration of discharge

Three studies did not list the duration of discharge (Loock 2012; van Hasselt 1997; Vishwakarma 2015). Where reported, the information was provided in different ways making comparison difficult. The minimum duration of discharge in Gupta 2015 was four weeks, Macfadyen 2005 reported a median duration of eight weeks and the mean duration of discharge in Fradis 1997 was 24 months. Jaya 2003 provided the most information and identified that 15 participants (37.5%) had symptoms for less than one week, 20 participants (50%) for between one and four weeks, and five participants (12.5%) had symptoms for longer than four weeks. The paper noted that 27 participants (67.5%) had CSOM for more than five years.

Intervention

Details of the interventions, background treatments and treatment durations for each of the included studies are summarised in Table 4. The treatment durations lasted between 10 days and 4 weeks.

Comparisons

The included studies presented information for five comparisons:

- Topical antibiotics versus acetic acid: two studies used quinolones (Loock 2012; van Hasselt 1997) and one study used aminoglycosides (Vishwakarma 2015).
- Topical antibiotics versus aluminium acetate: one study arm used quinolones and the other used aminoglycosides (Fradis 1997).
- Topical antibiotics versus boric acid (either ear drops or a single administration of boric acid powder): two studies both used quinolones (Loock 2012; Macfadyen 2005).
- Topical antibiotics versus povidone-iodine: one study used quinolones (Jaya 2003).
- Topical antibiotics and systemic antibiotics (quinolones) versus acetic acid and aural toileting: one study (Gupta 2015).

Outcomes

Resolution of ear discharge

All seven studies reported resolution of ear discharge as an outcome, although the definitions, methods and timing of

assessment differed between studies. These are summarised in Table 5

Health-related quality of life using a validated instrument

No studies reported this outcome.

Ear pain (otalgia) or discomfort or local irritation

Three studies reported this outcome, although the definitions are different and the methods of assessment are not always clear. Loock 2012 gave the number of participants who reported unpleasant taste and burning sensation, Vishwakarma 2015 reported one case of "mild irritability" with the use of acetic acid and Macfadyen 2005 recorded "ear pain, irritation, and bleeding".

Hearing

One study presented the average change in hearing (air conduction) from baseline at four weeks as decibels (dB) averaged over 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz (Macfadyen 2005). Four studies noted that audiometry was completed as part of the study but results were either not presented (Fradis 1997; Gupta 2015) or only presented narratively (Jaya 2003; Loock 2012). No hearing outcomes were measured or reported in two studies (van Hasselt 1997; Vishwakarma 2015).

Serious complications (including intracranial complications, extracranial complications and death)

Serious complications were not consistently reported. One study reported that no serious complications occurred (Loock 2012).

Suspected ototoxicity

This outcome was not consistently reported. Two studies attempted to record ototoxicity (Jaya 2003; Vishwakarma 2015).

Excluded studies

We excluded 52 studies (78 papers) after reviewing the full text. Further details for the reasons for exclusion can be found in the Characteristics of excluded studies table. The main reasons for exclusion were as follows:

We excluded 47 studies (73 papers) because the comparisons were not appropriate for this review, but were relevant to another review in this suite:

- Topical antibiotics (CSOM-1): Asmatullah 2014; de Miguel 1999; Esposito 1990; Gyde 1978; Jamallulah 2016; Kasemsuwan 1997; Kaygusuz 2002; Liu 2003; Mira 1993; Nawasreh 2001; Ramos 2003; Siddique 2016; Tutkun 1995; van Hasselt 1998a.
- Systemic antibiotics (CSOM-2): de Miguel 1999; Eason 1986; Esposito 1990; Fliss 1990; Ghosh 2012; Legent 1994; Nwokoye 2015; Onali 2018; Picozzi 1983; Ramos 2003; Renuknanada 2014; Rotimi 1990; Sanchez Gonzales 2001; Somekh 2000; van der Veen 2007.
- Topical versus systemic antibiotics (CSOM-3): de Miguel 1999; Esposito 1990; Esposito 1992; Povedano 1995; Ramos 2003; Yuen 1994.
- Topical antibiotics with steroids (CSOM-4): Boesorire 2000; Browning 1988; Couzos 2003; Crowther 1991; Eason 1986; Gendeh 2001; Helmi 2000; Indudharan 2005; Kaygusuz 2002; Lazo Saenz 1999; Leach 2008; Miro 2000; Panchasara 2015; Ramos 2003; Subramaniam 2001; Tong 1996.
- Topical antiseptics (CSOM-5): Eason 1986; Minja 2006; Papastavros 1989.
- Aural toileting (CSOM-7): Eason 1986; Kiris 1998; Smith 1996.

We excluded the remaining five studies (five papers) for the following reasons:

- Browning 1983: although the comparison was antibiotics compared with topical antiseptics, the antibiotics were prescribed based on the results of the culture and so no standard antibiotic treatment was given.
- Clayton 1990: less than 20% of participants within the study had CSOM.
- Roydhouse 1981: the intervention was a mucolytic agent (bromhexine), which was not classified as an antiseptic.
- Thorpe 2000: compared three concentrations of the same topical antiseptic (aluminium acetate), which is not a question included in this review.
- van Hasselt 1998b: although the comparison was topical antibiotics with topical antiseptics, the antibiotics were given as a single dose, which does not meet the inclusion criteria for this review.

Risk of bias in included studies

See Figure 2 for the 'Risk of bias' graph (our judgements about each risk of bias item presented as percentages across all included studies) and Figure 3 for the 'Risk of bias' summary (our judgements about each risk of bias item for each included study).

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

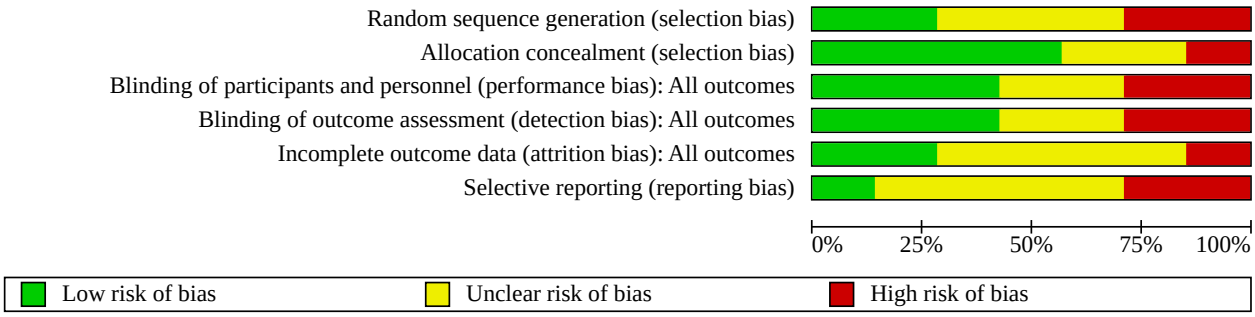
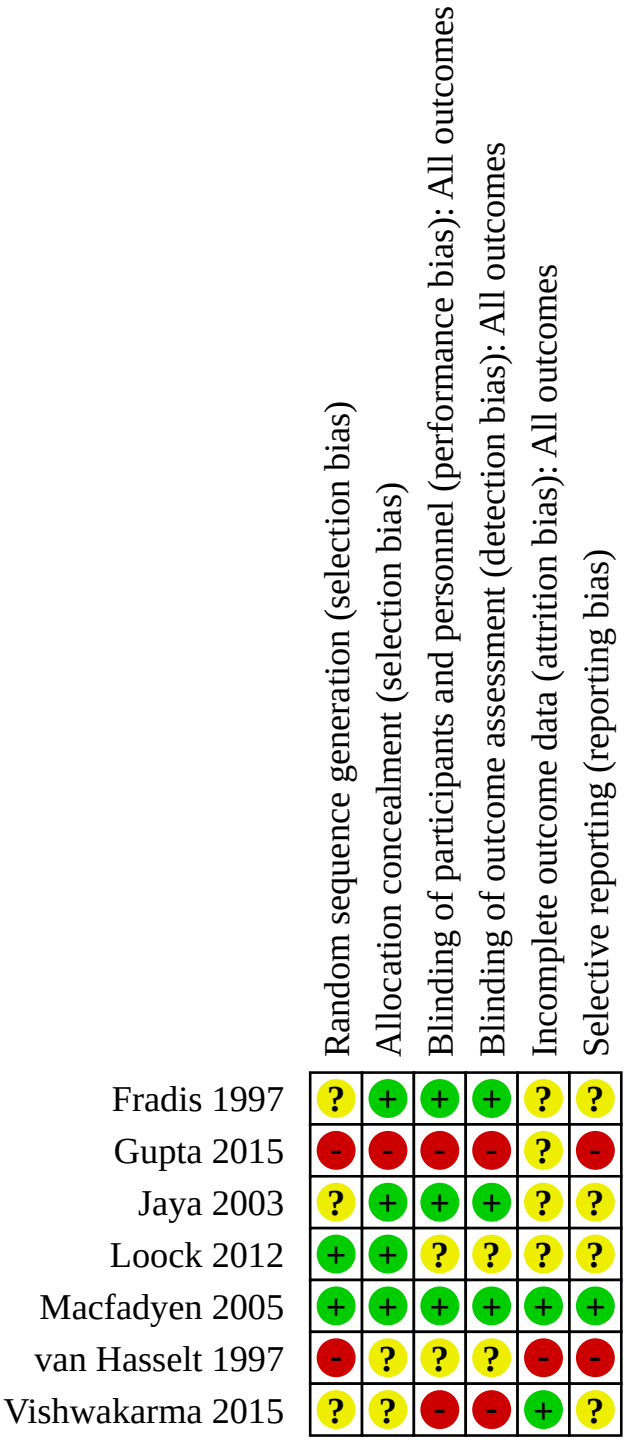


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

We judged two studies to be at high risk of bias (Gupta 2015; van Hasselt 1997). Neither study reported methods for sequence generation and Gupta 2015 indicated that participants who were already using antibiotics were allocated to the antiseptic treatment group, which may have created biases between the groups but the baseline characteristics are not provided. For van Hasselt 1997, the original report did not mention randomisation and this was only mentioned in passing as part of the introduction to a different study.

We judged three studies as at unclear risk of bias as they did not provide clear data on how the randomisation schedule was generated (Fradis 1997; Jaya 2003; Vishwakarma 2015). We judged two studies as at low risk as they reported randomisation well (Loock 2012; Macfadyen 2005).

Allocation concealment

We judged the same two studies that are at high risk of selection bias to be at high risk of allocation concealment bias (Gupta 2015; van Hasselt 1997). In Gupta 2015, as there was selection of participants to one of the groups (those using antibiotics to the acetic acid group), we have to assume allocation concealment to have been broken. For van Hasselt 1997, as there were an unequal number of people between the groups (46 versus 38 versus 12) without any explanation, there is a risk of bias due to selective allocation.

We judged Vishwakarma 2015 as at unclear risk of bias as it does not provide information on allocation concealment. We judged three studies as at low risk of bias because they reported measures to protect bias from allocation concealment well (Fradis 1997; Loock 2012; Macfadyen 2005).

Blinding

Performance bias

We assessed two studies to be at high risk of performance bias: Gupta 2015 did not mention blinding and Vishwakarma 2015 reported that the study was an "open study".

We assessed two studies to be at unclear risk of bias. Although Loock 2012 made some attempts to blind participants to treatment, because one of the treatments (boric acid) was given as a powder and the other two as ear drops blinding was not likely to be effective. van Hasselt 1997 did not mention blinding and as one of the treatments was acetic acid ear drops, which have a distinctive smell, blinding would have been difficult.

We assessed three studies as at low risk of bias because they provided sufficient descriptions of how they kept participants and professionals blinded the allocated treatments (Fradis 1997; Jaya 2003; Macfadyen 2005).

Detection bias

Similar to performance bias, we assessed two studies to be at high risk of bias (Gupta 2015; Vishwakarma 2015), two studies as at unclear risk (Loock 2012; van Hasselt 1997) and three studies as at low risk of detection bias (Fradis 1997; Jaya 2003; Macfadyen 2005).

Incomplete outcome data

We assessed one study to be at high risk of attrition bias: van Hasselt 1997 reported a high loss to follow-up (27/96; 28%) despite being a short trial. No reasons were provided and the loss is not balanced across groups, ranging from 8% to 40% of participants by group.

We assessed four studies to be at unclear risk of attrition bias:

- Fradis 1997: presented a loss to follow-up of 10% (6/60) but no reasons were provided or details of to which group the lost participants were allocated.
- Gupta 2015: the study does not report any patients dropping out but as the study lasted three months and the participants were advised to visit the hospital every other day its seems unlikely that there was no loss to follow-up.
- Jaya 2003: only four participants (10%) did not provide results; the reasons were not given and these missing data points could have affected the efficacy results due to the small sample size. In particular, it may have been important if they withdrew due to adverse events.
- Loock 2012: provided the loss to follow-up rates in the three treatment groups as 5.8%, 15.1% and 18.5% but did not provide reasons within the paper.

We assessed two studies as at low risk of attrition bias because they reported low dropout rates (Macfadyen 2005; Vishwakarma 2015).

Selective reporting

We assessed one study to be at high risk of publication bias (van Hasselt 1997). It was unpublished and makes reference to longer-term results that were not found in our searches.

We assessed five studies to be at unclear risk of selective reporting bias (Fradis 1997; Gupta 2015; Jaya 2003; Loock 2012; Vishwakarma 2015). Four of these studies stated that hearing assessment was completed pre- and post-treatment but either did not report the results or only reported vague narrative statements (Fradis 1997; Gupta 2015; Jaya 2003; Loock 2012). Vishwakarma 2015 used symptom scales as their primary outcome but failed to provide information on the definition or validation of these scales.

We assessed one study as at low risk of selective reporting bias as it was a well-reported study (Macfadyen 2005).

None of the studies had protocols identified through our searches of clinical trials registries.

Other potential sources of bias

Funding

Three papers did not provide information about funding (Fradis 1997; Gupta 2015; Jaya 2003) and a further paper declared that there were no funding sources (Vishwakarma 2015).

Two studies were funded through national or international research grants: Loock 2012 was funded by the ENT Society of South Africa, National Health Laboratory Service of South Africa (NHLS) but "received no sponsorship or incentive from manufacturers of any of the treatments used"; Macfadyen 2005 was funded by the Wellcome Trust (grant reference number: 056756/Z/99/Z) but the study also declared that "Alcon (Denmark and Belgium) provided the Ciloxan supplies".

It appears that van Hasselt 1997 was funded by the Christian Blind Mission International.

Declaration of interest

Four studies did not make a statement about any interests (Fradis 1997; Gupta 2015; Macfadyen 2005; van Hasselt 1997), whilst the remaining three either declared that they had no interests (Loock 2012; Vishwakarma 2015) or that they had no financial interests (Jaya 2003).

Effects of interventions

See: **Summary of findings 1** Topical antibiotics compared to acetic acid for chronic suppurative otitis media; **Summary of findings 2** Topical antibiotics (quinolones) compared to boric acid for chronic suppurative otitis media; **Summary of findings 3** Topical antibiotics (quinolones) compared to povidone-iodine for chronic suppurative otitis media

See also Summary of findings 1; Summary of findings 2; Summary of findings 3.

Comparison 1: Topical antibiotics versus acetic acid

Three studies including participants with CSOM compared topical antibiotics to acetic acid (Loock 2012; van Hasselt 1997; Vishwakarma 2015; 303 participants), although van Hasselt 1997 had two relevant comparisons as there were two antibiotic arms each of which used different antibiotics. Two studies compared topical quinolones to acetic acid (Loock 2012; van Hasselt 1997; 165 participants). One study compared aminoglycosides with acetic acid (Vishwakarma 2015; 100 participants). One study compared acetic acid against neomycin/polymyxin B (van Hasselt 1997; 85 participants).

Primary outcomes

Resolution of ear discharge

van Hasselt 1997 only reported the results of ear discharge by ear and it was not possible to determine how many participants were allocated to each group; these results therefore cannot be used in the analysis.

Between one week and up to two weeks

One study using aminoglycosides reported this outcome (Vishwakarma 2015), but it was not clear if there was a difference in resolution of ear discharge (unclear if this was otoscopically confirmed) between the groups receiving acetic acid and gentamicin (risk ratio (RR) 0.88, 95% confidence interval (CI) 0.72 to 1.08; 100 participants; Analysis 1.1). Using GRADE we assessed the evidence as being very low certainty.

Two weeks to up to four weeks

Loock 2012 reported that more participants in the ciprofloxacin group had resolution of ear discharge (otoscopically confirmed) compared with acetic acid (RR 2.93, 95% CI 1.71 to 5.04; 89 participants; Analysis 1.2).

After four weeks

No study reported resolution of ear discharge at this time point.

Health-related quality of life using a validated instrument

No studies reported this outcome.

Ear pain (otalgia) or discomfort or local irritation

Two studies reported this outcome, although the definitions used were different (Loock 2012; Vishwakarma 2015). Vishwakarma 2015 reported "mild irritability" in one case in the acetic acid group, whereas Loock 2012 reported "unpleasant taste and burning sensation" in four cases in the acetic acid group. No events were reported in the antibiotic group.

There may be more ear pain or discomfort or local irritation with acetic acid compared to topical antibiotics but we are very uncertain about the results (RR 0.16, 95% CI 0.02 to 1.34; 2 studies; 189 participants; $I^2 = 0\%$; very low-certainty evidence; Analysis 1.3).

Secondary outcomes

Hearing

Loock 2012 measured the outcome of hearing but only presented the results narratively in their report: "audiometric tests showed no detectable overall, isolated not idiosyncratic hearing loss from any treatment" (very low-certainty evidence). None of the other studies reported this outcome.

Serious complications (including intracranial complications, extracranial complications and death)

No studies reported that any participant died or had any intracranial or extracranial complications.

Suspected ototoxicity

Vishwakarma 2015 noted that "... none of the patients had any kind of ear damage or toxicity" (very low-certainty evidence). No other study reported this outcome.

Subgroup analyses

No subgroup analyses were possible for this comparison:

- High-risk populations: no studies reported high-risk populations as defined in our protocol.
- Patients with ventilation tubes: no studies reported the inclusion of participants with ventilation tubes.
- Diagnosis of CSOM: all included studies used CSOM as the inclusion criterion.
- Duration of ear discharge: none of the studies reported the duration of discharge.
- Patient age: all studies that provided age information included both adults and children, but did not stratify between the two populations.

Comparison 2: Topical antibiotics versus aluminium acetate

One study of participants with a diagnosis of CSOM was included in this comparison: Fradis 1997, which used ears as the unit of randomisation. Pairwise adjustments were not completed and sufficient data could not be obtained for us to be able to make the adjustments, therefore none of the outcomes could be used in the analysis (Unit of analysis issues).

Primary outcomes

Resolution of ear discharge

The study reported results for resolution of ear discharge at two to four weeks, but the results were not presented in a useable form. No other results for other time points were available.

Health-related quality of life using a validated instrument

The study did not measure this outcome.

Ear pain (otalgia) or discomfort or local irritation

The study did not measure this outcome.

Secondary outcomes

Hearing

The study did not measure this outcome.

Serious complications (including intracranial complications, extracranial complications and death)

The study did not report that any participant died or had any intracranial or extracranial complications.

Suspected ototoxicity

The study did not measure this outcome.

Comparison 3: Topical antibiotics versus boric acid/boric acid powder

Two studies including participants with CSOM were included in this comparison (Loock 2012; Macfadyen 2005; 532 participants). Both studies used ciprofloxacin (quinolone) but in comparison Macfadyen 2005 used boric acid ear drops whereas Loock 2012 used a single application of boric acid powder.

Primary outcome

Resolution of ear discharge

Between one week and up to two weeks

Macfadyen 2005 reported that topical quinolones are likely to increase the number of people with resolution of ear discharge (otoscopically confirmed) at two weeks compared with topical boric acid ear drops (RR 1.86, 95% CI 1.48 to 2.35; 411 participants; Analysis 3.1). This means that one additional person would have resolution of ear discharge for every four people (95% CI 3 to 7) receiving topical antibiotics (compared with boric acid) at two weeks. The evidence was of moderate certainty.

Two weeks to up to four weeks

Both studies reported that more people had resolution of ear discharge with topical quinolones at between two to four weeks compared with boric acid (RR 1.27, 95% CI 1.07 to 1.49; 488 participants; 2 studies; I^2 = 16%; Analysis 3.2) (Loock 2012; Macfadyen 2005).

After four weeks

No study reported the results for this outcome at this time point.

Health-related quality of life using a validated instrument

Neither study measured this outcome.

Ear pain (otalgia) or discomfort or local irritation

Both studies measured this outcome. Macfadyen 2005 reported "pain, irritation, and bleeding" and Loock 2012 did not report any episodes of ear pain, discomfort or irritation in either group within this comparison. The results showed that topical quinolones may result in less ear pain, discomfort or irritation at four weeks compared to topical boric acid (RR 0.56, 95% CI 0.32 to 0.98; 510 participants; 2 studies; I^2 = 0%; low-certainty evidence; Analysis 3.3).

Secondary outcomes

Hearing

Both studies measured hearing, although Loock 2012 only reported results narratively: "Audiometric tests showed no detectable overall, isolated not idiosyncratic hearing loss from any treatment". Macfadyen 2005 compared the mean change in hearing from baseline between the two treatment groups. Although both groups had mean improvements in hearing, topical antibiotics (quinolones) appeared to result in a greater improvement in mean hearing compared with topical boric acid (mean difference (MD) 2.79 decibels (dB), 95% CI 0.48 to 5.10 Hz; 390 participants; low-certainty evidence; Analysis 3.4). It is not clear whether this change is clinically meaningful.

Serious complications (including intracranial complications, extracranial complications and death)

No study reported that any participant died or had any intracranial or extracranial complications.

Suspected ototoxicity

Neither study reported this outcome.

Subgroup analyses

No subgroup analyses were possible for this comparison:

- High-risk populations: neither study reported high-risk populations as defined in our protocol.
- Patients with ventilation tubes: neither study reported the inclusion of patients with ventilation tubes.
- Diagnosis of CSOM: both studies used CSOM as the inclusion criterion.
- Duration of ear discharge: only one study reported the duration of discharge.
- Patient age: one study included only children and the other included both adults and children, but did not stratify the two populations.

Comparison 4: Topical antibiotics versus povidone-iodine

One study of participants with CSOM was included for this comparison and compared ciprofloxacin with povidone-iodine ear drops (Jaya 2003; 40 participants).

Primary outcomes

Resolution of ear discharge

Between one week and up to two weeks

In Jaya 2003 it was uncertain if there was a difference between topical antibiotics (ciprofloxacin) and topical povidone-iodine in the resolution of ear discharge (otoscopically confirmed) at two

weeks (RR 1.02, 95% CI 0.82 to 1.26; 39 participants; very low-certainty evidence; Analysis 4.1).

Two weeks to up to four weeks

In Jaya 2003 it was uncertain if there was a difference between topical antibiotics (ciprofloxacin) and topical povidone-iodine in the resolution of ear discharge at four weeks (RR 1.03, 95% CI 0.81 to 1.30; 36 participants; Analysis 4.2).

After four weeks

The study did not report this outcome at this time point.

Health-related quality of life using a validated instrument

The study did not measure this outcome.

Ear pain (otalgia) or discomfort or local irritation

The study did not measure this outcome.

Secondary outcomes

Hearing

Jaya 2003 measured hearing but only provides narrative results, stating that, "There was no deterioration of hearing as assessed by pure-tone audiometry" (very low-certainty evidence).

Serious complications (including intracranial complications, extracranial complications and death)

The study did not report that any participant died or had any intracranial or extracranial complications.

Suspected ototoxicity

Jaya 2003 reported that "No patient developed allergic manifestations or ototoxic effects" (very low-certainty evidence).

Comparison 5: Topical and systemic antibiotics versus acetic acid and aural toileting

Gupta 2015 (100 participants with CSOM) compared treatment with both topical and systemic antibiotics (ciprofloxacin) with daily acetic acid ear drops alongside an intensive aural toileting regimen, which involved microsuction of the ear every two days.

Primary outcomes

Resolution of ear discharge

Between one week and up to two weeks

No results were available for this outcome at this time point.

Two weeks to up to four weeks

Gupta 2015 reported that fewer people in the group receiving topical and systemic quinolones had resolution of ear discharge (otoscopically confirmed) compared with those receiving acetic acid and intensive aural toileting at 15 days (RR 0.61, 95% CI 0.40 to 0.93; 100 participants; Analysis 5.1).

After four weeks

Gupta 2015 reported that fewer people in the group receiving topical and systemic quinolones had resolution of ear discharge compared with those receiving acetic acid and intensive aural toileting at one month (RR 0.69, 95% CI 0.53 to 0.90; 100 participants; Analysis 5.2).

Health-related quality of life using a validated instrument

The study did not measure this outcome.

Ear pain (otalgia) or discomfort or local irritation

The study did not measure this outcome.

Secondary outcomes

Hearing

Although Gupta 2015 mentioned in the methods section that hearing was measured pre- and post-treatment, no results were presented.

Serious complications (including intracranial complications, extracranial complications and death)

The study did not report that any participant died or had any intracranial or extracranial complications.

Suspected ototoxicity

The study did not measure this outcome.

DISCUSSION

Summary of main results

We identified seven studies that we included in this review (Fradis 1997; Gupta 2015; Jaya 2003; Loock 2012; Macfadyen 2005; van Hasselt 1997; Vishwakarma 2015). All of the studies included patients with CSOM; none included patients with chronic ear discharge. Due to the limited number of included studies, the methods and the choice of outcome measures used in these studies and the incomplete reporting of some results, for many of the comparisons there was not much evidence. Adverse events (ear pain, discomfort or irritation) were not well reported. Only studies using topical antibiotics without steroids were included in this review.

Comparison 1: Topical antibiotics versus acetic acid

See also Summary of findings 1.

Three studies (303 participants) compared topical antibiotics with acetic acid (Loock 2012; van Hasselt 1997; Vishwakarma 2015). One of these was a three-arm study comparing two different topical antibiotics with acetic acid. Two studies used quinolones, one used aminoglycosides and one used neomycin/polymyxin B. It is very uncertain if there is a difference in resolution of ear discharge between aminoglycosides and acetic acid at one to two weeks (very low-certainty evidence). At between two to four weeks the only study with useable results reported a higher rate of people with dry ear with topical antibiotics (quinolones) compared to acetic acid (risk ratio (RR) 2.93, 95% confidence interval (CI) 1.71 to 5.04; 89 participants). No study reported results for ear discharge after four weeks.

More ear pain, discomfort or local irritation was reported with acetic acid compared to topical antibiotics (quinolones or aminoglycosides) but the results were very uncertain (RR 0.16, 95% CI 0.02 to 1.34; 189 participants; 2 studies; I^2 = 0%; very low-certainty evidence). No differences between the groups were found for hearing (quinolones) or suspected ototoxicity (aminoglycoside) in a narrative report. No results were available for quality of life or serious complications.

Comparison 2: Topical antibiotics versus aluminium acetate

The only available study for this comparison randomised participants by ear and did not present the results in a way that allowed for adjustment due to the correlation of results between ears; the results for resolution of ear discharge could therefore not be used. No other results were reported.

Comparison 3: Topical antibiotics versus boric acid

See also Summary of findings 2.

Two studies (532 participants) compared topical antibiotics (quinolones) with boric acid, although one study used boric acid ear drops (Macfadyen 2005) and the other used a single administration of borax powder (Loock 2012). Results at both between one to two weeks (RR 1.86, 95% CI 1.48 to 2.35; 411 participants; 1 study; moderate-certainty evidence) and between two to four weeks (RR 1.27, 95% CI 1.07 to 1.49; 488 participants; 2 studies; I^2 = 16%) showed that topical antibiotics (quinolones) are likely to increase the number of people with resolution of ear discharge compared with boric acid. Neither study reported results for ear discharge after four weeks.

There was a bigger change in hearing (improvement) in the topical antibiotic group compared to the topical antiseptic group (mean difference (MD) 2.79 dB, 95% CI 0.48 to 5.10; 390 participants; 1 study; low-certainty evidence) but this difference may not be clinically significant. There may be more adverse events (ear pain, discomfort or irritation) with boric acid compared with quinolones (RR 0.56, 95% CI 0.32 to 0.98; 510 participants; 2 studies; I^2 = 0%; low-certainty evidence). Neither study reported quality of life, serious complications or suspected ototoxicity.

Comparison 4: Topical antibiotics versus povidone-iodine

See also Summary of findings 3.

One study (40 participants) compared topical antibiotics (quinolones) with povidone-iodine. It is uncertain if there is a difference between topical antibiotics and povidone-iodine with respect to resolution of ear discharge at between one to two weeks (very low-certainty evidence) and at between two to four weeks. The study reported qualitatively that there were no differences between the groups in hearing and reported that none of the patients developed ototoxic effects. No results for resolution of ear discharge beyond four weeks, adverse effects (ear pain/discomfort/irritation), serious complications or quality of life were reported.

Comparison 5: Topical and systemic antibiotics versus acetic acid and aural toileting

One study (100 participants) compared participants taking both topical and oral antibiotics (quinolone) with participants who received daily acetic acid ear drops and suction aural toileting every other day. Fewer patients receiving topical and oral antibiotics had resolution of ear discharge compared with acetic acid ear drops and aural toileting at both two to four weeks (RR 0.61, 95% CI 0.40 to 0.93; 100 participants) and at one month (RR 0.69, 95% CI 0.53 to 0.90; 100 participants). Although no analysis of the results using GRADE was completed, the study was identified as having a high risk of bias with regards to randomisation sequence generation, allocation concealment and selective reporting, and the study was unblinded (Figure 3). Caution should be taken when interpreting these results.

Short-term results for resolution of ear discharge (between one to two weeks) were not reported. Health-related quality of life, ear pain, discomfort or irritation, serious complications, hearing and suspected ototoxicity were not reported.

One interesting finding was the difference in the result between comparison one (topical antibiotics (quinolone) versus acetic acid) and comparison five (topical and systemic antibiotic (quinolone) versus acetic acid and daily aural toileting). Comparison one shows a higher rate of people with dry ear with topical antibiotics (quinolones) compared to acetic acid at between two to four weeks, whereas the results from comparison five indicate that fewer patients receiving topical and oral antibiotics had resolution of ear discharge compared with acetic acid ear drops and suction aural toileting every two days, at the same time point (two to four weeks) (RR 0.61, 95% CI 0.40 to 0.93; 100 participants). This result would appear to indicate that the addition of daily aural toileting to acetic acid had a large impact on the results. However, the absolute resolution rates for the group receiving both topical and systemic antibiotics in Gupta 2015 was very low (38%) compared with the resolution of ear discharge of 73% in Loock 2012, which used topical antibiotics alone. More research into the effects of aural toileting is required.

Overall completeness and applicability of evidence

None of the studies included participants that met the criteria for being a **'high-risk' population** as defined in our Methods section, although the recruitment was from regions that are likely to have a relatively high incidence of CSOM (Monasta 2012). All studies only included participants with CSOM (without alternative diagnoses) and most studies included adults and children.

The available evidence included four different **antiseptic agents**. This does not represent the full range of antiseptics available and differences in their use (such as method of administration) made it difficult to draw conclusions about specific agents.

Most of the **antibiotics** used within the studies were quinolones (seven study arms) with aminoglycosides being tested in only three study arms. No data for other antibiotics were available.

Data for many of the **outcomes** were missing. None of the studies reported health-related quality of life or serious complications and hearing, ear pain and suspected ototoxicity. The length of follow-up in most studies was between one to four weeks, meaning that there was limited evidence regarding the long-term effects of treatment for the resolution of ear discharge in people with CSOM.

Quality of the evidence

Generally the included studies were small (the median sample size was 100 participants) with many being poorly reported, which led to some having an unclear risk of bias, particularly for incomplete data (attrition bias).

We consider that there is a high risk of publication bias in this area: one included study was reported only as a non-peer reviewed report and made reference to further follow-up for which we were unable to find any information. We are aware of unpublished data in other comparisons in CSOM (Brennan-Jones 2018b) and we felt this to also be a risk for this comparison. We know of one study that appears from the abstract to compare antibiotics with topical

antiseptics but we are unable to obtain an abstract or full copy of the paper (Abdul 2005).

We noted a large variation in the rates of resolution of ear discharge across all studies. Even between studies where participants were treated with ciprofloxacin the resolution rates varied from 38% at two weeks where patients were receiving both topical and oral ciprofloxacin (Gupta 2015) to 90% at two weeks where participants were only treated with topical ciprofloxacin (Jaya 2003). The reasons for this variation were not clear from the reported characteristics of the studies but could have been due to the baseline characteristics of the population, efficacy, frequency of application or compliance with treatment, local levels of antibiotic resistance or even quality of antibiotic manufacture. This adds to the difficulty in drawing conclusions.

Potential biases in the review process

By only including studies that provided their results by person, there was one study which we could not use for the primary outcome. This reduced the amount of data that we were able to analyse. However, as we know that the correlation of results between ears is likely to be high, we felt that the inclusion of the results of both ears into the analysis would be likely to lead to double counting and results that could generate spurious conclusions.

Agreements and disagreements with other studies or reviews

This review is part of a series of Cochrane Reviews on CSOM (Bhutta 2018; Brennan-Jones 2018a; Brennan-Jones 2018b; Chong 2018a; Chong 2018b; Head 2018a; Head 2018b). The review that compared topical antiseptics with placebo or no treatment concluded that the effectiveness of antiseptics in the treatment of CSOM (compared with no treatment) is uncertain due to the paucity of the evidence and the very low certainty of that which is available (Head 2018a).

These reviews supersede a pair of previous Cochrane Reviews examining topical antibiotics for CSOM (Macfadyen 2005a; Macfadyen 2006).

There are few previous reviews or guidelines for CSOM. The World Health Organization (WHO) in 2004 suggested that first-line treatment of CSOM should comprise aural toilet and topical antibiotic drops, with second-line treatment comprising an alternative topical antibiotic (guided by results of microbiological culture) or parenteral antibiotics (WHO 2004). The Australian government recommendations from 2010 for the treatment of Aboriginal and Torres Strait Islanders gave similar recommendations, with first-line treatment comprising aural toilet (or antiseptic washout) followed by topical antibiotics, and second-line treatment with parenteral antibiotics (Morris 2010). An expert panel of the American Academy of Otolaryngology in 2000 came to a similar conclusion (Hannley 2000).

The *BMJ Best Evidence* series on CSOM, Morris 2012, based their review comparing topical antiseptics with topical antibiotics on the previous Cochrane Review (Macfadyen 2005a). It concluded that for adults it was not possible to tell if topical antiseptics were more effective at resolving otorrhoea than topical antibiotics. In children the review concluded that "topical antibiotics improve resolution of ear discharge compared with topical antiseptics" based on one study. There was not enough information to draw any conclusions about adverse event data for adults or children.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence that treating chronic suppurative otitis media (CSOM) with topical antibiotics (quinolones) is more effective at resolving ear discharge than topical antiseptic (boric acid) at up to four weeks. There may be a greater improvement in hearing in the topical antibiotic group compared with the topical antiseptic group but there is uncertainty about the result. Other outcomes were poorly reported. There was limited evidence for the efficacy of other topical antibiotics or topical antiseptics so we are unable to draw further conclusions. Adverse events were not well reported in the included studies.

Implications for research

The results of this review, current to April 2019, show that there is a lack of evidence comparing antibiotics with topical antiseptics. Much of the evidence comes from small, often poorly reported studies. The low certainty of evidence for CSOM treatments in this review is common throughout this suite of seven reviews of CSOM treatments.

There is insufficient evidence to address the implications of the use of topical antiseptics for high-risk groups such as children under two years, immunocompromised patients or Indigenous populations. Potential adverse effects and hearing outcomes were poorly reported and the impact of background treatment with aural toileting is also unclear.

Prior to commencing these reviews, we conducted a scoping review that identified one key question that clinicians, researchers and consumers would like to see answered, which is covered in this review:

- What are the relative effects of topical antibiotics compared with antiseptics when added on to other interventions?

Due to the low quality of the available evidence this question cannot yet be addressed with any certainty. There is clearly room for more trials examining the impact of topical antiseptics and antibiotics for people with CSOM, including trials that assess the type of topical antiseptic used.

Long-term effects (effectiveness and harms) are also important. In addition to clinical trials, health services should establish prospective databases for patients with CSOM to record (long-term) outcomes for resolution of discharge, adverse effects and hearing outcomes for people receiving treatment for CSOM.

Suggestions for future trials

This review is one of a suite of reviews of treatments for CSOM, each of which features its own research recommendations. Across all reviews, key features of future research are as follows:

Design and methods

- Where the intent is to assess the effectiveness of interventions, randomised controlled trials should be conducted. These trials

(including those testing non-systemic interventions) should randomise, analyse and report results by person (not ears).

- In patients with bilateral CSOM, for outcomes that can be reported by ear, such as resolution of ear discharge or recurrence, only one finding should be analysed and reported per person. We suggest that a single ear be included in the trial (the decision on which ear is to be included and analysed must be made *a priori*, and the method or criteria for the decision must explicitly specified in the trial protocol and report). Since there are limited data on whether people with bilateral CSOM respond to treatment in the same way as people with unilateral CSOM, and whether both ears respond in the same way to treatment, reporting these factors would be useful.
- Trials need to use appropriate methods for randomisation and allocation concealment to avoid selection bias, and should be adequately powered.
- Attempts should be made by the investigators to blind participants, healthcare professionals and study personnel to the treatment allocation. This could be through the use of placebo and ensuring that the treatment regimens are the same between treatment arms. A double placebo design should be used where dosage form and/or regimen are different. Where it is not possible to blind participants and/or clinicians to the treatment received, efforts to blind the outcome assessment and analysis personnel should be made.

Population

- Diagnosis of CSOM should be according to the WHO criteria, be otoscopically confirmed and include an assessment of hearing level.
- Potentially important patient characteristics (such as existence of ear grommets) should be recorded and presented in the report.
- If patients from 'high-risk' groups are included, these characteristics should be accounted for and explored in the design of the study.

Interventions

- All interventions (adjunctive therapies and/or allowed treatment) should be the same apart from the treatments being evaluated.
- Clear reporting of the therapies used, including dose, frequency and duration, and clear descriptions of any adjunctive therapies used across the treatment groups (including aural toileting), should be provided.

Outcomes

- There is currently no core outcome set for CSOM, or a widely agreed set of priority outcomes and definitions for CSOM trials. The development of core outcome sets, using established methods (Kirkham 2017), for CSOM would be beneficial for future trials. This would help to ensure that trials are consistent, high-quality and examine appropriate outcomes. The standardisation of outcomes allows for analysis and comparison of data across trials (and treatments) using network meta-analysis or individual participant data meta-analysis.
- The assessment of adverse effects should be defined in the protocol and these should be systematically sought during the trial using explicit methods.
- All outcomes (including hearing) should be measured and reported using valid and predefined methods.
- A validated quality of life instrument should be used whenever possible.
- Studies should follow up patients for at least six months and preferably over one year to identify the rate of recurrence of ear discharge, using a pre-agreed definition of recurrence.
- Trials should be registered in a regional or international clinical trials registry and, when published, adhere to reporting guidelines, such as CONSORT (CONSORT 2010). Where publication in a peer-reviewed journal is not possible, results should be included in the clinical trial report.

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CHARACTERISTICS OF STUDIES

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

Fradis 1997

Study characteristics	
Methods	Three-arm, double-blind, parallel-group RCT, with 3 weeks duration of treatment and follow-up

Participants	**Location:** Israel, 1 site
	
	Setting of recruitment and treatment: otolaryngology outpatient clinic of Bnai Zion Medical Centre, January 1994 to December 1995
	
	Sample size:
	
	• **Number randomised:** 51 patients; 60 ears: 20 (ears) in ciprofloxacin, 20 (ears) in tobramycin, 20 (ears) in Burow solution (1% aluminium acetate)
	• **Number completed:** 19 (ears) in ciprofloxacin, 18 (ears) in tobramycin, 17 (ears) in Burow solution (1% aluminium acetate)
	
	Participant (baseline) characteristics:
	
	• Age: mean: 44.4 years (range 18 to 73)
	• Gender (F/M): 34 (57%)/26 (43%)
	• Main diagnosis: chronic otitis media
	
	High-risk population: unclear
	
	• Cleft palate (or other craniofacial malformation): not reported
	• Down syndrome: not reported
	• Indigenous groups (Australian Aboriginals/Greenland natives): not reported
	• Immunocompromised: not reported
	
	Diagnosis method:
	
	• Confirmation of perforated tympanic membrane: yes in most patients
	  * Fradis 1997: perforation confirmed in all but 8 participants who could not be seen due to granulation tissue (microscopic evaluation of the ears)
	  * Podoshin 1998: in 3 participants it was impossible to recognise a perforation due to granulation tissue in the ear and an additional 5 participants had undergone a mastoidectomy
	• Presence of mucopurulent discharge: yes 100%
	• Duration of symptoms (discharge): range 1 to 240 months (Fradis 1997: mean 24 months, Podoshin 1998: mean 74 months)
	
	Other important effect modifiers:
	
	• Alternative diagnosis of ear discharge: not reported

Fradis 1997 *(Continued)*

- Number who have previously had grommets inserted: not reported
- Number who have had previous ear surgery:
- * Fradis 1997: "patients who had… undergone a prior middle ear operation…were excluded from the study")
  * Podoshin 1998: 8 patients had undergone an operation in the affected ear (5 radial mastoidectomy and 3 tympanoplasty)
- Number who had previous antibiotic treatment for CSOM:
  * Fradis 1997: 34/51 (67%) had used systemic antibiotics; 12/51 (22%) had used ear drops containing neomycin and polymyxin B
  * Podoshin 1998: 34 out of 60 were treated with antibiotics prior to initiation of the study, without improvement. Of these 22 were treated with otic drops and 12 additional participants were given antibiotics by mouth.

Inclusion criteria:

- Chronic otitis media (no definition)

Exclusion criteria:

- Patients younger than 18 years
- Had undergone a prior middle ear operation
- Had a suspicion of cholesteatoma
- Had general health problems
- History of allergy to aminoglycosides or fluoroquinolone derivatives

Interventions	**Group A (n = 20 ears):** ciprofloxacin (no concentration given), ear drops, 5 drops, 3 times daily for a period of 3 weeks **Group B (n = 20 ears)**: tobramycin (no concentration given), ear drops, 5 drops, 3 times daily for a period of 3 weeks **Group C (n = 20 ears)**: Burow's solution (1% aluminium acetate solution), ear drops, 5 drops 3 times daily for a period of 3 weeks **Concurrent treatment:** no information about concurrent treatment All other medications were discontinued 2 weeks prior to beginning participation in the study
Outcomes	Outcomes of interest in the review: **Primary outcomes:** • Resolution of ear discharge ("dry ear"), measured at between 2 to 4 weeks **Secondary outcomes** • Hearing loss (measured as change in hearing threshold from baseline or at endpoint)
Funding sources	No information provided
Declarations of interest	No information provided
Notes	This is a 3-arm trial comparing topical ciprofloxacin, topical tobramycin and Burow solution (aluminium acetate – topical antiseptic) **Unit of randomisation:** ears **Methods for including patients with bilateral disease:** not stated. No adjustments made. Unclear how many patients had bilateral ear disease in each group.

Risk of bias

Fradis 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly divided into 3 groups of 20 ears each…" Comment: sufficient information about the sequence generation is not available to determine whether this is a 'high' risk or 'low' risk
Allocation concealment (selection bias)	Low risk	Quote: "… All patients … received similar appearing bottles of ear drops in a randomized manner. Neither the patients nor the treating physician knew what type of ear drops was given to each patient." Comment: it does not appear that the treating physician could determine the allocation to treatment group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All numbered bottles were retained in the hospital pharmacy and during the study only the head of the pharmacy department knew what each bottle contained. The code of bottle contents was broken only at the end of the study to summarize the results of the investigation." Comment: participants and trial personnel were sufficiently blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All numbered bottles were retained in the hospital pharmacy and during the study only the head of the pharmacy department knew what each bottle contained. The code of bottle contents was broken only at the end of the study to summarize the results of the investigation." Comment: those assessing outcomes were blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Only 54 of 60 ears were available for re-examination after 3 weeks of treatment. Six patients (1 from group 1, 2 from group 2, and 3 from group 3) who entered the study were unavailable for follow-up." Comment: loss to follow-up was 10% (6/60) in total. No reasons for loss to follow-up are provided
Selective reporting (reporting bias)	Unclear risk	Quote: "All patients underwent an audiological examination at the end of the treatment period" Comment: the methods section states that audiological examination was completed at the end of treatment but this is not presented in the results section. No protocol for the trial was identified.

Gupta 2015

Study characteristics	
Methods	Two-arm, non-blinded, parallel-group RCT, with up to 3 months duration of treatment and 3 months duration of follow-up
Participants	**Location:** India, single site **Setting of recruitment and treatment:** Department of Otorhinolaryngology, tertiary care hospital, November 2011 to September 2013 (specific location not reported) **Sample size:** • **Number randomised:** 50 in each group

Gupta 2015 *(Continued)*

- **Number completed:** 50 in each group

Participant (baseline) characteristics:

- Age: mean age 36.4 years (range 6 to 72 years)
- Gender (F/M): 46 (46%)/54 (54%)
- Main diagnosis: CSOM

High-risk population: no

- Cleft palate (or other craniofacial malformation): not reported
- Down syndrome: not reported
- Indigenous groups (Australian Aboriginals/Greenland natives): not reported
- Immunocompromised: not reported

Diagnosis method:

- Confirmation of perforated tympanic membrane: yes (otoscopically confirmed), 35/134 ears had small perforation
- Presence of mucopurulent discharge: yes (inclusion criterion)
- Duration of symptoms (discharge): 4 weeks minimum

Other important effect modifiers:

- Alternative diagnosis of ear discharge: 0%
- Number who have previously had grommets inserted: not reported
- Number who have had previous ear surgery: not reported
- Number who had previous antibiotic treatment for CSOM: not reported

Inclusion criteria:

- Active mucosal disease with defect of pars tensa, inflamed middle ear mucosa and mucopurulent discharge for more than 4 weeks

Exclusion criteria:

- Dry ear with CSOM
- CSOM with atticoantral type
- Serous otitis media
- CSOM with otomycosis
- CSOM with vertigo
- Patients on systemic antibiotics or any topical ear drop preparation in the preceding 2 weeks in the group of patients selected for irrigation with acetic acid

Interventions	**Topical plus systemic ciprofloxacin (n = 50):** the external auditory canal and middle ear cavity were thoroughly cleaned by dry mopping and suction, followed by instillation of topical ciprofloxacin for 3 months, PLUS ciprofloxacin, orally, 500 mg twice daily for 15 days **Aural toileting plus acetic acid irrigation (n = 50):** the external auditory canal and middle ear cavity were cleaned with a suction tube as clearly as possible and irrigated with diluted **acetic acid** (2 mL, 37 C) using 1 mL syringe, every other day. Patients self-irrigated with acetic acid once a day at home (not clear whether they also self-irrigated on days with visits). No specific duration; the criteria for discontinuing the treatment were no discharge in morning, external canal should be dry and clean and thirdly the ear mucosa should not be wet or oedematous. **Concurrent treatment:** use of additional interventions (common to both treatment arms): both groups had dry mopping at initial visit
Outcomes	Outcomes of interest in the review: **Primary outcomes:**

Gupta 2015 *(Continued)*

	• Resolution of ear discharge or "dry ear" (whether otoscopically confirmed or not) measured at between 1 week to 2 weeks, 2 to 4 weeks and after 4 weeks. Otoscopically confirmed. **Secondary outcomes:** None reported
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for reporting outcomes of patients with bilateral disease:** unclear and no baseline information to inform distribution. Results were presented by participant, 34% had bilateral discharge.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Patients …were randomly distributed in two groups." "Patient on systemic antibiotics or any topical ear drop preparation preceding 2 weeks in group of patients selected for irrigation with acetic acid." Comment: no information about sequence generation, but participants who were on antibiotics were excluded from the acetic acid group. This could have created serious baseline imbalances and probably suggested that randomisation and allocation concealment was compromised.
Allocation concealment (selection bias)	High risk	Comment: as above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding was mentioned. The study regimens differed – one treatment arm had to visit the hospital every other day and irrigate the ear with 2 mL of diluted acetic acid, whereas the other had to take oral antibiotics for 2 weeks and use ear drops (concentration and frequency not reported). It is unclear how frequently the antibiotics groups were followed up.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no blinding of outcomes assessment was mentioned within the paper
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: study stated that a "hundred such patients were selected" and results for 100 patients were reported, without any information on loss to follow-up. Given that this is a 3-month study, and patients in one of the treatment arms were "advised to visit the hospital every other day", it seems unlikely that patients could attend all sessions and follow-ups.
Selective reporting (reporting bias)	High risk	Comment: no protocol was found. Pure-tone audiometry was described in the methods sections but was not reported. There was also no information about side effects.

Jaya 2003

Study characteristics

Jaya 2003 *(Continued)*

Methods	Two-arm, double-blind, parallel-group RCT, with 10 days of treatment and 4 weeks of follow-up

Participants	**Location:** Vellore, India
	
	Setting of recruitment and treatment: otolaryngology outpatient department of Christian Medical College and Hospital (single centre); March to November 2000
	
	Sample size:
	
	• **Number randomised:** 21 in topical antibiotics group, 19 in topical antiseptic group
	• **Number completed:** 21 in intervention group, 19 in comparison group
	
	Participant (baseline) characteristics:
	
	• Age: above 10 years old. Mean age not given.
	  * 10 to 20 years: 14 (35%)
	  * 21 to 40 years: 20 (50%)
	  * > 40 years: 6 (15%)
	• Gender (F/M): 26 (65%)/14 (35%)
	• Main diagnosis: actively discharging CSOM with moderate to large central perforation
	• High-risk population: no
	  * Cleft palate (or other craniofacial malformation): not reported
	  * Down syndrome: not reported
	  * Indigenous groups: not reported
	  * Immunocompromised: 0/40 (0%) (exclusion criteria: patients with debilitating illness such as diabetes mellitus, tuberculosis, renal failure or AIDS)
	• Diagnosis method:
	  * Confirmation of perforated tympanic membrane: yes (microscopic examination of ears), 14 participants had moderate perforations, 26 participants had large perforations
	  * Presence of mucopurulent discharge: not reported
	  * Duration of symptoms (discharge):
	  ☐ < 1 week: 15 (37.5%)
	  ☐ 1 to 4 weeks: 20 (50%)
	  ☐ > 4 weeks: 5 (12.5%)
	  * Total duration of disease (years)
	  ☐ ≤ 5 years: 13 (32.5%)
	  ☐ > 5 years: 27 (67.5%)
	• Other important effect modifiers:
	  * Alternative diagnosis of ear discharge: 0/40 (0%)
	  * Number who have previously had grommets inserted: not reported
	  * Number who have had previous ear surgery: not reported
	  * Number who had previous antibiotic treatment for CSOM: unclear
	
	Inclusion criteria:
	
	• Patients older than 10 years with actively discharging CSOM with moderate to large central perforation
	
	Exclusion criteria:
	
	• Cholesteatoma, aural polyps, impending complications
	• Debilitating illness such as diabetes mellitus, tuberculosis, renal failure or AIDS
	• Known allergy to iodine or fluoroquinolone
	• Prior systemic or topical antibiotic therapy within 10 days of starting the study

Interventions	**Intervention (n = 21):** ciprofloxacin 0.3% ear drops, 3 drops 3 times daily. Treatment duration = 10 days.

Jaya 2003 *(Continued)*

	Comparator group (n = 19): povidone-iodine 5% solution, 3 drops 3 times daily. Treatment duration = 10 days. **Concurrent treatment:** participants were instructed to instil the drops using the tragal displacement method, after dry mopping. Aural toileting (aural suctioning under microscopic examination) was completed at the start of the trial. Aural toilet was done for both groups at subsequent weekly visit if the ear was producing discharge.
Outcomes	Outcomes of interest in the review: **Primary outcomes:** • Resolution of ear discharge or "dry ear" (whether otoscopically confirmed or not) measured at between 1 week to 2 weeks, 2 to 4 weeks. Otoscopically confirmed. **Secondary outcomes:** • Hearing measured as the pure-tone average of air conduction thresholds across 4 frequencies tested (at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz) of the affected ear. If this was not available, the pure-tone average of the thresholds measured was reported.
Funding sources	No information provided
Declarations of interest	"The authors have no relevant financial interest in this article."
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "After obtaining informed consent, the 2 drugs (5% PVP-I and 0.3% ciprofloxacin) were randomly distributed among the study groups……" Comment: no details about how sequence generation was conducted
Allocation concealment (selection bias)	Low risk	Quote: "After obtaining informed consent, the 2 drugs (5% PVP-I and 0.3% ciprofloxacin) were randomly distributed among the study groups … Both drugs were coloured identically and were dispensed in identical bottles, labelled with code numbers only …" Comment: randomisation was conducted after informed consent and enrolment, therefore risk is low. It is not clear who completed the randomisation to the study group, or how this was completed. It is assumed from the second quote that the people completing the 'random distribution' were not aware of the bottle contents.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both drugs were coloured identically and were dispensed in identical bottles, labelled with code numbers only … At the end of the study, the randomisation code was decoded." Comment: both drugs looked identical and this should be sufficient to mask the treatment options to most patients
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both drugs were coloured identically and were dispensed in identical bottles, labelled with code numbers only ... At the end of the study, the randomisation code was decoded"

Jaya 2003 *(Continued)*

		Comment: there may have been a difference in smell between the two solutions but it was not felt that this would affect the blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there is a lack of information regarding the patients who did not complete the trial. There were 3 participants from the povidone-iodine group and 1 participant from the ciprofloxacin group who did not provide results at the 4-week time point. No reasons for not completing were given in the paper. These missing data points could have affected the efficacy results, if they withdrew due to adverse events it may have been important.
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol was identified through clinicaltrials.gov or the Indian Clinical Trials registry. Some of the outcomes mentioned in the methods section were not fully reported in the results section (hearing results and adverse events).

Loock 2012

Study characteristics	
Methods	Three-arm, partially blinded, parallel-group RCT, with up to 8 weeks duration of treatment and follow-up
Participants	**Location:** South Africa, Cape Town, 1 site **Setting of recruitment and treatment:** otology clinic of the ENT outpatient clinic, Tygerberg Hospital; September 2007 to June 2010 **Sample size:** 159 • **Number randomised:** 53 in ciprofloxacin group, 54 in acetic acid group, 52 in boric acid group (single administration) • **Number completed:** 45 in ciprofloxacin group, 44 in acetic acid group, 49 in boric acid group (single administration) **Participant (baseline) characteristics:** • Age: average 25 to 26 years (90% range: 20 to 34) • Gender (F/M): 55.3%/44.7% • Main diagnosis: otorrhoea because of active mucosal COM High-risk population: no • Cleft palate (or other craniofacial malformation): not reported • Down syndrome: not reported • Indigenous groups (Australian Aboriginals/Greenland natives): not reported • Immunocompromised: none (exclusion criteria) Diagnosis method: • Confirmation of perforated tympanic membrane: yes (ear cleaning until perforation was visible (see concurrent treatment section)). Perforation size at baseline was: 35% acetic acid group; 28% boric acid powder group; 35% ciprofloxacin group. • Presence of mucopurulent discharge: not reported • Duration of symptoms (discharge): not reported Other important effect modifiers: • Alternative diagnosis of ear discharge: 0%

Loock 2012 *(Continued)*

- Number who have previously had grommets inserted: none (exclusion criterion)
- Number who have had previous ear surgery: none (exclusion criterion)
- Number who had previous antibiotic treatment for CSOM: not reported

Inclusion criteria:

- Aged over 6 years of age presenting with otorrhoea because of active mucosal COM

Exclusion criteria:

- Cholesteatoma
- Signs of tuberculous otitis media
- Systemic immunosuppressive disease (e.g. diabetes mellitus, HIV/AIDS)
- Grommets (ventilation tubes)
- Aural polyp
- A history of previous middle ear surgery
- Local ear treatment or systemic antibiotics within the previous week

Interventions	**Topical antibiotics (n = 53):** ciprofloxacin, ear drops (no concentration given), 6 drops, 2 times per day for an unspecified period (likely to be 4 weeks) **Topical antiseptics (acetic acid) (n = 54):** 1% acetic acid, ear drops, 6 drops, 2 times per day for an unspecified period (likely to be 4 weeks) **Topical antiseptics (boric acid) (n = 52):** boric acid powder, single administration. After ear toilet and flushing of the middle ear and Eustachian tube with 6 drops of saline, the clinician 'tapped' boric acid powder into the external ear canal using a 50 mL 'urological' syringe with a wide mouth, an aural speculum and ambient light and compacted the boric acid powder into the external ear canal using an 'ear bud' until the external ear canal was filled with powder. The patient was instructed not to disturb the boric acid powder and to keep the ear dry. **Concurrent treatment:** Aural toileting: at the first visit the clinician performed ear toilet by syringing the ear using a naked eye and ambient light only, a 50 mL syringe with a Luer lock and an angled 1 mm diameter suction tip, a clean technique and clean body-temperature tap water, with or without dry mopping, until the perforation was clearly visible. Participants were advised not to get water into the ear. No details of other additional treatments were listed. In all cases, ear drops were 'pumped' down the Eustachian tube using tragal pressure, 6 drops/twice per day.
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge ("dry ear"), measured after 4 weeks. Unclear if otoscopically confirmed. • Ear pain (otalgia) or discomfort or local irritation **Secondary outcomes:** • Hearing (measured as change in hearing threshold from baseline or at end point) • Serious complications, including intracranial complications (such as otitic meningitis, lateral sinus thrombosis and cerebellar abscess), extracranial complications (such as mastoid abscess, postauricular fistula and facial palsy) and death
Funding sources	"Funding for purchase of the ciprofloxacin eardrops, audiological services and patient follow-up visits was obtained through research funds generously provided by the ENT Society of South Africa. Fund-

Loock 2012 *(Continued)*

	ing for the microbiological investigations was generously sponsored by the National Health Laboratory Service of South Africa (NHLS)." "… the investigator received no sponsorship or incentive from manufacturers of any of the treatments used."
Declarations of interest	"There was no conflict of interest …"
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not stated This was a 3-arm trial, but only 2 arms (acetic acid and boric acid) are relevant for this review. Although some results are given at 8 weeks, these are only for the participants who failed initial treatment. Therefore only the 4-week results are presented.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomised series (Randomisation.com) generated for three groups in 30-patient blocks …" Comment: appropriate sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "A computer-generated randomised series …was kept by a pharmacist at a distant site. This pharmacist supplied sequential opaque dispensing envelopes, numbered in advance according to the randomised sequence, containing the allocated treatment. These envelopes were held by the research nurse, who gave the sealed envelope containing the allocated treatment to the investigator after the patient had been enrolled in the trial." Comment: allocation code only revealed after enrolment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The nurse would then supply the sequentially numbered envelope pre-prepared by the pharmacist containing the allocated treatment. Each envelope contained an identical unlabelled bottle with one of: 1% acetic acid eardrops; ciprofloxacin eardrops; or normal saline with an added instruction to administer boric acid powder." Comment: although bottles were identical and unlabelled, it is possible to find out the allocated treatment because one of the groups had an additional powder, and it is possible that the acetic acid drops have a characteristic smell
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "At follow-up, another clinician, unaware of the treatment allocation and hence 'blind' as far as possible, assessed the activity of the ear. Unavoidably, remnants of boric acid powder at times interfered with blinding of this clinician's assessment…. The main outcome measure was whether the clinician judged the perforation to be inactive (dry), active (wet) or 'moist'." Comment: blinding of outcome assessment was attempted, but it is possible that for some patients the treatment used could be guessed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: loss to follow-up was 10/54 (18.5%), 3/49 (5.8%) and 8/53 (15.1%) at the assessment at 4 weeks. The paper states that no participant withdrew but the reasons for loss to follow-up were not provided.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was available from clinicaltrial.gov or from the South African registry of clinical trials. The outcomes planned in the methods section were presented in the results, even where there was a reason that the outcome was not possible to report.

Loock 2012 *(Continued)*

	Results of the audiometric tests were not well presented.

Macfadyen 2005

Study characteristics	
Methods	Two-arm, double-blind, parallel-group RCT, with 2-week duration of treatment and 4-week duration of follow-up

Participants	**Location:** Kenya, Kisuma district
	
	Setting of recruitment and treatment: rural areas known to be at higher risk of infant mortality and ear diseases. 141 (out of 165) primary schools, May to August 2002.
	
	Sample size:
	
	• **Number randomised:** 216 in ciprofloxacin, 211 in boric acid
	• **Number completed:** 200 in ciprofloxacin, 202 in boric acid
	
	Participant (baseline) characteristics:
	
	• Age: 11.1 ± 3.15 years
	• Gender (F/M): 176 (41%)/251 (59%)
	• Main diagnosis: children with CSOM
	
	High-risk population: no
	
	• Cleft palate (or other craniofacial malformation): not reported
	• Down syndrome: not reported
	• Indigenous groups (Australian Aboriginals/Greenland natives): not reported
	• Immunocompromised: not reported
	
	Diagnosis method:
	
	• Confirmation of perforated tympanic membrane: yes (otoscopy). 16% versus 15% in ciprofloxacin versus boric acid group at least one ear with small perforation
	• Presence of mucopurulent discharge: yes
	• Duration of symptoms (discharge): median 8 weeks (IQR 4 to 16 weeks for ciprofloxacin; 4 to 20 weeks for boric acid)
	
	Other important effect modifiers:
	
	• Alternative diagnosis of ear discharge: 0%
	• Number who have previously had grommets inserted: not reported
	• Number who have had previous ear surgery: not reported
	• Number who had previous antibiotic treatment for CSOM: not reported
	
	Inclusion criteria:
	
	• School children aged 5 years or older with:
	  • purulent aural discharge for 14 days or longer; or
	  • pus in the external canal on otoscopy; and
	  • perforation of the tympanic membrane.
	
	Exclusion criteria:
	
	• Treated for ear infection or received antibiotics for any other disorder in the previous 2 weeks
	• Had other ear problems (pre-existing disease, complicated otitis media, anatomical abnormalities)

Macfadyen 2005 *(Continued)*

Interventions	**Intervention (n = 216):** 0.3% ciprofloxacin, ear drops, no volume given, every 12 hours. Treatment duration = school days only for 2 weeks. **Comparator group (n = 211)**: 2% boric acid in 45% alcohol, ear drops, no volume given every 12 hours. Treatment duration = school days only for 2 weeks. **Concurrent treatment:** Ear drops were given twice daily (volume not reported) during school days only for 2 weeks (total of 10 days). Older children were trained to clean and treat (dry mopping with cotton bud?) infected ears under supervision of trained teachers. If discharge continued at 2 weeks, instructed to drug mop ears until week 40. If discharging at 4 weeks, instructed to dry mop, received additional supply of ear drop and referred.
Outcomes	Outcomes of interest in the review: **Primary outcomes:** • Resolution of ear discharge or "dry ear" (whether otoscopically confirmed or not) measured at between 1 week to 2 weeks, 2 to 4 weeks. Unclear if otoscopically confirmed. • Ear pain (otalgia) or discomfort or local irritation **Secondary outcomes:** • Hearing measured as the pure-tone average of air conduction thresholds across 4 frequencies tested (at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz) of the affected ear • Adverse effects from treatment
Funding sources	"The study was funded by a Project Grant from The Wellcome Trust (UK registered Charity Number 210183; Grant reference number: 056756/Z/99/Z). Alcon (Denmark and Belgium) provided the Ciloxan supplies"
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for reporting outcomes of patients with bilateral disease:** reported results for either ear and when both ears resolved (2 sets of results)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Children were randomized in a 1:1 ratio using computer generated block randomization, stratified by school" Comment: adequate methods
Allocation concealment (selection bias)	Low risk	Quote: "After completing all induction assessments, eligible children were allocated their sequential treatment pack…" and "each treatment pack contained two bottles of randomized treatment and remained sealed until allocated to a child." Comment: allocation was only conducted after patients were enrolled and could not be distinguished

Macfadyen 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each treatment pack contained two bottles of randomized treatment and remained sealed until allocated to a child; packs and the bottles were identical in appearance and both treatments identical in colour and smell. Participants, carers, and outcome assessors remained blind to the treatment allocated throughout the study." Comment: adequate blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "…identical in appearance and both treatments identical in colour and smell. Participants, carers, and outcome assessors remained blind to the treatment allocated throughout the study." Comment: adequate blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: dropout rates were low and similar for both groups (16/126 (7.4%) for ciprofloxacin and 9/211 (4.3%) for boric acid). Flow of participants through study very clearly presented
Selective reporting (reporting bias)	Low risk	Comment: no protocol of study found on WHO ICTRP database and clinicaltrials.gov. All outcomes identified in the methods section are reported in the results section. Results very clearly reported.

van Hasselt 1997

Study characteristics	
Methods	Three-arm, non-blinded, parallel-group RCT, with a 2-week duration of treatment and 8-week duration of follow-up

Participants	**Location:** Malawi, rural (Nkota Kota District)
	
	Setting of recruitment and treatment: Nkota Kota District. Community setting. Conducted between 4 to 23 August 1997.
	
	Sample size: 96
	
	• **Number randomised:** 12 in ofloxacin; 38 in neomycin/polymyxin B; 46 in acetic acid/spirit group
	• **Number completed:** 69 children (93 ears): 11 in ofloxacin ear drops, 30 in neomycin/polymyxin B and 28 in acetic acid/spirit group
	
	Participant (baseline) characteristics:
	
	• Age: not reported, "children"
	• Gender (F/M): not reported
	• Main diagnosis: children with CSOM (no details of criteria)
	• High-risk population: no, but hygiene was noted as 'poor'
	  * Cleft palate (or other craniofacial malformation): not reported
	  * Down syndrome: not reported
	  * Indigenous groups (Australian Aboriginals/Greenland natives): not reported
	  * Immunocompromised: not reported
	• Diagnosis method:
	  * Confirmation of perforated tympanic membrane: yes ("most perforations were medium or large")
	  * Presence of mucopurulent discharge: ("typically filled with mucoid pus and often flies. Granulation present in most cases")
	  * Duration of symptoms (discharge): not reported

van Hasselt 1997 *(Continued)*

- Other important effect modifiers:
  * Alternative diagnosis of ear discharge: not reported
  * Number who have previously had grommets inserted: not reported
  * Number who have had previous ear surgery: not reported
  * Number who had previous antibiotic treatment for CSOM: not reported

Inclusion criteria:

- Children with CSOM (not defined)

Exclusion criteria:

- Not reported

Interventions	**Intervention A (n = 12):** ofloxacin 0.3% (Exocin) ear drops, 3 drops/8 hours. Duration of treatment = 2 weeks. **Intervention B (n = 38):** neomycin 0.5%/polymixin B 0.1%, ear drops, 3 drops/8 hours. Duration of treatment = 2 weeks. **Comparator group (n = 46):** acetic acid 2% in spirit 25% and glycerine 30, ear drops, 3 drops/8 hours. Duration of treatment = 2 weeks In all groups the participants were asked to keep the affected ear uppermost for 10 minutes after instillation. **Concurrent treatment:** aural toileting: suction cleaning in all groups at the start of the trial and at the review appointments at 1 and 2 weeks after the start of the trial
Outcomes	Outcomes of interest in the review: **Primary outcomes:** • Resolution of ear discharge or "dry ear" whether otoscopically confirmed or not, measured at between 1 week to 2 weeks, and after 4 weeks. Unclear if otoscopically confirmed. **Secondary outcomes:** • Not reported
Funding sources	It is assumed the funding was from the Christian Blind Mission International
Declarations of interest	No information provided
Notes	**Unit of randomisation:** unclear if randomised by patient or by ear. Most likely by person. **Methods for reporting outcomes of patients with bilateral disease:** counting bilateral ears separately. All ears reported separately. Data come from an unpublished report. In the analysis 3/11 (27.27%), 10/30 (33%) and 11/28 (39%) of participants had bilateral disease in the ofloxacin, neomycin and antiseptic acid groups respectively. The costs of treatment were DM 10.00 for ofloxacin ear drop, DM 0.60 for neomycin/polymyxin B ear drop and DM 0.25 for acetic acid/spirit drops.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: the original report states that this is a "pilot trial" with no reference to blinding or randomisation. This was mentioned as a "randomised" trial in a 2002 paper by the author. If randomisation was done, it is unclear whether the

van Hasselt 1997 *(Continued)*

		unit of randomisation was the child or the ears (most likely per person). There was no clear ratio of randomisation, with 46 in the acetic acid group, 38 in the neomycin/polymyxin group and 12 in the ofloxacin group and the cheapest intervention had the most participants.
Allocation concealment (selection bias)	Unclear risk	Comment: there is no mention of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no mention of blinding. The same treatment regimen was used for each treatment group but the treatments would have been difficult to blind due to the differences in smell between the drops.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: as above, there is no mention of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: high overall dropout rate (27/96 = 28%). Unequally distributed between the treatment groups: 18 (39%); 8 (21%) and 1 (8%) did not complete the trial in the acetic acid/spirit; neomycin/polymyxin B and ofloxacin groups respectively.
Selective reporting (reporting bias)	High risk	Quote: "The children of the present trial will be reviewed after 8 weeks. The results will be presented at the next PAFOS Conference (Pan-African Federation of Otorhinolaryngological Societies) in Nairobi, 7-10 June 1998." Comment: no information on the planned outcomes. The report suggested that the patients were followed up to 8 weeks, but the outcome results could not be found. There is no protocol available on the WHO clinical trial registry.

Vishwakarma 2015

Study characteristics	
Methods	Two-arm, non-blinded, parallel-group RCT, with 2 weeks duration of treatment and follow-up
Participants	**Location:** India, Moradabad **Setting of recruitment and treatment:** Teethanker Mahaveer Medical College and Research Centre, TMU Moradabad, March 2014 to December 2014 **Sample size:** • **Number randomised:** 50 in gentamicin, 50 in acetic acid • **Number completed:** 50 in gentamicin, 50 in acetic acid **Participant (baseline) characteristics:** • Age, mean ± SD: gentamicin 27.08 ± 10.86; acetic acid 30.42 ± 13.49 (range 10 to 60) • Gender (F/M): 39 (39%)/61 (61%) • Main diagnosis: tubotympanic (safe) type of CSOM

Vishwakarma 2015 *(Continued)*

- High-risk population: no
  - Cleft palate (or other craniofacial malformation): not reported
  - Down syndrome: not reported
  - Indigenous groups (Australian Aboriginals/Greenland natives): not reported
  - Immunocompromised: 0% (exclusion criteria)
- Diagnosis method:
  - Confirmation of perforated tympanic membrane: yes (otoscopic examination)
  - Presence of mucopurulent discharge: not reported
  - Duration of symptoms (discharge): not reported
- Other important effect modifiers:
  - Alternative diagnosis of ear discharge: not reported
  - Number who have previously had grommets inserted: not reported
  - Number who have had previous ear surgery: not reported
  - Number who had previous antibiotic treatment for CSOM: not reported

Inclusion criteria:

- Age 10 years and above, diagnosed with tubotympanic (safe) type of CSOM based upon detailed history and otoscopic examination

Exclusion criteria:

- Patient with atticoantral types of CSOM
- Cholesteatoma
- Known case of hypersensitivity to acetic acid and aminoglycosides
- Cases in which culture and sensitivity showed resistance of bacteria to either gentamicin or acetic acid or both
- Immunocompromised patients
- Pregnant females and lactating mothers

Interventions	**Intervention (n = 50):** gentamicin (0.3%), ear drops, 3 drop every 8 hours. Duration of treatment = 2 weeks. **Comparator group (n = 50):** acetic acid (1.5%), ear drops, 3 drops every 8 hours. Duration of treatment = 2 weeks. **Concurrent treatment:** no aural toileting or additional interventions listed
Outcomes	Outcomes of interest in the review: **Primary outcomes:** • Resolution of ear discharge or "dry ear" (whether otoscopically confirmed or not) measured at between 1 week to 2 weeks. Unclear if otoscopically confirmed. • Ear pain (otalgia) or discomfort or local irritation **Secondary outcomes:** • Not reported
Funding sources	"No funding source"
Declarations of interest	"None declared"
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported The authors also completed a cost analysis for the trial

Vishwakarma 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A randomised, open label study was carried out in the department of …" Comment: the method of randomisation was not explained
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "A randomised, open label study was carried out in the department of …" Comment: there is no blinding in this study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "A randomised, open label study was carried out in the department of …" Comment: there is no blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants were reported as lost to follow-up and all participants were included in the results
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was identified on the WHO clinical trials registry. The primary outcome of the study was measured in two ways: an otological symptom score for which no reference to validation was made, and "treatment success" for which the definition was "clinical success" or "clinical improvement", neither of which was defined within the paper.

COM: chronic otitis media; CSOM: chronic suppurative otitis media; F: female; IQR: interquartile range; M: male; RCT: randomised controlled trial; SD: standard deviation; WHO: World Health Organization; WHO ICTRP: World Health Organization International Clinical Trials Registry Platform

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

Study	Reason for exclusion
Asmatullah 2014	COMPARISON: variety of topical antibiotics (see CSOM-1)
Boesorire 2000	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Browning 1983	INTERVENTION: standard antibiotics were not given, the choice was dependent on cultures
Browning 1988	COMPARISON: variety of topical antibiotics plus steroids (see CSOM-4)
Clayton 1990	POPULATION: less than 20% had otorrhoea with "central perforation", others were patients with otitis externa and mastoid cavity problems INTERVENTION: topical antiseptic compared with topical antibiotics
Couzos 2003	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)

Study	Reason for exclusion
Crowther 1991	COMPARISON: topical antibiotic plus variety of steroids (see CSOM-4)
de Miguel 1999	COMPARISON: variety of topical antibiotics (see CSOM-1), systemic antibiotics versus none (see CSOM-2) and topical versus systemic antibiotics (see CSOM-3)
Eason 1986	COMPARISON: 5-arm study but no direct comparison of topical antiseptics with topical antibiotics with steroids. Included in other reviews (see CSOM-2, CSOM-4, CSOM-5 and CSOM-7).
Esposito 1990	COMPARISON: systemic antibiotics versus none (see CSOM-2), topical antibiotics versus none (see CSOM-1), topical versus systemic antibiotic (see CSOM-3)
Esposito 1992	COMPARISON: topical versus systemic antibiotics (see CSOM-3)
Fliss 1990	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Gendeh 2001	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Ghosh 2012	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Gyde 1978	COMPARISON: variety of topical antibiotics (see CSOM-1)
Helmi 2000	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Indudharan 2005	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Jamallulah 2016	COMPARISON: variety of topical antibiotics (see CSOM-1)
Kasemsuwan 1997	COMPARISON: topical antibiotic versus none (see CSOM-1)
Kaygusuz 2002	COMPARISON: topical antibiotics versus none (see CSOM-1), variety of topical antibiotics plus steroids (see CSOM-4)
Kiris 1998	COMPARISON: daily aural toilet versus singular aural toilet (see CSOM-7)
Lazo Saenz 1999	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Leach 2008	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Legent 1994	COMPARSION: variety of systemic antibiotics (see CSOM-2)
Liu 2003	COMPARISON: variety of topical antibiotics (see CSOM-1)
Lorente 1995	COMPARISON: variety of topical antibiotics (see CSOM-1)
Minja 2006	COMPARISON: topical antiseptics versus placebo/no treatment (see CSOM-5)
Mira 1993	COMPARISON: adding topical antibiotic to systemic antibiotic (see CSOM-1)
Miro 2000	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Nawasreh 2001	COMPARISON: variety of topical antibiotics (see CSOM-1)
Nwokoye 2015	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Onali 2018	COMPARISON: systemic antibiotic versus none (see CSOM-2)

Study	Reason for exclusion
Panchasara 2015	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Papastavros 1989	COMPARISON: topical antiseptics versus placebo/no treatment (see CSOM-5)
Picozzi 1983	COMPARISON: systemic metronidazole versus placebo in people who already had gentamicin plus hydrocortisone ear drops (see CSOM-2)
Povedano 1995	COMPARISON: systemic versus topical antibiotics (see CSOM-3)
Ramos 2003	COMPARISON: variety of topical antibiotics (see CSOM-1), systemic antibiotics added onto topical antibiotics (see CSOM-2), systemic versus topical antibiotics (see CSOM-3) and topical antibiotics plus steroid (see CSOM-4)
Renuknanada 2014	COMPARISON: systemic antibiotics added onto topical antibiotics (see CSOM-2)-
Rotimi 1990	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Roydhouse 1981	INTERVENTION: intervention is not of interest for this review - bromhexine (mucolytic agent)
Sanchez Gonzales 2001	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Siddique 2016	COMPARISON: variety of topical antibiotics (see CSOM-1)
Smith 1996	COMPARISON: aural toilet versus no treatment (see CSOM-7)
Somekh 2000	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Subramaniam 2001	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Thorpe 2000	COMPARISON: no comparison of interest; study compares 3 different concentrations of the same topical antiseptic (aluminium acetate)
Tong 1996	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Tutkun 1995	COMPARISON: variety of topical antibiotics (see CSOM-1)
van der Veen 2007	COMPARISON: systemic antibiotics versus none (see CSOM-2)
van Hasselt 1998a	COMPARISON: variety of topical antibiotics (see CSOM-1)
van Hasselt 1998b	INTERVENTION: antibiotics given as a single dose in hydroxypropyl methylcellulose; does not meet the inclusion criteria for the duration of antibiotics (minimum 5 days)
Yuen 1994	COMPARISON: systemic versus topical antibiotics (see CSOM-3)

CSOM-1: Cochrane Review 'Topical antibiotics for chronic suppurative otitis media' (Brennan-Jones 2018a).
CSOM-2: Cochrane Review 'Systemic antibiotics for chronic suppurative otitis media' (Chong 2018a).
CSOM-3: Cochrane Review 'Topical versus systemic antibiotics for chronic suppurative otitis media' (Chong 2018b).
CSOM-4: Cochrane Review 'Topical antibiotics with steroids for chronic suppurative otitis media' (Brennan-Jones 2018b).
CSOM-5: Cochrane Review 'Topical antiseptics for chronic suppurative otitis media' (Head 2018a).
CSOM-7: Cochrane Review 'Aural toilet (ear cleaning) for chronic suppurative otitis media' (Bhutta 2018).

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

Abdul 2005

Methods	Unclear; "comparative study"
Participants	Active chronic suppurative otitis media
Interventions	Local ciprofloxacin versus aluminium acetate 3.5%
Outcomes	Unclear
Notes	Unable to locate paper It is not clear from the title of the paper whether there was a control arm

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

I-HEAR-BETA

Study name	I HEAR BETA (ACTRN12614000234617)
Methods	Multifactorial randomised controlled trial
Participants	Australian Aboriginal children (2 months of age and up to 17 years of age) with chronic suppurative otitis media
Interventions	All arms will receive standard recommended topical treatment (dry mopping with tissue spears and ciprofloxacin drops 5 drops twice a day) plus: Group 1: oral cotrimoxazole and topical povidone-iodine ear washouts Group 2: oral cotrimoxazole and NO topical povidone-iodine ear washouts Group 3: oral placebo and topical povidone-iodine ear washouts Group 4: oral placebo and NO topical povidone-iodine ear washouts
Outcomes	Presence of ear discharge in either ear, assessed by a trained research nurse using video-otoscopy before cleaning the ear canal at the end of treatment (16 weeks) and at 1 year
Starting date	2015
Contact information	Prof Peter Morris (peter.morris@menzies.edu.au) and Prof Amanda Leach (amanda.leach@menzies.edu.au)
Notes	—

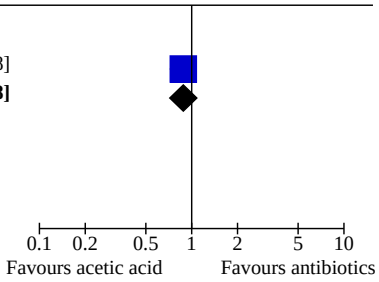
DATA AND ANALYSES

Comparison 1. Topical antibiotics versus acetic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Resolution of ear discharge (1 to 2 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 Aminoglycosides	1	100	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.72, 1.08]
1.2 Resolution of ear discharge (2 to 4 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 Quinolone vs acetic acid	1	89	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [1.71, 5.04]
1.3 Ear pain, discomfort, irritation	2	189	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.34]
1.3.1 Quinolones	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.96]
1.3.2 Aminoglycosides	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.99]

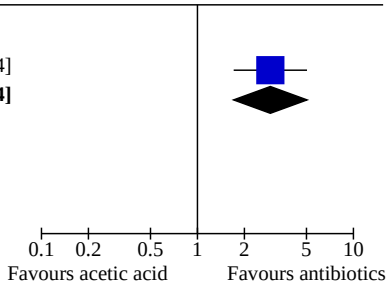
Analysis 1.1. Comparison 1: Topical antibiotics versus acetic acid, Outcome 1: Resolution of ear discharge (1 to 2 weeks)

Study or Subgroup	Antibiotics Events	Antibiotics Total	Acetic acid Events	Acetic acid Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Aminoglycosides						
Vishwakarma 2015	37	50	42	50	100.0%	0.88 [0.72 , 1.08]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.88 [0.72 , 1.08]**
Total events:	37		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Not applicable						



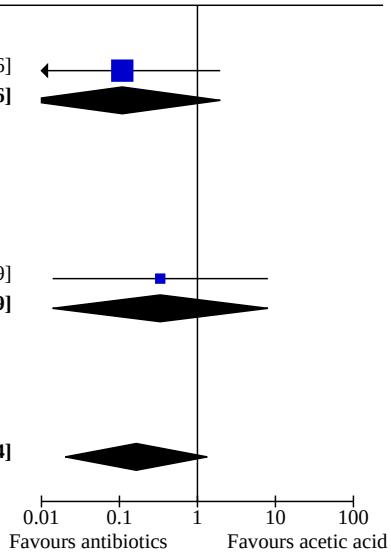
Analysis 1.2. Comparison 1: Topical antibiotics versus acetic acid, Outcome 2: Resolution of ear discharge (2 to 4 weeks)

Study or Subgroup	Antibiotics Events	Antibiotics Total	Acetic acid Events	Acetic acid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Quinolone vs acetic acid						
Loock 2012	33	45	11	44	100.0%	2.93 [1.71 , 5.04]
Subtotal (95% CI)		**45**		**44**	**100.0%**	**2.93 [1.71 , 5.04]**
Total events:	33		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.90 (P < 0.0001)						
Test for subgroup differences: Not applicable						



Analysis 1.3. Comparison 1: Topical antibiotics versus acetic acid, Outcome 3: Ear pain, discomfort, irritation

Study or Subgroup	Antibiotics Events	Antibiotics Total	Acetic acid Events	Acetic acid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Quinolones						
Loock 2012	0	45	4	44	75.2%	0.11 [0.01 , 1.96]
Subtotal (95% CI)		**45**		**44**	**75.2%**	**0.11 [0.01 , 1.96]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.50 (P = 0.13)						
1.3.2 Aminoglycosides						
Vishwakarma 2015	0	50	1	50	24.8%	0.33 [0.01 , 7.99]
Subtotal (95% CI)		**50**		**50**	**24.8%**	**0.33 [0.01 , 7.99]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**95**		**94**	**100.0%**	**0.16 [0.02 , 1.34]**
Total events:	0		5			
Heterogeneity: Chi² = 0.27, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.69 (P = 0.09)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						

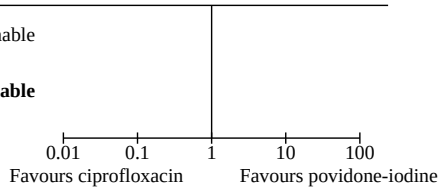


Comparison 2. Topical antibiotics versus aluminium acetate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Ototoxicity	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 2.1. Comparison 2: Topical antibiotics versus aluminium acetate, Outcome 1: Ototoxicity

Study or Subgroup	Ciprofloxacin Events	Ciprofloxacin Total	Povidone-iodine Events	Povidone-iodine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jaya 2003	0	21	0	19		Not estimable
Total (95% CI)		**21**		**19**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



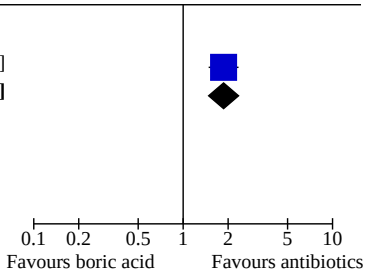
Comparison 3. Topical antibiotics versus boric acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Resolution of ear discharge (1 to 2 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.1 Quinolones	1	411	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.48, 2.35]
3.2 Resolution of ear discharge (2 to 4 weeks)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.2.1 Quinolones	2	488	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.07, 1.49]
3.3 Ear pain, discomfort, irritation	2	510	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.32, 0.98]
3.3.1 Quinolones	2	510	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.32, 0.98]
3.4 Change in hearing	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.4.1 Quinolone	1	390	Mean Difference (IV, Fixed, 95% CI)	2.79 [0.48, 5.10]

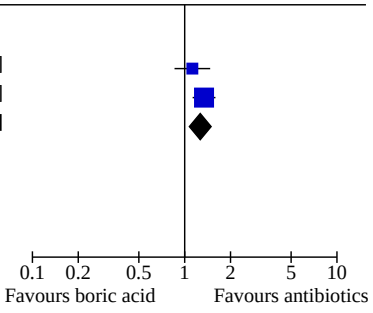
Analysis 3.1. Comparison 3: Topical antibiotics versus boric acid, Outcome 1: Resolution of ear discharge (1 to 2 weeks)

Study or Subgroup	Topical antibiotics Events	Total	Boric acid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Quinolones						
Macfadyen 2005	123	207	65	204	100.0%	1.86 [1.48 , 2.35]
Subtotal (95% CI)		**207**		**204**	**100.0%**	**1.86 [1.48 , 2.35]**
Total events:	123		65			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.31 (P < 0.00001)						
Test for subgroup differences: Not applicable						



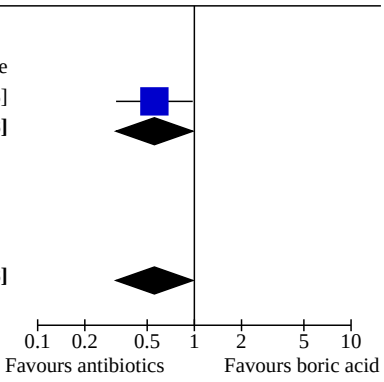
Analysis 3.2. Comparison 3: Topical antibiotics versus boric acid, Outcome 2: Resolution of ear discharge (2 to 4 weeks)

Study or Subgroup	Quinolones Events	Total	Boric acid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Quinolones						
Loock 2012	33	45	32	49	32.5%	1.12 [0.86 , 1.47]
Macfadyen 2005	130	196	98	198	67.5%	1.34 [1.13 , 1.59]
Subtotal (95% CI)		**241**		**247**	**100.0%**	**1.27 [1.07 , 1.49]**
Total events:	163		130			
Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 1 (P = 0.27); I² = 16%						
Test for overall effect: Z = 2.81 (P = 0.005)						
Test for subgroup differences: Not applicable						



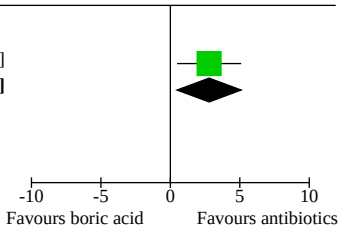
Analysis 3.3. Comparison 3: Topical antibiotics versus boric acid, Outcome 3: Ear pain, discomfort, irritation

Study or Subgroup	Quinolones Events	Total	Boric acid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Quinolones						
Loock 2012	0	45	0	49		Not estimable
Macfadyen 2005	17	210	30	206	100.0%	0.56 [0.32 , 0.98]
Subtotal (95% CI)		**255**		**255**	**100.0%**	**0.56 [0.32 , 0.98]**
Total events:	17		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.04 (P = 0.04)						
Total (95% CI)		**255**		**255**	**100.0%**	**0.56 [0.32 , 0.98]**
Total events:	17		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Not applicable						



Analysis 3.4. Comparison 3: Topical antibiotics versus boric acid, Outcome 4: Change in hearing

Study or Subgroup	Antibiotics Mean	SD	Total	Antiseptics Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.4.1 Quinolone								
Macfadyen 2005	5.42	11.03	196	2.63	12.18	194	100.0%	2.79 [0.48 , 5.10]
Subtotal (95% CI)			**196**			**194**	**100.0%**	**2.79 [0.48 , 5.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.37 (P = 0.02)								
Test for subgroup differences: Not applicable								

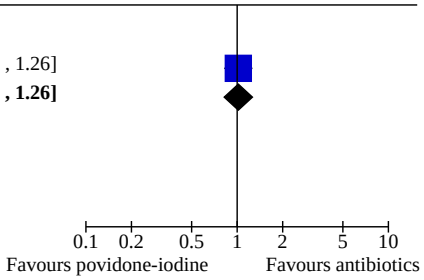


Comparison 4. Topical antibiotics versus povidone-iodine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Resolution of ear discharge (1 to 2 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1.1 Quinolones	1	39	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.26]
4.2 Resolution of ear discharge (2 to 4 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.2.1 Quinolone	1	36	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.81, 1.30]

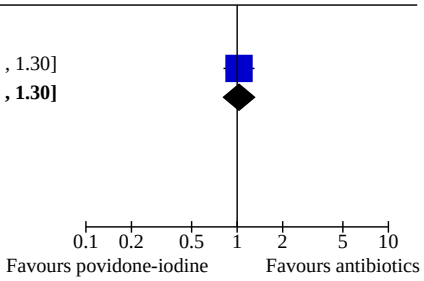
Analysis 4.1. Comparison 4: Topical antibiotics versus povidone-iodine, Outcome 1: Resolution of ear discharge (1 to 2 weeks)

Study or Subgroup	Antibiotics Events	Antibiotics Total	Povidone-iodine Events	Povidone-iodine Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Quinolones						
Jaya 2003	19	21	16	18	100.0%	1.02 [0.82 , 1.26]
Subtotal (95% CI)		**21**		**18**	**100.0%**	**1.02 [0.82 , 1.26]**
Total events:	19		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
Test for subgroup differences: Not applicable						



Analysis 4.2. Comparison 4: Topical antibiotics versus povidone-iodine, Outcome 2: Resolution of ear discharge (2 to 4 weeks)

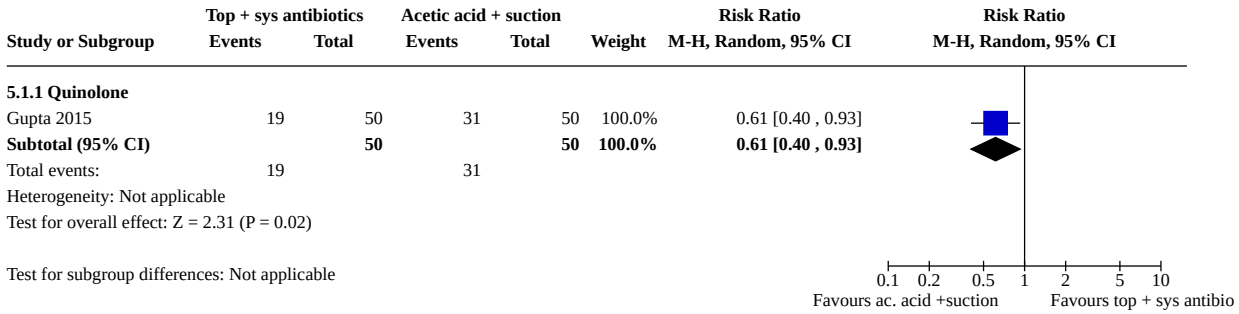
Study or Subgroup	Antibiotics Events	Antibiotics Total	Povidone-iodine Events	Povidone-iodine Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Quinolone						
Jaya 2003	18	20	14	16	100.0%	1.03 [0.81 , 1.30]
Subtotal (95% CI)		**20**		**16**	**100.0%**	**1.03 [0.81 , 1.30]**
Total events:	18		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.81)						
Test for subgroup differences: Not applicable						



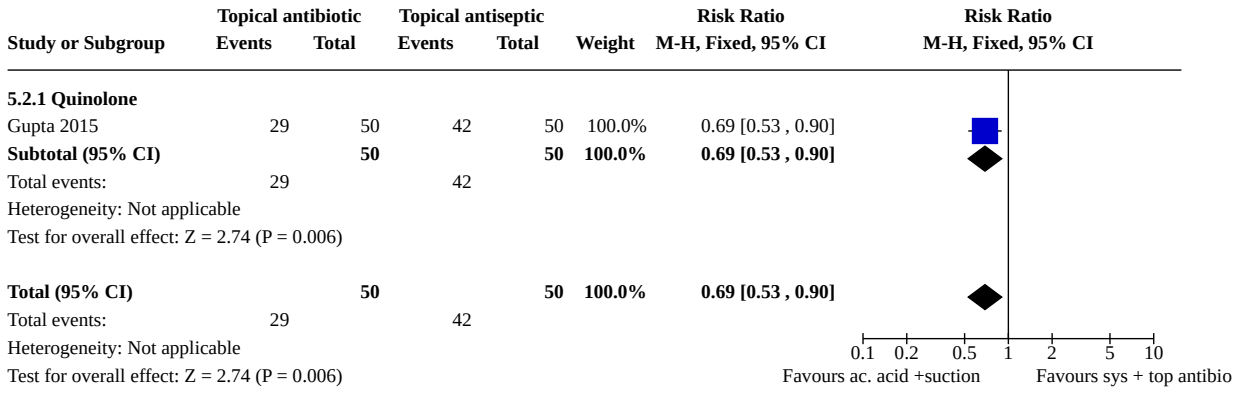
Comparison 5. Topical and systemic antibiotics versus acetic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Resolution of ear discharge (2 to 4 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1.1 Quinolone	1	100	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.40, 0.93]
5.2 Resolution of ear discharge (after 4 weeks)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.53, 0.90]
5.2.1 Quinolone	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.53, 0.90]

Analysis 5.1. Comparison 5: Topical and systemic antibiotics versus acetic acid, Outcome 1: Resolution of ear discharge (2 to 4 weeks)



Analysis 5.2. Comparison 5: Topical and systemic antibiotics versus acetic acid, Outcome 2: Resolution of ear discharge (after 4 weeks)



ADDITIONAL TABLES

Table 1. Table of Cochrane Reviews

	Topical antibiotics with steroids	Topical antibiotics	Systemic antibiotics	Topical antiseptics	Aural toileting (ear cleaning)
Topical antibiotics with steroids	Review CSOM-4				
Topical antibiotics	Review CSOM-4	Review CSOM-1			
Systemic antibiotics	Review CSOM-4	Review CSOM-3	Review CSOM-2		
Topical antiseptics	Review CSOM-4	Review CSOM-6	Review CSOM-6	Review CSOM-5	
Aural toileting	Review CSOM-4	Not reviewed	Not reviewed	Not reviewed	Review CSOM-7

Table 1. Table of Cochrane Reviews *(Continued)*

Placebo (or no intervention)	Review CSOM-4	Review CSOM-1	Review CSOM-2	Review CSOM-5	Review CSOM-7

CSOM-1: Topical antibiotics for chronic suppurative otitis media (Brennan-Jones 2018a).
CSOM-2: Systemic antibiotics for chronic suppurative otitis media (Chong 2018a).
CSOM-3: Topical versus systemic antibiotics for chronic suppurative otitis media (Chong 2018b).
CSOM-4: Topical antibiotics with steroids for chronic suppurative otitis media (Brennan-Jones 2018b).
CSOM-5: Topical antiseptics for chronic suppurative otitis media (Head 2018a).
CSOM-6: Antibiotics versus topical antiseptics for chronic suppurative otitis media (Head 2018b).
CSOM-7: Aural toilet (ear cleaning) for chronic suppurative otitis media (Bhutta 2018).

Table 2. Examples of antibiotics classes and agents with anti-*Pseudomonas* activity

Class of antibiotics	Examples	Route of administration
Quinolones	Ciprofloxacin, ofloxacin, levofloxacin	Oral, intravenous, topical
Aminoglycosides	Gentamicin, tobramycin	Topical or parenteral
	Neomycin/framycetin	Only topical
Cephalosporins	Ceftazidime	Parenteral
Penicillins	Ticarcillin plus clavulanic acid	Parenteral
Monobactams	Aztreonam	Parenteral

Table 3. Antiseptics that have been used to treat CSOM

Antiseptic agent used aurally	Target and mechanism of action
Rubbing alcohol (ethanol, isopropanol)	Penetrating agents that cause loss of cellular membrane function, leading to release of intracellular components, denaturing of proteins, and inhibition of DNA, RNA, protein and peptidoglycan synthesis.
Povidone-iodine	Highly active oxidising agents that destroy cellular activity of proteins. Disrupts oxidative phosphorylation and membrane-associated activities. Iodine reacts with cysteine and methionine thiol groups, nucleotides and fatty acids, resulting in cell death.
Chlorhexidine	Membrane-active agents that damage cell wall and outer membrane, resulting in collapse of membrane potential and intracellular leakage. Enhanced passive diffusion mediates further uptake, causing coagulation of cytosol.
Hydrogen peroxide	Produces hydroxyl free radicals that function as oxidants, which react with lipids, proteins and DNA. Sulfhydryl groups and double bonds are targeted in particular, thus increasing cell permeability.
Boric acid	It is likely that the change in the pH media of the ear canal interrupts the growth of bacteria by affecting the amino acid, which causes alteration in the three-dimensional structure of bacterial enzymes. Extreme changes in pH cause protein denaturation.
Aluminium acetate/acetic acid	Acetic acid changes the pH media of the ear canal and interrupts the growth of bacteria by affecting the amino acid, which causes alteration in the three-dimensional structure of bacterial enzymes.

Table 3. Antiseptics that have been used to treat CSOM *(Continued)*

	Extreme changes in pH cause protein denaturation. Aluminium acetate is an astringent that helps reduce itching, stinging and inflammation.

Sources: Gupta 2015; McDonnell 1999; Sheldon 2005.

Table 4. Summary of study characteristics

Ref ID (no. participants)	Setting	Population	Antibiotic	Topical antiseptic	Treatment	Follow-up	Background treatment	Notes
Topical antibiotics versus acetic acid								
Loock 2012 (159 participants)	South Africa, city (secondary care)	Patients with otorrhoea because of active mucosal COM Age over 6 years (90% between 20 and 34 years)	Ciprofloxacin, ear drops, (no concentration), 6 drops/8 hours	1% acetic acid 6 drops/12 hours	4 weeks	Up to 8 weeks	Aural cleaning at 1st visit	Part of a 3-arm trial; third arm used boric acid (see below)
van Hasselt 1997 (58 participants in relevant arms)	Malawi (community setting)	CSOM (no details) "Children" - no age information provided	0.3% ofloxacin 3 drops/8 hours Neomycin 0.5%/ polymixin B 0.1%, 3 drops/8 hours	2% acetic acid in spirit 25% and glycerine 30% 3 drops/8 hours	2 weeks	8 weeks	Suction cleaning at the start of trial, at 1-week and 2-week follow-up	Part of a 3-arm trial; third arm used topical antiseptics + steroids
Vishwakarma 2015 (100 participants)	India (secondary care)	Tubotympanic (safe) type of CSOM Mean age 69 years (range: 10 to 60 years)	Gentamicin (0.3%), ear drops, 3 drops every 8 hours	Acetic acid (1.5%), ear drops, 3 drops every 8 hours	2 weeks	2 weeks	None listed	Resolution of ear discharge measured as symptom score
Topical antibiotics versus aluminium acetate (Burow's solution)								
Fradis 1997 (51 participants, 60 ears)	Israel (ENT outpatient clinic)	Chronic otitis media Mean: 44.4 years (range 18 to 73 years)	Ciprofloxacin (no concentration), 15 drops per day Tobramycin (no concentration), 15 drops per day	1% aluminium acetate solution 5 drops/8 hours	3 weeks	3 weeks	None mentioned	Randomisation by ear Not possible to use results 3-arm trial
Topical antibiotics versus boric acid								

Table 4. Summary of study characteristics *(Continued)*

Loock 2012 (159 participants)	South Africa, city (secondary care)	Patients with otorrhoea because of active mucosal COM Age over 6 years (90% between 20 and 34 years)	Ciprofloxacin, ear drops, (no concentration), 6 drops/8 hours	Boric acid powder Single administration	4 weeks (antibiotics)	Up to 8 weeks	Aural cleaning at 1st visit	Part of a 3-arm trial; third arm used acetic acid (see above)
Macfadyen 2005 (427 participants)	Kenya, rural (community, school setting)	Children (aged over 5 years) with CSOM Mean age 11.1 ± 3.15 years	0.3% ciprofloxacin, ear drops, no volume given every 12 hours	2% boric acid in 45% alcohol, ear drops, no volume given every 12 hours	School days only for 2 weeks	4 weeks	Daily dry mopping before application	—
Topical antibiotics versus povidone-iodine								
Jaya 2003 (40 participants)	India, city (ENT outpatient clinic)	Actively discharging CSOM with moderate to large central perforation Age over 10 years (50% between 21 to 21 to 40)	Ciprofloxacin 0.3% ear drops, 3 drops 3 times daily	Povidone-iodine 5% solution, 3 drops 3 times daily	10 days	4 weeks	Suction cleaning before trial and then daily dry mopping	—
Systemic and topical antibiotics versus acetic acid and aural toileting								
Gupta 2015 (100 participants)	India (secondary care)	CSOM Mean age: 36.4 years (range: 6 to 72 years)	Topical ciprofloxacin (no concentration/volume) daily for 3 months, **plus** oral ciprofloxacin, 500 mg twice daily for 15 days	Diluted acetic acid (2 mL) daily. Every second day this was completed at the hospital with suction ear cleaning. Continued until no further discharge	See details for each treatment arm	3 months	Dry mopping at 1st visit	—

Table 5. Resolution of ear discharge outcome

Reference	Unit of randomisation	Discharge results reported by	Definition	Otoscopically confirmed?	Time points	Notes
Fradis 1997	Ear	Ear	"Clinical success" defined as cessation of otorrhoea and eradication of the micro-organisms in the post-treatment culture	Unclear	2 to 4 weeks: 21 days	Not possible to use these results as randomisation by ear (9/51 patients had bilateral disease)
Gupta 2015	Person	Person	"Absence of discharge"	Otoscopically confirmed	2 to 4 weeks: 15 days After 4 weeks: 1 month	—
Jaya 2003	Person	Person	"Inactive" ear	Microscopic examination	1 to 2 weeks: 2 weeks 2 to 4 weeks: 4 weeks	—
Loock 2012	Person	Person	"Inactive" ear (dry)	Otoscopically confirmed	2 to 4 weeks: 4 weeks	Also measured patient satisfaction, which asked patients whether their ears were 'completely dry', 'better but not completely dry', 'no better, still running'
Macfadyen 2005	Person	Both by person	Resolution of aural discharge	Otoscopically confirmed	1 to 2 weeks: 2 weeks 2 to 4 weeks: 4 weeks	For bilateral disease results were reported for when either ear was dry and when both ears were dry. For this review we have used the 'both ears' results.
van Hasselt 1997	Unclear	Results reported by ear	"Dry ear"	Unclear	1 to 2 weeks: 1 week 2 to 4 weeks: 2 weeks	Results not used as it was not possible to account for correlation between ears due to bilateral disease
Vishwakarma 2015	Person	Person	"Clinical cure" defined as a score of < 3 on a symptom scale[1]	Unclear	1 to 2 weeks: 14 days	—

[1]Symptom scale; tinnitus: absent (0), mild (1), moderate (2), severe (3); amount of discharge: absent (0), mild (1), moderate (2), severe (3); type of discharge: absent (0), mucoid (1), mucopurulent (2), purulent (3). Sum scores in each category to give range of 0 to 9.

APPENDICES

Appendix 1. Search strategies

CENTRAL (the Cochrane Register of Studies)	MEDLINE (Ovid)	Embase (Ovid)
1 MESH DESCRIPTOR Otitis Media EXPLODE ALL AND CENTRAL:TARGET 2 ("otitis media" or OME):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 3 MESH DESCRIPTOR Tympanic Membrane Perforation EXPLODE ALL AND CENTRAL:TARGET 4 MESH DESCRIPTOR Tympanic Membrane EXPLODE ALL AND CENTRAL:TARGET 5 ("ear drum*" or eardrum* or tympanic):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 6 #4 OR #5 AND CENTRAL:TARGET 7 (perforat* or hole or ruptur*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 8 #6 AND #7 AND CENTRAL:TARGET0 9 #1 OR #2 OR #3 OR #8 AND CENTRAL:TARGET 10 MESH DESCRIPTOR Suppuration EXPLODE ALL AND CENTRAL:TARGET 11 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or discomfort or earach* or mucopurulen*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 12 (pain):AB,TI,TO AND CENTRAL:TARGET 13 #10 or #11 or #12 AND CENTRAL:TARGET 14 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND CENTRAL:TARGET 15 MESH DESCRIPTOR Recurrence EXPLODE ALL AND CENTRAL:TARGET 16 (chronic* or persist* or recurr* or repeat*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 17 #14 OR #15 OR #16 AND CENTRAL:TARGET 18 #9 AND #17 AND #13 AND CENTRAL:TARGET 19 ((chronic* or persist* or recurr* or repeat*) NEAR (ear or ears or aural) NEAR (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort or disease*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 20 ((earach* near (chronic or persist* or recurr* or repeat*))):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 21 MESH DESCRIPTOR Otitis Media, Suppurative EXPLODE ALL AND CENTRAL:TARGET 22 (CSOM):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 23 #20 OR #21 OR #22 OR #18 OR #19 AND CENTRAL:TARGET	1 exp Otitis Media/ 2 ("otitis media" or OME).ab,ti. 3 exp Tympanic Membrane Perforation/ 4 exp Tympanic Membrane/ 5 ("ear drum*" or eardrum* or tympanic).ab,ti. 6 4 or 5 7 (perforat* or hole or ruptur*).ab,ti. 8 6 and 7 9 1 or 2 or 3 or 4 or 8 10 exp Suppuration/ n 11 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or moist or wet or mucopurulen* or discomfort or pain* or earach*).ab,ti. 12 10 or 11 13 exp Chronic Disease/ 14 exp Recurrence/ 15 (chronic* or persist* or recurr* or repeat*).ab,ti. 16 13 or 14 or 15 17 9 and 12 and 16 18 ((chronic or persist*) adj3 (ear or ears or aural) adj3 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort)).ab,ti.	1 exp otitis media/ 2 ("otitis media" or OME).ab,ti. 3 exp eardrum perforation/ 4 exp eardrum/ 5 ("ear drum*" or eardrum* or tympanic).ab,ti. 6 4 or 5 7 (perforat* or hole or ruptur*).ab,ti. 8 6 and 7 9 1 or 2 or 3 or 8 10 exp suppuration/ 11 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or moist or wet or mucopurulen* or discomfort or pain* or earach*).ab,ti. 12 10 or 11 13 exp chronic disease/ 14 exp recurrent disease/ 15 (chronic* or persist* or recurr* or repeat*).ab,ti. 16 13 or 14 or 15 17 9 and 12 and 16 18 exp suppurative otitis media/ 19 CSOM.ab,ti. 20 ((chronic or persist*) adj3 (ear or ears or aural) adj3 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort or disease*)).ab,ti.

(Continued)

	19 CSOM.ab,ti. 20 exp Otitis Media, Suppurative/ 21 (earach* adj6 (chronic or persist* or recurr* or repeat*)).ab,ti. 22 17 or 18 or 19 or 20 or 21	21 (earach* adj3 (chronic or persist* or recurr* or repeat*)).ab,ti. 22 17 or 18 or 19 or 20 or 21

Web of Science (Web of Knowledge)	**CINAHL (EBSCO)**	**Cochrane ENT Register (the Cochrane Register of Studies)**
#1 TOPIC: ("otitis media" or OME) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years #2 TOPIC: (("ear drum*" or eardrum* or tympanic) AND (perforat* or hole or ruptur*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years #3 #2 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years #4 TOPIC: ((suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or moist or wet or mucopurulen* or discomfort or pain* or earach*) AND (chronic* or persist* or recurr* or repeat*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years #5 #4 AND #3 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years #6 TOPIC: (((chronic or persist*) NEAR/3 (ear or ears or aural) NEAR/3 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort))) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years #7 TOPIC: ((earach* NEAR/3 (chronic or persist* or recurr* or repeat*))) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years #8 #7 OR #6 OR #5 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	S21 S17 OR S18 OR S19 OR S20 S20 TX ((chronic or persist*) N3 (ear or ears or aural) N3 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort)) S19 TX (earach* N3 (chronic or persist* or recurr* or repeat*)) S18 TX csom S17 S9 AND S12 AND S16 S16 S13 OR S14 OR S15 S15 TX chronic* or persist* or recurr* or repeat* S14 (MH "Recurrence") S13 (MH "Chronic Disease") S12 S10 OR S11 S11 TX suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or moist or wet or mucopurulen* or discomfort or pain* or earach*) S10 (MH "Suppuration+") S9 S1 OR S2 OR S3 OR S8 S8 S6 AND S7	1 ("otitis media" or OME):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 2 (("ear drum*" or eardrum* or tympanic)):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 3 (perforat* or hole or ruptur*):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 4 #2 AND #3 AND INREGISTER 5 #4 OR #1 AND INREGISTER 6 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or discomfort or earach* or mucopurulen*):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 7 (pain):AB,TI,TO AND INREGISTER 8 #6 OR #7 AND INREGISTER 9 (chronic* or persist* or recurr* or repeat*):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 10 #5 AND #8 AND #9 AND INREGISTER 11 (csom):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 12 (((chronic* or persist* or recurr* or repeat*) and (ear or ears or aural) and (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort

(Continued)

	S7 TX perforat* or hole or ruptur*	or disease*))):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER
	S6 S4 OR S5	13 ((earach* and (chronic or persist* or recurr* or repeat*))):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER
	S5 TX "ear drum*" or eardrum* or tympanic	14 #10 OR #11 OR #12 OR #13 AND INREGISTER
	S4 (MH "Tympanic Membrane")	
	S3 (MH "Tympanic Membrane Perforation")	
	S2 TX "otitis media" or OME	
	S1 (MH "Otitis Media+")	

ClinicalTrials.gov	ICTRP (WHO Portal)	Other
Search 1 (clinicaltrials.gov): (chronic OR persistent OR recurrence OR recurrent) AND (suppuration OR pus OR discharge OR otorrhea or active OR mucopurulent) AND Condition: "Otitis Media" OR OME AND Study type: interventional **Search 2 (clinicaltrials.gov):** (chronic OR persistent OR recurrence OR recurrent) AND (earache OR "ear ache" OR "ear pain" OR "ear discharge" OR "wet ear" OR "moist ear" OR "weeping ear") AND Study type: interventional **Search 3 (clinicaltrials.gov)**: ("ear drum" OR eardrum OR "tympanic membrane") AND (hole OR perforation OR rupture) AND Study type: interventional **Search 4 (the Cochrane Register of Studies):** 1 ("otitis media" or OME):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT 2 (("ear drum*" or eardrum* or tympanic)):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT 3 (perforat* or hole or ruptur*):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT 4 #2 AND #3 AND INSEGMENT	otitis media AND chronic OR ear discharge OR earache OR wet ear OR weeping ear OR moist ear OR CSOM OR OME AND chronic OR tympanic membrane AND perforation OR eardrum AND hole OR eardrum AND perforation	**LILACS** TW:"otitis media" OR "TW:"ear discharge" OR TW:earache OR ((TW:eardrum OR TW:tympanic) AND (TW:perforation OR hole)) OR ((TW:wet OR moist OR weeping) AND TW:ear) AND: Filter: Controlled Clinical Trial **IndMed** Chronic Suppurative Otitis Media OR Chronic Otitis Media OR CSOM **African Index Medicus** “chronic suppurative otitis media" OR "chronic otitis media“ OR CSOM

(Continued)

5 #4 OR #1 AND INSEGMENT

6 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or discomfort or earach* or Mucopurulen*):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT

7 (pain):AB,TI,TO AND INSEGMENT

8 #6 OR #7 AND INSEGMENT

9 (chronic* or persist* or recurr* or repeat*):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT

10 #5 AND #8 AND #9 AND INSEGMENT

11 (csom):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT

12 (((chronic* or persist* or recurr* or repeat*) and (ear or ears or aural) and (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or Mucopurulen* or pain* or discomfort or disease*))):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT

13 ((earach* and (chronic or persist* or recurr* or repeat*))):AB,EH,KW,KY,MC,MH,TI,TO AND INSEGMENT

14 #10 OR #11 OR #12 OR #13 AND INSEGMENT

15 (nct*):AU AND INSEGMENT

16 #14 AND #15

Appendix 2. Data extraction form

REF ID:	Study title:
Date of extraction:	Extracted by:
Name and email address of correspondence authors:	

General comments/notes (internal for discussion):

FLOW CHART OF TRIAL:

	Intervention	**Comparison**
	(name the intervention)	*(name the intervention)*

(Continued)

No. of people screened
No. of participants randomised - all
No. randomised to each group
No. receiving treatment as allocated
No. not receiving treatment as allocated - Reason 1 - Reason 2
No. that dropped out[1] (no follow-up data for any outcome available)
No. excluded from analysis[2] (for all outcomes) - Reason 1 - Reason 2

[1]This includes patients who withdrew and provided no data, or did not turn up for follow-up.
[2]This should be the people who were excluded from all analyses (e.g. because the data could not be interpreted or the outcome was not recorded for some reason). This is the number of people who dropped out, plus the people who were excluded by the authors for some reason (e.g. non-compliant).

INFORMATION TO GO INTO THE 'CHARACTERISTICS OF INCLUDED STUDIES' TABLE:

Methods	X arm, double-/single-/non-blinded, [multicentre] parallel-group/cross-over/cluster RCT, with x duration of treatment and x duration of follow-up

Participants	**Location:** [country, rural?, no. of sites etc.]
	Setting of recruitment and treatment: [specialist hospital? general practice? school? state YEAR]
	Sample size:
	• **Number randomised:** x in intervention, y in comparison
	• **Number completed:** x in intervention, y in comparison
	Participant (baseline) characteristics:
	• Age:
	• Gender (F/M): number of females (%)/number of males (%)
	• Main diagnosis: *[as stated in paper – state the diagnostic criteria used]*
	• High-risk population: Yes/No
	  * Cleft palate (or other craniofacial malformation): y/N (%)
	  * Down syndrome: n/N (%)
	  * Indigenous groups (Australian Aboriginals/Greenland natives): n/N (%)
	  * Immunocompromised: n/N (%)

(Continued)

	• Diagnosis method *[if reported]:*
	  * Confirmation of perforated tympanic membrane: Yes/No/NR or unclear *[Method]*
	  * Presence of mucopurulent discharge: Yes/No/NR or unclear – if 'yes', record n/N (%)
	  * Duration of symptoms (discharge): x weeks
	• Other important effect modifiers, if data available:
	  * Alternative diagnosis of ear discharge (where known): n/N (%)
	  * Number who have previously had grommets inserted (and, where known, number where grommets are still in place): n/N (%)
	  * Number who have had previous ear surgery: n/N (%)
	  * Number who have had previous antibiotic treatment for CSOM: n/N (%)
	
	Inclusion criteria:
	
	• *[State diagnostic criteria used for CSOM, if available]*
	
	Exclusion criteria:

Interventions	**Intervention (n = x):** drug name, method of administration, dose per day/frequency of administration, duration of treatment For aural toileting: who does it, methods or tools used, frequency, duration **Comparator group (n = y):** **Concurrent treatment:** Use of additional interventions (common to both treatment arms):
Outcomes	**Outcomes of interest in the review:** ***Primary outcomes:*** • Resolution of ear discharge or 'dry ear' (whether otoscopically confirmed or not), measured at between 1 week to 2 weeks, 2 to 4 weeks and after 4 weeks • Health-related quality of life using a validated instrument (e.g. COMQ-12, COMOT-15, CES) • Ear pain (otalgia) or discomfort or local irritation ***Secondary outcomes*** • Hearing, measured as the pure-tone average of air conduction thresholds across 4 frequencies tested (at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz), of the affected ear. If this is not available, the pure-tone average of the thresholds measured. • Serious complications, including intracranial complications (such as otitic meningitis, lateral sinus thrombosis and cerebellar abscess) and extracranial complications (such as mastoid abscess, postauricular fistula and facial palsy), and death. • Adverse effects from treatment (this will be dependent on the type of treatment reviewed).
Funding sources	"No information provided"/"None declared"/State source of funding
Declarations of interest	"No information provided"/"None declared"/State conflict
Notes	**Clinical trial registry no:** (if available) **Unit of randomisation:** person/ears/other (e.g. cluster-randomised by hospital/school) *[In the case of randomisation by person]:* **Methods for including patients with bilateral disease, for example:** • Random selection of one ear as the 'study ear' • Selecting worse/least affected ear as the 'study ear'

(Continued)

- Counting bilateral ears separately
- Reporting 2 sets of results (please specify)
- Other (please state)
- Not stated

RISK OF BIAS TABLE:

(See table 8.5d in the *Cochrane Handbook for Systematic Reviews of Interventions*: http://handbook.cochrane.org/).

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High/low/unclear risk	Quote: "…" Comment:
Allocation concealment (selection bias)	High/low/unclear risk	Quote: "…" Comment:
Blinding of participants and personnel (performance bias)	High/low/unclear risk	Quote: "…" Comment:
Blinding of outcome assessment (detection bias)	High/low/unclear risk	Quote: "…" Comment:
Incomplete outcome data (attrition bias)	High/low/unclear risk	Quote: "…" Comment:
Selective reporting (reporting bias)	High/low/unclear risk	Quote: "…" Comment:

FINDINGS OF STUDY

CONTINUOUS OUTCOMES

Results (continuous data table)							
Outcome	Intervention (name the intervention)			Comparison (name the intervention)			Other summary statistics/Notes
	Mean	SD	N	Mean	SD	N	Mean difference (95% CI), P values etc.
Disease-specific health-related quality of life (COMQ-12, COMOT-15, CES)[1] Time point: (state)							
Hearing: [Measurement method: include frequencies and report results separately if they are presented in the paper] Time point: [xx]							
Comments: [If there is no information apart from (vague) narration, quote here] [If information is in the form of graphs, used this software to read it: http://arohatgi.info/WebPlotDigitizer/app/, and save a copy of your charts in a folder]							

[1]State the measurement method: this will be instrument name/range for patient-reported outcomes.

DICHOTOMOUS OUTCOMES

Results (dichotomous data table)						
Outcome	Applicable review/ Intervention[1]	Group A - intervention arm		Group B – control		Other summary statistics/Notes
		No. of people with events	No. of people analysed	No. of people with events	No. of people analysed	P values, RR (95% CI), OR (95% CI)
Resolution of ear discharge or 'dry ear' at 1 to 2 weeks [Measurement method or definition used: not/unclear if/otoscopically confirmed][1] Time point: [State actual time point]						
Resolution of ear discharge or 'dry ear' at 2 to 4 weeks [Measurement method or definition used: not/unclear if/otoscopically confirmed] Time point: [xx]						
Resolution of ear discharge or 'dry ear' after 4 weeks [Measurement method or definition used: not/unclear if/otoscopically confirmed] Time point: [xx]						
Ear pain/discomfort/local irritation [Measurement method or definition used e.g. patient-reported] Time point: [xx]						
Suspected ototoxicity [Measurement method or definition used] Time point: [xx]						
Sensorineural hearing loss [Measurement method or definition used] Time point: [xx]						
Tinnitus [Measurement method or definition used]						

(Continued)

Time point: [xx]

Dizziness/vertigo/balance

[Measurement method or definition used]

Time point: [xx]

Serious complications: [State whether the paper had prespecified looking for this event, how it was diagnosed] Time point: state length of follow-up of the trial	Note down the page number/table where info was found for ease of checking

Otitic meningitis

[How was this diagnosed?]

Lateral sinus thrombosis

[How was this diagnosed?]

Cerebellar abscess

[How was this diagnosed?]

Mastoid abscess/mastoiditis

[How was this diagnosed?]

Postauricular fistula

[How was this diagnosed?]

Facial palsy

[How was this diagnosed?]

Other complications

[How was this diagnosed?]

Death

[How was this diagnosed?]

Multiple serious complications

[How was this diagnosed?]

Comment/additional notes:

If any calculations are needed to arrive at the data above, note this down here.

[1]State briefly how this was measured in the study, especially whether there was deviation from what was expected in the protocol.

For adverse events, note down how these were collected, e.g. whether the adverse event was one of the prespecified events that the study planned to collect, when it was collected and how/who measured it (e.g. as reported by patients, during examination and whether any scoring system was used).

WHAT'S NEW

Date	Event	Description
26 May 2020	Amended	A data entry error was identified and corrected. The boric acid arm of Analysis 3.1 (Macfadyen 2005) had incorrectly been input as 77/202. This has now been corrected to 65/204. The modified risk ratio (and associated NNT) has been amended in the Abstract, Results (Effects of interventions), Discussion (Summary of main results) and Summary of findings 2.

HISTORY

Protocol first published: Issue 6, 2018
Review first published: Issue 1, 2020

CONTRIBUTIONS OF AUTHORS

Karen Head: scoped the review, and designed and wrote the protocol. Screened the search results and selected studies, carried out data extraction, 'Risk of bias' assessment and statistical analyses, and wrote the text of the review.
Lee Yee Chong: scoped the review, and designed and wrote the protocol. Screened the search results and selected studies, carried out data extraction, 'Risk of bias' assessment and statistical analyses, and reviewed and edited the text of the review.
Mahmood F Bhutta: helped to scope, design and write the protocol; reviewed the analyses of results and provided clinical guidance at all stages of the review. Reviewed and edited the text of the review.
Peter S Morris: clinical guidance at all stages of the review; reviewed the analyses and reviewed and edited the text of the review.
Shyan Vijayasekaran: clinical guidance at all stages of the review; reviewed the analyses and reviewed and edited the text of the review.
Martin J Burton: clinical guidance at all stages of the review; reviewed the analyses and reviewed and edited the text of the review. Wrote the abstract for the review.
Anne GM Schilder: clinical guidance at all stages of the review; reviewed the analyses and reviewed and edited the text of the review.
Christopher G Brennan-Jones: helped to scope, design and write the protocol; clinical guidance at all stages of the review; reviewed the analyses and reviewed and edited the text of the review.

DECLARATIONS OF INTEREST

Karen Head: none known.
Lee Yee Chong: none known.
Mahmood F Bhutta: Mahmood Bhutta has received an honorarium from Novus Therapeutics for advice on an experimental treatment for otitis media (not related to any treatment in this review).
Peter S Morris: Peter Morris has contributed to an Expert Advisory Group on chronic suppurative otitis media and conjugate pneumococcal vaccines in Australia for GlaxoSmithKline. He has also been a Chief Investigator on project grants from National Health and Medical Research Council of Australia addressing treatments for chronic suppurative otitis media.
Shyan Vijayasekaran: none known.
Martin J Burton: Professor Martin Burton is joint Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this review.
Anne GM Schilder: Professor Anne Schilder is joint Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this review. Her evidENT team at UCL is supported in part by the National Institute of Health Research (NIHR) University College London Hospitals Biomedical Research Centre. The research is funded by the NIHR and EU Horizon2020. She is the national chair of the NIHR Clinical Research Network ENT Specialty. She is the Surgical Specialty Lead for ENT for the Royal College of Surgeons of England's Clinical Trials Initiative. In her role as director of the NIHR UCLH BRC Deafness and Hearing Problems Theme, she acts as an advisor on clinical trial design and delivery to a range of biotech companies, most currently Novus Therapeutics.
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