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Topical antibiotics for chronic suppurative otitis media (Review)

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[Intervention Review]

Topical antibiotics 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 often polymicrobial infection (involving more than one micro-organism) 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. Topical antibiotics, the most common treatment for CSOM, act to kill or inhibit the growth of micro-organisms that may be responsible for the infection. Antibiotics can be used alone or in addition to other treatments for CSOM, such as antiseptics or ear cleaning (aural toileting).

Objectives

To assess the effects of topical antibiotics (without steroids) for people with CSOM.

Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Register; Central Register of Controlled Trials (CENTRAL 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Ovid MEDLINE; Ovid Embase; CINAHL; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials.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 participants (adults and children) who had chronic ear discharge of unknown cause or CSOM, where the ear discharge had continued for more than two weeks.

The interventions were any single, or combination of, topical antibiotic agent(s) of any class, applied directly into the ear canal as ear drops, powders or irrigations, or as part of an aural toileting procedure.

The two main comparisons were topical antibiotic compared to a) placebo or no intervention and b) another topical antibiotic (e.g. topical antibiotic A versus topical antibiotic B).

Within each comparison we separated studies where both groups of participants had received topical antibiotic a) alone or with aural toileting 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; ear pain (otalgia) or discomfort or local irritation. Secondary outcomes included hearing, serious complications and ototoxicity measured in several ways.

Main results

We included 17 studies with a total of 2198 participants. Twelve studies reported the sample size in terms of participants (not ears); these had a total of 1797 participants. The remaining five studies reported both the number of participants and ears, representing 401 participants, or 510 ears.

A: Topical antibiotics versus placebo or no treatment (with aural toilet in both arms and no other background treatment)

One small study compared a topical antibiotic (ciprofloxacin) with placebo (saline). All participants received aural toilet. Although ciprofloxacin was better than saline in terms of resolution of discharge at one to two weeks: 84% versus 12% (risk ratio (RR) 6.74, 95% confidence interval (CI) 1.82 to 24.99; 35 participants, very low-certainty evidence), the very low certainty of the evidence means that it is very uncertain whether or not one intervention is better or worse than the other. The study authors reported that "no medical side-effects and worsening of audiological measurements related to this topical medication were detected" (very low-certainty evidence).

B: Topical antibiotics versus placebo or no treatment (with use of oral antibiotics in both arms)

Four studies compared topical ciprofloxacin to no treatment (three studies; 190 participants) or topical ceftizoxime to no treatment (one study; 248 participants). In each study all participants received the same antibiotic systemically (oral ciprofloxacin, injected ceftizoxime). In at least one study all participants received aural toilet. Useable data were only available from the first three studies; ciprofloxacin was better than no treatment, resolution of discharge occurring in 88.2% versus 60% at one to two weeks (RR 1.47, 95% CI 1.20 to 1.80; 2 studies, 150 participants; low-certainty evidence). None of the studies reported ear pain or discomfort/local irritation.

C: Comparisons of different topical antibiotics

The certainty of evidence for all outcomes in these comparisons is very low.

Quinolones versus aminoglycosides

Seven studies compared an aminoglycoside (gentamicin, neomycin or tobramycin) with ciprofloxacin (734 participants) or ofloxacin (214 participants). Whilst resolution of discharge at one to two weeks was higher in the quinolones group the very low certainty of the evidence means that it is very uncertain whether or not one intervention is better or worse than the other (RR 1.95, 95% CI 0.88 to 4.29; 6 studies, 694 participants). One study measured ear pain and reported no difference between the groups.

Quinolones versus aminoglycosides/polymyxin B combination ±gramicidin

We identified three studies but data on our primary outcome were only available in one study. Comparing ciprofloxacin to a neomycin/polymyxin B/gramicidin combination, for an unknown treatment duration (likely four weeks), ciprofloxacin was better (RR 1.12, 95% CI 1.03 to 1.22, 186 participants). A "few" patients experienced local irritation upon the first instillation of topical treatment (numbers/groups not stated).

Others

Other studies examined topical gentamicin versus a trimethoprim/sulphacetamide/polymixin B combination (91 participants) and rifampicin versus chloramphenicol (160 participants). Limited data were available and the findings were very uncertain.

Authors' conclusions

We are uncertain about the effectiveness of topical antibiotics in improving resolution of ear discharge in patients with CSOM because of the limited amount of low-quality evidence available. However, amongst this uncertainty there is some evidence to suggest that the use of topical antibiotics may be effective when compared to placebo, or when used in addition to a systemic antibiotic. There is also uncertainty about the relative effectiveness of different types of antibiotics; it is not possible to determine with any certainty whether or not quinolones are better or worse than aminoglycosides. These two groups of compounds have different adverse effect profiles, but there is insufficient evidence from the included studies to make any comment about these. In general, adverse effects were poorly reported.

PLAIN LANGUAGE SUMMARY

Topical antibiotics for people with chronic suppurative otitis media

What is the aim of this review?

The aim of this Cochrane Review was to find out if topical antibiotics are effective in treating chronic suppurative otitis media and whether one type of topical antibiotic treatment is more effective than any other. We collected and analysed all relevant studies to answer this question.

Key messages

There is a lot of uncertainty as to whether or not topical antibiotics improve the resolution of ear discharge in patients with chronic suppurative otitis media (CSOM). However, among this uncertainty there is some evidence to suggest that the use of topical antibiotics may be effective when compared to placebo, or when used in addition to a systemic antibiotic (oral or injected). There is also lots of uncertainty about which type of topical antibiotic is the most effective. Overall, the certainty of the evidence was very low.

What was studied in the review?

Chronic suppurative otitis media, sometimes referred to as chronic otitis media (COM), 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. Topical antibiotics (administered into the ear canal as ear drops, ointments, sprays or creams) are the most commonly used treatment for CSOM. Topical antibiotics kill or stop the growth of the micro-organisms that may be responsible for the infection. Topical antibiotics can be used on their own or added to other treatments for CSOM, such as antiseptics or ear cleaning (aural toileting) or systemic antibiotics (antibiotics taken either by mouth or by an injection into a muscle or vein). It was important in this review to examine whether there were any adverse effects from using topical antibiotics as they can cause irritation of the skin within the outer ear, which may cause discomfort, pain or itching. This review also examined whether different types of antibiotics were more effective at treating CSOM than others, as some antibiotics (such as aminoglycosides) may have the potential to be toxic to the inner ear (ototoxicity), with potential to cause irreparable hearing loss (sensorineural), dizziness or ringing in the ear (tinnitus).

What are the main results of the review?

We found 17 studies examining at least 2126 participants, but it was difficult to determine precisely how many participants were included as a number of studies did not clearly report the number. A number of different types of antibiotics and combinations of antibiotics were used.

Comparison of topical antibiotics to placebo or no treatment

One study compared topical antibiotics to a saline (salt water) ear wash. The topical antibiotics appeared to be more effective than the saline ear wash when assessed one to two weeks after treatment, but this study was too small to provide any certainty of the findings (very low-certainty evidence).

Comparison of topical antibiotics in addition to systemic (oral or injected) antibiotics

Four studies compared treatment with topical antibiotic (ciprofloxacin) drops in addition to a systemic (oral or injected) antibiotic. Treatment marginally favoured the combined topical and oral antibiotics compared to oral antibiotics only for resolution of discharge at one to two weeks and two to four weeks. These studies were too small to provide any certainty of the findings (low-certainty evidence).

Comparisons of different topical antibiotics

There were 12 studies that examined the effectiveness of different types of antibiotics. The certainty of the evidence for all outcomes in these comparisons is very low. Two studies did not report the number of included participants, or reported only the number of ears treated, so the total number of participants could not be calculated. Due to the low certainty of evidence it is not known which type of topical antibiotic is the most effective.

How up to date is this review?

The evidence is up to date to April 2019.

Summary of findings for the main comparison. Topical antibiotics versus placebo/no treatment for chronic suppurative otitis media

Topical antibiotics (ciprofloxacin) versus placebo/no treatment for chronic suppurative otitis media

Patient or population: patients with mucopurulent otorrhoea

Settings: specialist hospital in Thailand

Intervention: ciprofloxacin ear drops

Comparison: saline

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	Comments
			Without topical antibiotic	With topical antibiotic	Difference		
Resolution of ear discharge - measured at 1 to 2 weeks Follow-up: 7 days	RR 6.74 (1.82 to 24.99)	35 (1 RCT)	Study population			⊕⊖⊖⊖ **very low**[1]	Topical antibiotics may increase the number of patients with resolution of ear discharge at 7 days compared with placebo, but we are very uncertain about the results.
			12.5%	84.2% (22.8 to 100.0)	71.8% more (10.3 to 299.9)		
Resolution of ear discharge - measured after 4 weeks	No study measured this outcome.						
Health-related quality of life	No study measured this outcome.						
Ear pain (otalgia) or discomfort or local irritation Follow-up: 7 days	—	35 (1 RCT)	Authors reported "no medical side-effects and worsening of audiological measurements related to this topical medication were detected".			⊕⊖⊖⊖ **very low**[2]	—
Hearing Follow-up: 7 days	—	35 (1 RCT)	Authors reported "no ... worsening of audiological measurements related to this topical medication were detected."			⊕⊖⊖⊖ **very low**[3]	—
Serious complications	No studies reported that any participant died or had any intracranial or extracranial complications.						

Suspected ototoxicity Follow-up: 7 days	—	35 (1 RCT)	Authors report "no suspected ototoxicity" but it is unclear how this was measured.	⊕⊖⊖⊖ **very low**[2]	—

*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: downgraded by one level due to study limitations (risk of bias) because there were concerns about incomplete data (50 people entered the study but results are only reported for 35). Downgraded by two levels due to imprecision as there was one very small study (35 participants) with wide confidence intervals.
[2]Downgraded to very low certainty: downgraded by two levels due to study limitations (risk of bias) because there were concerns about incomplete data (50 people entered the study but results are only reported for 35) and it is unclear how this outcome was measured as the paper just reports "no medical side effects". Downgraded by one level due to imprecision as numeric results were not provided and it was only one very small study (35 participants).
[3]Downgraded to very low certainty: downgraded by two levels due to study limitations (risk of bias) because of concerns about incomplete data (50 people entered the study but results are only reported for 35) and the methods used for measuring hearing were not provided in the paper. Downgraded by one level due to imprecision as numeric results were not reported and it was only one very small study (35 participants).

Summary of findings 2. Topical antibiotics on top of systemic antibiotics for chronic suppurative otitis media

Topical antibiotics (ciprofloxacin) on top of systemic antibiotics (ciprofloxacin) for chronic suppurative otitis media

Patient or population: CSOM, recurrence of CSOM or suppuration following mastoidectomy or tympanoplasty

Settings: secondary care clinics in Spain and Italy

Intervention: ciprofloxacin (topical) plus ciprofloxacin (systemic)

Comparison: ciprofloxacin (systemic)

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	Comments
			Without topical antibiotics	With topical antibiotics	Difference		
	RR 1.47	150 (2 RCTs)	Study population			⊕⊕⊖⊖ **low**[1]	

Resolution of ear discharge- measured at 1 to 2 weeks Follow-up: 7 to 10 days	(1.20 to 1.80)	60.0%	88.2% (72.0 to 100)	28.2% more (12 more to 48 more)		Topical antibiotics in addition to systemic antibiotics may increase the number of patients with resolution of ear discharge at 7 to 10 days compared with systemic antibiotics alone. The NNTB is 4 (95% CI 3 to 9).
Resolution of ear discharge - measured after 4 weeks	No studies reported this outcome.					
Health-related quality of life	No studies reported this outcome.					
Ear pain (otalgia) or discomfort or local irritation	No studies reported this outcome.					
Hearing	No studies reported results for this outcome.					
Serious complications	No studies reported that any participant died or had any intracranial or extracranial complications.					
Suspected ototoxicity Follow-up: 7 to 10 days	—	190 (3 RCTs)	Three studies reported that they did not suspect ototoxicity in any participants, but it is unclear how this was measured (de Miguel 1999; Esposito 1990; Ramos 2003).	⊕⊖⊖⊖ **very low**[2]		—

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; **NNTB:** number needed to treat to benefit; **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 low certainty: downgraded by one level due to study limitations (risk of bias) as both studies had unclear randomisation and allocation concealment and were unblinded. Downgraded by one level due to imprecision as there were only two small studies (150 participants) with the confidence interval crossing the line of minimally important benefit.
[2]Downgraded to very low certainty: downgraded by two levels due to study limitations (risk of bias) as all three studies had unclear randomisation, allocation concealment and were unblinded studies. It was also unclear how the outcome was reported. Downgraded by one level due to imprecision as numeric results were not reported and there were only three small studies (190 participants).

Summary of findings 3. Quinolones versus aminoglycosides for chronic suppurative otitis media

Quinolones versus aminoglycosides for chronic suppurative otitis media

Patient or population: CSOM

Settings: secondary care settings in Israel, Turkey, Jordan, Spain and Pakistan

Intervention: ciprofloxacin versus tobramycin (2 studies); ciprofloxacin versus gentamycin (3 studies); ofloxacin versus gentamycin (2 studies)

Comparison: other antibiotic

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	Comments
			Aminoglycosides	Quinolones	Difference		
Resolution of ear discharge - measured at 1 to 2 weeks Follow-up: range 8 days to 2 weeks	RR 1.95 (0.88 to 4.29)	694 (6 RCTs)	33.7%[1]	65.7 (29.7% to 100%)	32.0% more (4.0% lower to 110.9% higher)	⊕⊖⊖⊖ **very low**[2]	We used a random-effects model due to high heterogeneity. Resolution of ear discharge at 1 to 2 weeks was higher in the quinolones group but the very low certainty of the evidence means that it is very uncertain whether or not one intervention is better or worse than the other.
Resolution of ear discharge - Measured after 4 weeks	None of the studies measured this outcome.						
Health-related quality of life	None of the studies measured this outcome.						

Ear pain (otalgia) or discomfort or local irritation Follow-up: 30 days	—	308 (1 RCT)	One study measured ear pain on a 3-point scale (Lorente 1995). Results were presented as a mean score. Both groups had a mean score of 0 at 30 days. There was no difference between the groups.	⊕⊖⊖⊖ **very low**[3]	—
Hearing Follow-up: 10 days	—	132 (4 RCTs)	One study presents the hearing levels per group but does not present the data in a way that can be analysed (Tutkun 1995). One study stated in the methods that hearing was measured but only mentioned that neither group showed significant differences (Nawasreh 2001).	⊕⊖⊖⊖ **very low**[4]	—
Serious complications Follow-up: 10 to 30 days	None of the studies reported that any participant died or had any intracranial or extracranial complications.				
Suspected ototoxicity Follow-up: 10 to 30 days	—	352 (2 RCTs)	One study (Lorente 1995) assessed for ototoxicity and did not find any cases. One study (Tutkun 1995) reported assessment of ototoxicity in the methods but did not provide results. None of the studies reported assessment nor any cases of suspected ototoxicity.	⊕⊖⊖⊖ **very low**[5]	—

*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; **CSOM:** chronic suppurative otitis media; **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]Average event rates in the control group were calculated without the Lorente 1995 study, as this seemed to show a very high rate of resolution (94%) compared to the other studies (range between 28% and 55%).

[2]Downgraded to very low certainty. Downgraded due to study limitations (risk of bias) as six of seven studies were unblinded and in general the methods were poor. Downgraded due to imprecision as the point estimate shows that more people with quinolones had resolution of discharge compared with aminoglycosides BUT there is a large confidence interval, which includes 'no effect' and a very large effect (four times as many people had resolution with quinolones compared to aminoglycosides). Downgraded due to inconsistency as there was high heterogeneity (I^2 = 97%) within the results.

[3]Downgraded to very low certainty: downgraded by two levels due to study limitations (risk of bias) as all elements of the risk of bias assessment were unclear. Downgraded by one level due to imprecision as the results come from one relatively small study (308 patients).

[4]Downgraded to very low certainty: downgraded by two levels due to study limitations (risk of bias) as the studies were assessed as either high risk or unclear risk for all elements of the risk of bias assessment. Downgraded by one level due to imprecision as numeric results were not presented and the results came from two small studies (132 patients).

[5]Downgraded to very low certainty: downgraded by two levels due to study limitations (risk of bias) as many were unblinded and in general the studies had methodological issues and/or were badly reported. In addition, it is not clear how the outcome was measured. Downgraded by one level due to imprecision as numeric results were not reported and there were only two studies (352 participants) that identified ototoxicity as an outcome.

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 corticosteroids) against placebo/no treatment, or another topical antibiotic 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 as the discharge is often visible and odorous (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 health care, 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 to repair the tympanic membrane are an option in cases where complications arise or in patients who have not responded to other treatments; 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 antibiotics are often used in preference to systemic antibiotics as there may be immediate adverse effects of systemic antibiotics such as gastrointestinal upset. A broader concern is the association of the overuse of systemic antibiotics with increasing bacterial resistance among community- and hospital-acquired pathogens (Costelloe 2010; ECDC 2011; Laxminarayan 2013).

Topical application 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 both children and adults. In these cases, systemic antibiotics may have an advantage.

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 to 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. Some antibiotics (such as aminoglycosides) may have the potential to be toxic to the inner ear (ototoxicity), which might be experienced as sensorineural hearing loss, dizziness or tinnitus, but this is less likely to be a risk when applied topically in patients with CSOM (Phillips 2007). Local discomfort, ear pain or itching may occur through the action of putting ear drops into the ear or because the topical antibiotics or their excipients cause chemical or allergic irritation of the skin of the outer ear.

Why it is important to do this review

Topical antibiotics (without steroids) are widely recommended as a first-line treatment for CSOM. Opinions about the safety of topical antibiotics for treatment of CSOM, particularly the use of aminoglycosides, differ between professional groups and amongst ENT specialists across different countries. There remain concerns about local toxicity to the inner ear (ototoxicity), particularly with the use of topical aminoglycosides (Phillips 2007; Youngs 2016). Quinolone antibiotics are considered by many to have the best overall risk-benefit profile, but the evidence base contains only a few small trials with high risk of bias. They are also not licensed for the treatment of CSOM (Youngs 2016). In addition, the cost of treatment, especially with quinolones, may be an issue in some settings. Evidence-based knowledge of their effectiveness and the relative effectiveness of different topical antibiotics could help to optimise their use.

OBJECTIVES

To assess the effects of topical antibiotics (without steroids) 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.

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

Intervention

We included all (topical) antibiotics applied directly into the ear canal. The most common formulations are ear drops but we also included other formulations such as sprays.

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 proven to be equivalent.

Dose

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

Comparisons

The following were the comparators:

- Placebo, no intervention (topical antibiotic versus placebo; topical antibiotic versus no intervention).
- Another topical antibiotic (topical antibiotic A versus topical antibiotic B).

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

- **Topical antibiotics 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 antibiotics as an add-on therapy to antiseptics**: this included studies where all participants in both treatment groups also used a daily antiseptic, with or without aural toileting.
- **Topical antibiotics as an add-on therapy to systemic or another topical antibiotic**: 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.

If either one or both intervention and comparison arms also received a topical steroid, we considered the data in an accompanying review in this series ('Topical antibiotics with steroids for chronic suppurative otitis media') (Brennan-Jones 2018a).

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

- topical antibiotics as a single treatment (main therapy) versus placebo or no intervention;
- topical antibiotics as a single treatment (main therapy) versus placebo or no intervention, on top of systemic antibiotics; and
- topical quinolone versus topical aminoglycoside (both as single 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) (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 search 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 the adverse effects described in the 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 CSOM (as opposed to patients with chronic ear discharge but without a diagnosis of CSOM);
- number of participants 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 of participants who had previously had ventilation tubes (grommets) inserted (and, where known, the number who had tubes still in place);
- number of participants who had previous ear surgery;
- number of participants 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 participants available at the time points based on the treatment randomised whenever possible, irrespective of compliance or whether participants 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 did not expect 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 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 participants, 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 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 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 trials (more than 10) were available for an outcome. If we 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 was from the same scale, we pooled the 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 the following two 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.

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' table presents 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 was reduced to 3147 after removal of duplicates. We screened the titles and abstracts and subsequently removed 2935 references. We assessed 212 full-text references for eligibility of which we discarded 187; we excluded 150 (including unpublished studies) of these references (122 studies) with reasons recorded in the review (see Excluded studies).

We included 23 references (17 studies). There are two references awaiting classification (Abdul 2005; Abes 1998). See Characteristics of studies awaiting classification. We did not identify any ongoing studies.

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

Figure 1. Study flow diagram

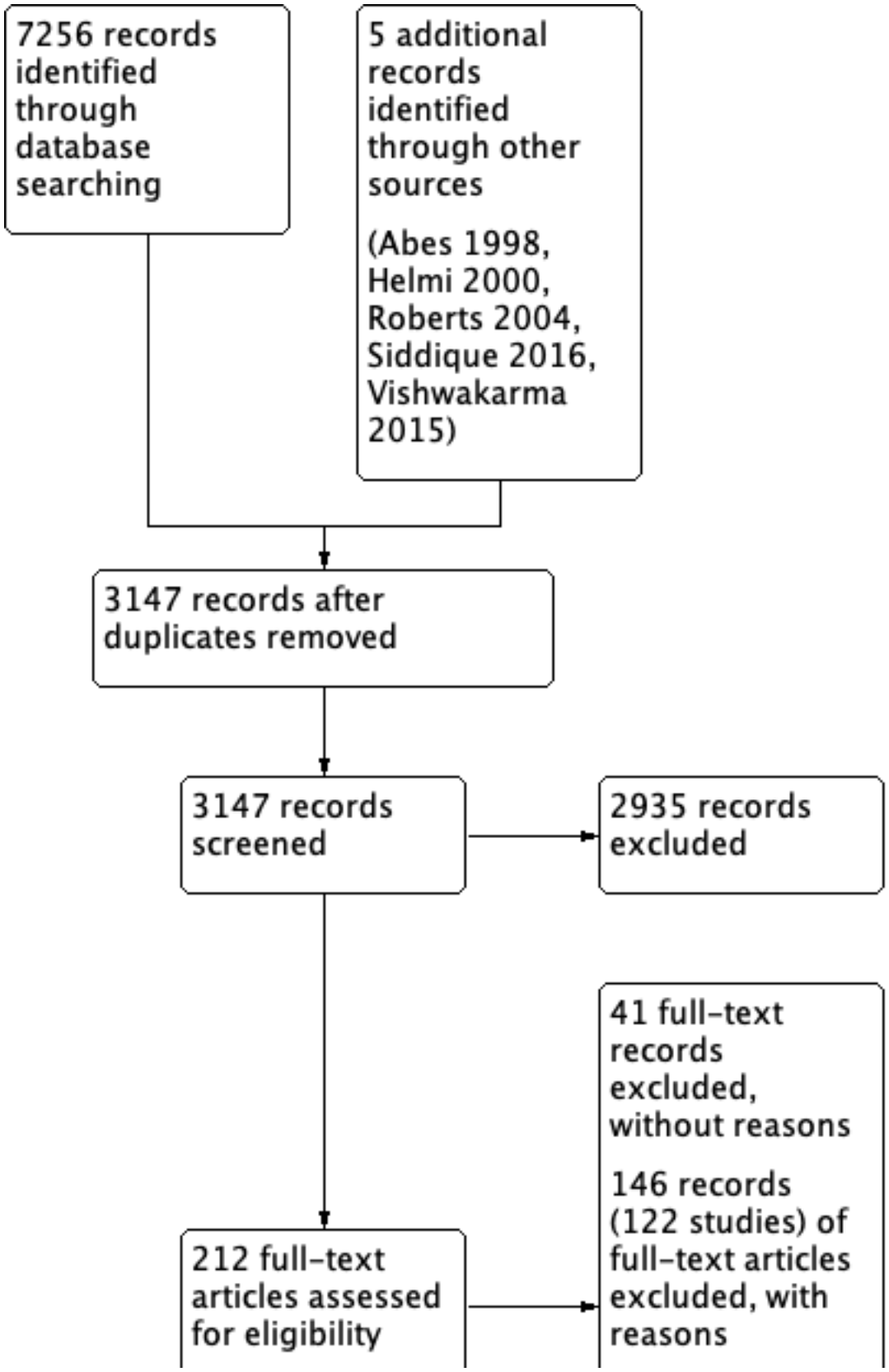


Figure 1. (Continued)

Included studies

Seventeen studies were included (Asmatullah 2014; de Miguel 1999; Esposito 1990; Fradis 1997; Gyde 1978; Jamalullah 2016; Kasemsuwan 1997; Kaygusuz 2002; Liu 2003; Lorente 1995; Mira 1993; Nawasreh 2001; Ramos 2003; Siddique 2016; Tutkun 1995; van Hasselt 1997; van Hasselt 1998a). Table 3 provides a summary of the included studies.

Study design

Ten studies were two-arm trials (Asmatullah 2014; Gyde 1978; Jamalullah 2016; Kasemsuwan 1997; Liu 2003; Lorente 1995; Mira 1993; Nawasreh 2001; Siddique 2016; Tutkun 1995) and three studies were three-arm trials (Esposito 1990; Fradis 1997; van Hasselt 1997). Two studies were part of a five-arm trial (de Miguel 1999; Ramos 2003), where only the arms that compared topical antibiotics plus systemic antibiotics with systemic antibiotics alone were used in this review. Two studies were part of a four-arm trial (Kaygusuz 2002; van Hasselt 1998a), but only two arms are presented in this review. Details of the other study arms for each study can be found in the Characteristics of included studies table.

All studies provided an indication that they were 'randomised controlled trials' and were parallel-group studies, apart from Gyde 1978, which was a cross-over RCT.

Sample size

The total number of participants was 2198. Twelve studies reported the sample size in terms of participants (not ears); these had a total of 1797 participants (Asmatullah 2014; de Miguel 1999; Esposito 1990; Jamalullah 2016; Kasemsuwan 1997; Liu 2003; Lorente 1995; Mira 1993; Nawasreh 2001; Ramos 2003; Siddique 2016; Tutkun 1995). The remaining five studies reported both the number of patients and ears, representing 401 participants, or 510 ears (Fradis 1997; Gyde 1978; Kaygusuz 2002; van Hasselt 1997; van Hasselt 1998a).

Unit of randomisation

The individual (rather than the ear) was randomised to treatment group in 14 studies (Asmatullah 2014; de Miguel 1999; Esposito 1990; Gyde 1978; Jamalullah 2016; Kasemsuwan 1997; Kaygusuz 2002; Liu 2003; Lorente 1995; Mira 1993; Nawasreh 2001; Ramos 2003; Siddique 2016; Tutkun 1995). (See Table 4). Of these 14 studies, only one reported the number of patients with bilateral disease (15 patients (8%) had bilateral disease), but as the denominator was by person, it is assumed that no double counting occurred (Siddique 2016). Although Gyde 1978 was randomised by person, the results were reported by ear. The study Gyde 1978 stated that if there was a treatment failure 'ears' were transferred to the alternative treatment group, thus effectively breaking randomisation. These results have not been included in the analysis.

In the remaining one study randomisation occurred by ear and it appears that the analysis occurred without allowing for correlation/adjustment for the response between paired ears (Fradis 1997). The unit of randomisation for two other studies is unclear: it is most likely by person but the results are reported by ear (van Hasselt 1997; van Hasselt 1998a). In the two studies by van Hasselt, bilateral ears were counted separately, but the number of patients per group was not reported. Data from van Hasselt 1997 come from an unpublished report, with the analysis indicating that 3/11 (27.27%), 10/30 (33%) and 11/28 (39%) of patients had bilateral disease in the ofloxacin, neomycin and antiseptic acid groups respectively. The results of these studies were not included in the analysis due to the risk of double counting.

Location

The studies were conducted in 10 countries including: Israel, Thailand, China, Canada, Jordan, Turkey, Italy, Malawi, Pakistan and Spain (see Table 3).

Setting of trial

With regard to clinical setting, six studies were in outpatient departments of hospitals/medical centres (Fradis 1997; Gyde 1978; Jamalullah 2016; Liu 2003; Mira 1993; Ramos 2003); two studies were based in secondary care from the ENT departments of hospitals (Asmatullah 2014; Lorente 1995); two were in a specialist hospital (Kasemsuwan 1997; Siddique 2016); and one study was in the general hospital (de Miguel 1999). Three studies were undertaken in university clinics/hospitals (Esposito 1990; Kaygusuz 2002; Tutkun 1995), while two studies were community studies taking place in rural settings (van Hasselt 1997; van Hasselt 1998a). The setting of the study was unclear in one trial (Nawasreh 2001).

The years in which the studies were conducted were often not well reported. There was one study from the 1970s (Gyde 1978), and one study in which it is unclear but was most likely to have been conducted in the 1980s (Esposito 1990). Nine studies were conducted in the 1990s (de Miguel 1999; Fradis 1997; Kasemsuwan 1997; Lorente 1995; Mira 1993; Nawasreh 2001; Tutkun 1995; van Hasselt 1997; van Hasselt 1998a), three were published in the 2000s (Kaygusuz 2002; Liu 2003; Ramos 2003), and three were published post 2010 (Asmatullah 2014; Jamalullah 2016; Siddique 2016). See Table 3 for further details.

Population

Age and sex

Two studies did not provide any patient characteristics, with the age only referred to as "mainly children" (van Hasselt 1997; van Hasselt 1998a).

Fifteen studies provided information on the age of participants, with the mean age ranging from 25.8 to 44.4 years old (Asmatullah 2014; de Miguel 1999; Esposito 1990; Fradis 1997; Gyde 1978; Jamalullah 2016; Kasemsuwan 1997; Kaygusuz 2002; Liu 2003; Lorente 1995; Mira 1993; Nawasreh 2001; Ramos 2003; Siddique 2016; Tutkun 1995). The de Miguel 1999 study reported a mean age of 39.6 years, however 17/25 participants were children.

All 15 studies that provided participant characteristics reported that they included both males and females. Of the 2010 participants reported, 860 (43%) were female, with the percentage of females in studies ranging from 18% to 63%.

High-risk populations

None of the studies reported the inclusion of any of the 'high-risk' populations as defined by our inclusion criteria (cleft palate, Down syndrome, Indigenous groups, immunocompromised patients). Two studies specifically stated "no diabetes or other comorbidities" (Esposito 1990) or "0% immunocompromised" (Siddique 2016), while the remaining 15 did not report any high-risk populations (Asmatullah 2014; de Miguel 1999; Fradis 1997; Gyde 1978; Jamalullah 2016; Kasemsuwan 1997; Kaygusuz 2002; Liu 2003; Lorente 1995; Mira 1993; Nawasreh 2001; Ramos 2003; Tutkun 1995; van Hasselt 1997; van Hasselt 1998a). However, the two van Hasselt studies were conducted in rural community areas in Malawi, with the van Hasselt 1997 study noting that hygiene was 'poor'.

Diagnosis

Eight studies provided the diagnosis method for confirmation of tympanic membrane perforation or presence of mucopurulent discharge via otoscopy or microscopic examination (de Miguel 1999; Fradis 1997; Jamalullah 2016; Kasemsuwan 1997; Kaygusuz 2002; Ramos 2003; Tutkun 1995; van Hasselt 1997), while an additional study confirmed perforation of the tympanic membrane but did not provide a method (Lorente 1995). The diagnostic method was not reported in eight studies (Asmatullah 2014; Esposito 1990; Gyde 1978; Liu 2003; Mira 1993; Nawasreh 2001; Siddique 2016; van Hasselt 1998a).

Duration of ear discharge

Nine studies reported the duration of symptoms/mucopurulent discharge for diagnosis, with one study including patients with ear discharge for more than six weeks or sporadically with three or more episodes in a year (Ramos 2003), one study with discharge for more than two months (van Hasselt 1998a), four studies with ear discharge for more than three months (Jamalullah 2016; Kasemsuwan 1997; Kaygusuz 2002; Lorente 1995), and a further three studies longer than one year (Fradis 1997; Nawasreh 2001; Tutkun 1995). Eight studies did not have inclusion criteria or provide details of the average duration of ear discharge at the start of the study (Asmatullah 2014; de Miguel 1999; Esposito 1990; Gyde 1978; Liu 2003; Mira 1993; Siddique 2016; van Hasselt 1997).

Other important effect modifiers

Nine studies did not report on any important effect modifiers (Asmatullah 2014; Kasemsuwan 1997; Liu 2003; Lorente 1995; Nawasreh 2001; Siddique 2016; Tutkun 1995; van Hasselt 1997; van Hasselt 1998a). One study reported the previous use of grommets (Ramos 2003; n = 12; 4%). Five studies provided alternative diagnoses (de Miguel 1999 (n = 17; 13.6%); Gyde 1978 (n = 24; 21%); Mira 1993 (n = 52; 21%); Ramos 2003 (n = 42; 14%)). Five studies reported the number having previous surgery (de Miguel 1999 (n = 31; 24.8%); Fradis 1997 (n = 8; 15.7%); Kaygusuz 2002 (none); Mira 1993 (n = 52; 21%); Ramos 2003 (n = 73; 24.3%)). Four studies reported the number having previous antibiotic treatment for CSOM (de Miguel 1999 (n = 79; 63.2%); Esposito 1990 (n = 38; 63%); Fradis 1997 (n = 46; 90.2%); Ramos 2003 (n = 197; 65.6%)).

Intervention

Intervention details

Details of the interventions, background treatments and treatment durations for each of the included studies are summarised in Table 3.

Topical antibiotics

Fourteen studies used topical quinolones, with four of these using ofloxacin (Asmatullah 2014; Jamalullah 2016; van Hasselt 1997; van Hasselt 1998a) and the remaining 10 using ciprofloxacin (de Miguel 1999; Esposito 1990; Fradis 1997; Kasemsuwan 1997; Kaygusuz 2002; Lorente 1995; Nawasreh 2001; Ramos 2003; Siddique 2016; Tutkun 1995).

Nine studies used aminoglycosides, with six using gentamycin or gentamicin (Asmatullah 2014; Gyde 1978; Jamalullah 2016; Lorente 1995; Nawasreh 2001; Tutkun 1995), two using tobramycin (Fradis 1997; Kaygusuz 2002), and one using neomycin (Siddique 2016).

Two studies used neomycin/polymixin B (van Hasselt 1997; van Hasselt 1998a). The remaining four studies used other topical antibiotics, including rifampicin (Liu 2003), chloramphenicol (Liu 2003), ceftizoxime (Mira 1993) and trimethoprim, sulphacetamide and polymixin B (TSP) combination (Gyde 1978).

Background treatment

Nine studies used aural toileting at different frequencies: two at the start of trial (Jamalullah 2016; Mira 1993), four before each treatment (de Miguel 1999; Gyde 1978; Kaygusuz 2002; Liu 2003), two at the start of trial and at one and two weeks (van Hasselt 1997; van Hasselt 1998a), and one at days one, four and seven (Kasemsuwan 1997).

Three studies used systemic antibiotics as a background treatment, with three via the oral route (de Miguel 1999; Esposito 1990; Ramos 2003) and one via the intramuscular route (Mira 1993). One study also had a background treatment of analgesics and antipyretics (de Miguel 1999).

A further six studies did not mention the use of any background treatments (Esposito 1990; Fradis 1997; Lorente 1995; Nawasreh 2001; Siddique 2016; Tutkun 1995).

Duration of intervention

Nine studies treated for less than two weeks (Asmatullah 2014; de Miguel 1999; Esposito 1990; Kasemsuwan 1997; Lorente 1995; Mira 1993; Nawasreh 2001; Ramos 2003; Tutkun 1995). Seven studies treated for between two to four weeks (Fradis 1997; Gyde 1978; Jamalullah 2016; Kaygusuz 2002; Liu 2003; van Hasselt 1997; van Hasselt 1998a). One study treated for four weeks (Siddique 2016).

Comparison

One study analysed topical antibiotic versus placebo:

- Kasemsuwan 1997 - ciprofloxacin versus placebo (saline).

Sixteen studies compared different topical antibiotics (topical antibiotic A versus topical antibiotic B).

- Four studies analysed topical antibiotic versus no treatment/ placebo (with systemic antibiotics as background):
  - de Miguel 1999 - ciprofloxacin versus no treatment;
  - Esposito 1990 - ciprofloxacin versus no treatment;
  - Mira 1993 - ceftizoxime versus placebo (saline);
  - Ramos 2003 - ciprofloxacin versus no treatment.
- Seven studies analysed quinolones versus aminoglycosides:
  - Asmatullah 2014 - ofloxacin versus gentamycin;
  - Fradis 1997 - ciprofloxacin versus tobramycin;
  - Jamalullah 2016 - ofloxacin versus gentamycin;
  - Kaygusuz 2002 - ciprofloxacin versus tobramycin;
  - Lorente 1995 - ciprofloxacin versus gentamycin;
  - Nawasreh 2001 - ciprofloxacin versus gentamicin;
  - Tutkun 1995 - ciprofloxacin versus gentamicin.
- Three studies analysed quinolones versus aminoglycosides/ polymixin B combination ± gramicidin:
  - Siddique 2016 - ciprofloxacin versus neomycin/polymixin/ gramicidin-D;
  - van Hasselt 1997 - ofloxacin versus neomycin/polymixin B;
  - van Hasselt 1998a - ofloxacin versus neomycin/polymixin B.
- Two studies analysed other antibiotics:
  - Gyde 1978 - aminoglycosides (gentamicin) versus trimethoprim, sulphacetamide and polymixin B (TSP);
  - Liu 2003 - rifampicin versus chloramphenicol.

Outcome

Resolution of ear discharge

The definitions, methods and timing of assessment differed between studies, and these are summarised in Table 4.

Health-related quality of life using a validated instrument

No studies reported health-related quality of life.

Ear pain (otalgia) or discomfort or local irritation

Four studies measured adverse effects associated with treatment: one described measuring local sensitivity (Gyde 1978), one specified symptoms further, examining ear pain, itching and stinging (measured on a four-point scale: 0 = none, 3 = severe) (Lorente 1995), whilst the other two broadly mentioned that this was measured in relation to the topical medication (Kasemsuwan 1997; Siddique 2016).

Hearing

Six studies indicated that they measured hearing pre- and post-treatment, however none of these provided details regarding the

methods used including whether air or bone conduction methods were used or the frequencies of testing (Fradis 1997; Gyde 1978; Kasemsuwan 1997; Nawasreh 2001; Tutkun 1995; van Hasselt 1997). All results were reported narratively.

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

Although 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 were not specifically listed in the methods as outcomes that would be recorded, three papers report that no side effects occurred in any participants, which would include the defined serious complications (Gyde 1978; Siddique 2016; Tutkun 1995).

Suspected ototoxicity

One study stated that they tested audiometric and vestibular function to measure suspected ototoxicity outcomes (Esposito 1990). Another study assessed suspected ototoxicity with an audiogram, although a specific definition was not stated, and reported that 0/125 suffered from ototoxicity associated with treatment (Ramos 2003). Three additional studies listed suspected ototoxicity as a potential outcome, but did not describe how it would be assessed (de Miguel 1999; Kasemsuwan 1997; Siddique 2016).

Excluded studies

We excluded 146 papers (150 papers including unpublished studies) (122 studies) after reviewing the full text. Further details for the reasons for exclusion can be found in the Characteristics of excluded studies table. These are the main reasons for the exclusion:

We excluded 40 studies (59 references, 63 including unpublished studies)) because the comparisons were not appropriate for this review, but were relevant to another review in this suite of reviews (Boesorire 2000; Browning 1988; Couzos 2003; Crowther 1991; Eason 1986; Esposito 1992; Fliss 1990; Gendeh 2001; Ghosh 2012; Gupta 2015; Helmi 2000; I-HEAR-BETA (in progress study); Indudharan 2005; Jaya 2003; Kiris 1998; Lazo Saenz 1999; Leach 2008; Legent 1994; Loock 2012; Macfadyen 2005; Minja 2006; Miro 2000; Nwokoye 2015; Onali 2018; Panchasara 2015; Papastavros 1989; Picozzi 1983; Picozzi 1984; Povedano 1995; Renukananda 2014; Rotimi 1990; Sanchez Gonzales 2001; Smith 1996; Somekh 2000; Subramaniam 2001; Tong 1996; van der Veen 2007; van Hasselt 1998b; Vishwakarma 2015; Yuen 1994).

We excluded 38 studies (39 references) on the basis of their study design (Baba 1986; Baba 2008; Bluestone 2001; Brook 1979; Brook 1980; Deguchi 1985; Deguchi 1986; Deitmer 2002; Dohar 2002; Esposito 2000; Gehanno 1997; Harris 2016; Hwang 2015; Jahn 1984; Jang 2004; Kadar 2003; Kashiwamura 2004; Kenna 1986; Kothari 1969; Kovacic 1999; Kurilin 1976; Lancaster 1999; Lancaster 2003; Lang 1992; Lautala 1983; Manolidis 2004; Merifield 1993; Morgon 1976; Otwombe 2003; Poliakova 1991; Singhal 1992; Sultan 2017; Sumitsawan 1995; Supiyaphun 1995; Tachibana 1986; Thomsen 1976; Wintermeyer 1997; Wright 2009).

We excluded 22 studies (24 references) due to the population characteristics included in their study (Abbott 2016; Alper 2000; Baba 1982b; Baba 1983; Baba 1983b; Baba 1987; Berman 1990; Block 2000; Bross Soriano 1996; Clayton 1990; Garcia-Rodriguez 1993; Granath 2007; Gyde 1981; Gyde 1982; Mendelman 1992; Mesure 1973; Principi 1995; Quick 1973; Quick 1975; Saez-Llorens 2005; Stenstrom 1991; van Dongen 2014).

We excluded 17 studies (18 references) because the interventions were outside of the protocol (Blekher 1967; Browning 1983; Connolly 1997; Dellamonica 1995; Fraysse 1988; ISRCTN12149720; ISRCTN84220089; ISRCTN86106121; Jiang 2016; Khanna 2000; Li 2004; Mora 2012; NCT02592096; NCT02817347; Shkil' 1964; Wilde 1995; Xu 1999).

Five studies (six references) had multiple reasons for exclusion (Baba 1980; Fombeur 1994; Hemlin 1997; Khon 2012; Lorentzen 1978).

Risk of bias in included studies

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

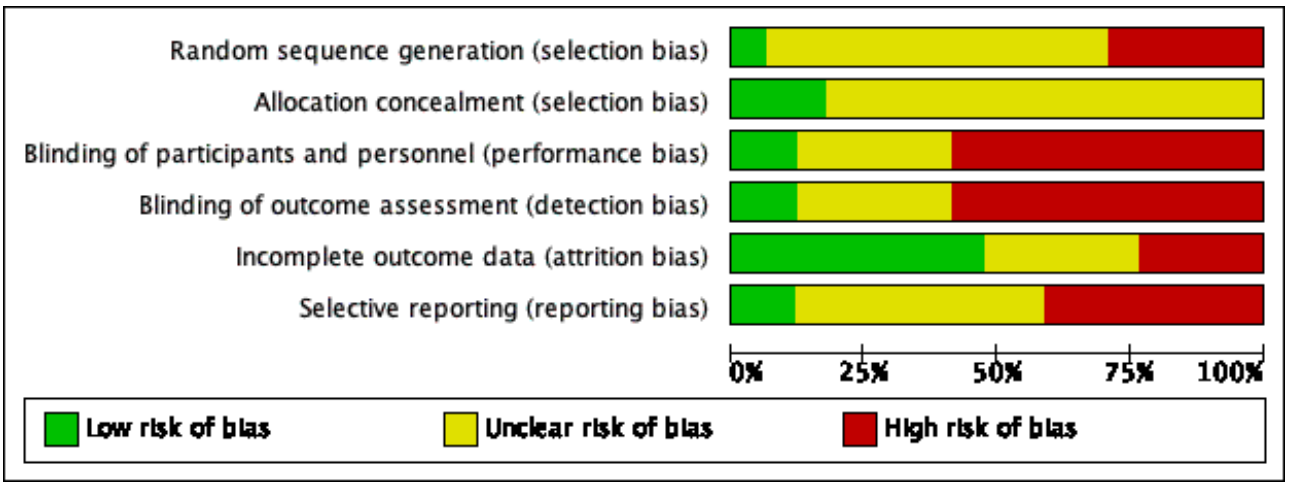


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

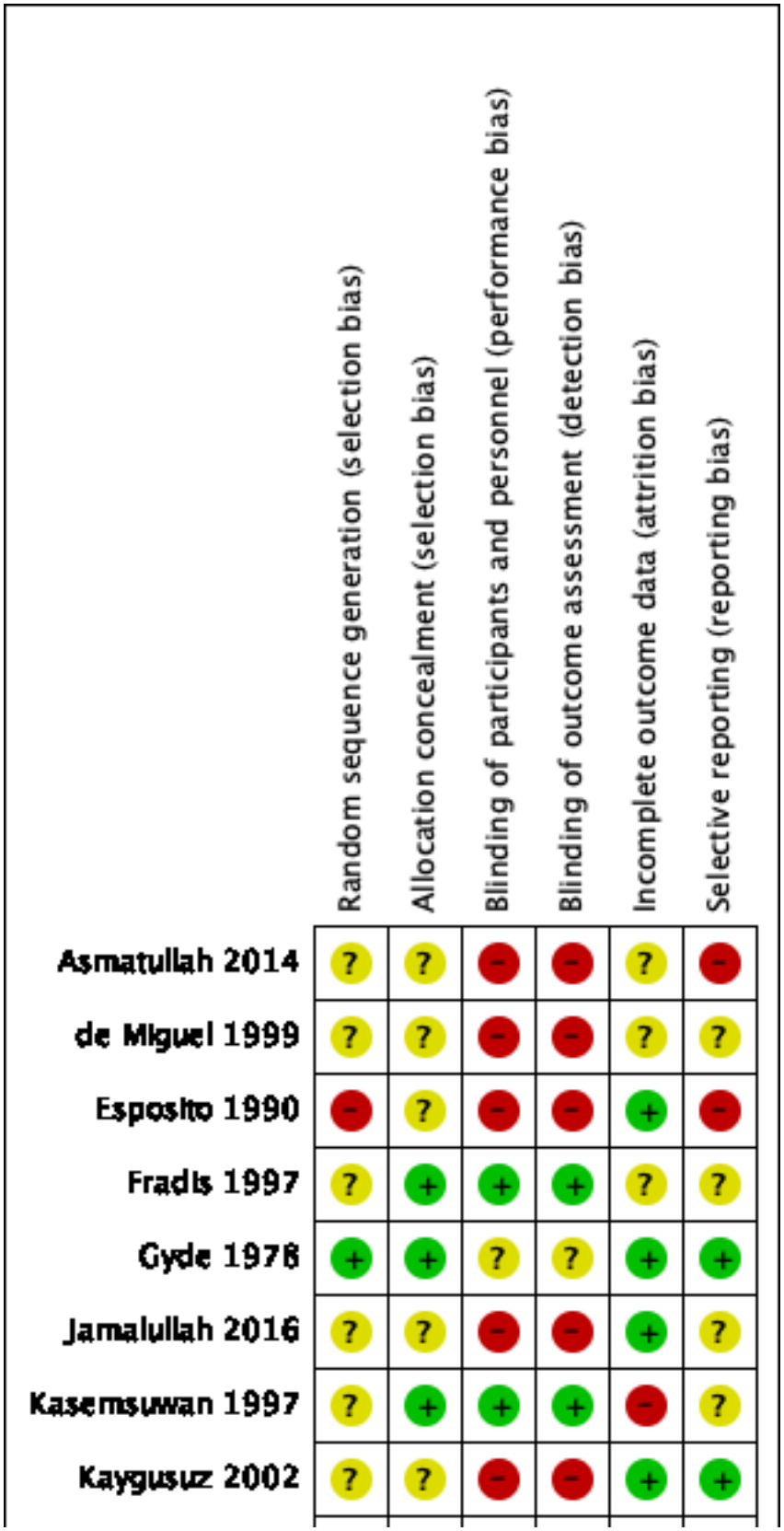
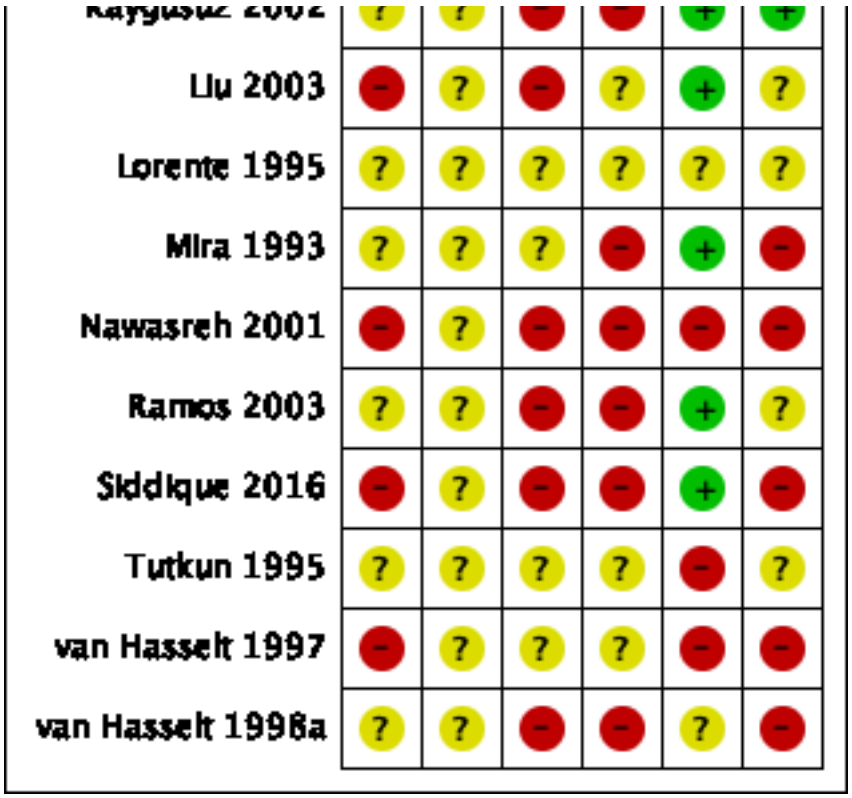


Figure 3. (Continued)



Allocation

Sequence generation

We assessed five studies to be at high risk of selection bias with regards to randomisation (Esposito 1990; Liu 2003; Nawasreh 2001; Siddique 2016; van Hasselt 1997). For Liu 2003, it is not clear whether or not the patients were randomised. Similarly for Siddique 2016 it was unclear what the actual process for the 'non-probability' sampling was and how to ensure that the allocation was random. Esposito 1990 did not clearly specify the randomisation method and while it was noted that 38/60 patients were previously unsuccessfully treated with at least five days of antibiotics, it was unclear how this was distributed across groups. The abstract for Nawasreh 2001 mentions that randomisation occurred but there was no mention of randomisation or methods for randomisation in the full paper, which only described patients as being "divided" between the two groups. It is unclear if the groups were evenly distributed as there was 40 in one group and 48 in the other, with baseline characteristics between the group not provided. The original report for van Hasselt 1997 indicates this was a "pilot trial", with no reference to blinding or randomisation. However, this was mentioned as a "randomised" trial in the introduction of a 2002 paper by the author. If randomisation was done, there was also no clear ratio for randomisation, with 46, 38 and 12 in the three treatment groups and the cheapest intervention having the most participants.

We assessed one study as low risk (Gyde 1978) and the remaining 11 studies as 'unclear risk' as they did not provide enough information (Asmatullah 2014; de Miguel 1999; Fradis 1997; Jamalullah 2016; Kasemsuwan 1997; Kaygusuz 2002; Lorente 1995; Mira 1993; Ramos 2003; Tutkun 1995; van Hasselt 1998a).

Allocation concealment

We assessed three studies to be at low risk of allocation concealment bias (Fradis 1997; Gyde 1978; Kasemsuwan 1997).

We assessed the remaining 14 studies as at unclear risk as they did not provide enough information with regards to allocation concealment (Asmatullah 2014; de Miguel 1999; Esposito 1990; Jamalullah 2016; Kaygusuz 2002; Liu 2003; Lorente 1995; Mira 1993; Nawasreh 2001; Ramos 2003; Siddique 2016; Tutkun 1995; van Hasselt 1997; van Hasselt 1998a).

Blinding

Performance bias

We assessed 11 studies as high risk for performance bias. Two were at high risk due to a lack of blinding for patients and healthcare practitioners even when it was possible to do (Asmatullah 2014; Jamalullah 2016). Seven were at high risk due to blinding being impossible because of the differences in treatment regimens/administration that mean it is likely to be known to which group they were allocated (de Miguel 1999; Esposito 1990; Liu 2003; Nawasreh 2001; Ramos 2003; Siddique 2016; van Hasselt 1998a). One study was at high risk due to the absence of a clear statement on blinding (Kaygusuz 2002), and one study did not provide details of who was blinded during the "single-blinded" study (Mira 1993). In this case we assumed that it was the patients who were blinded

to treatment, but as the main outcomes were physician-reported, blinding the patients would not have prevented performance bias. We assessed two studies as low risk because the used sufficient blinding methods (Fradis 1997; Kasemsuwan 1997), while four were at unclear risk due to lack of information (Gyde 1978; Lorente 1995; Tutkun 1995; van Hasselt 1997).

Detection bias

We assessed nine studies to be at high risk of bias. Four of these were due to the subjective nature of the judgement of outcomes (Asmatullah 2014; de Miguel 1999; Esposito 1990; Ramos 2003), whereas three did not mention any attempts to blind assessors even though it would have been feasible (Jamalullah 2016; Nawasreh 2001; Siddique 2016). One study stated that it was double-blind, although the treatment regimens were not the same and no placebo was used (Kaygusuz 2002). One study did not provide a clear statement on blinding (van Hasselt 1998a). We assessed two studies to be low risk because blinding appeared to be adequate to make detection unlikely (Fradis 1997; Kasemsuwan 1997). We assessed six studies as at unclear risk because there was no mention of blinding or further clarification was necessary but omitted (Gyde 1978; Liu 2003; Lorente 1995; Mira 1993; Tutkun 1995; van Hasselt 1997).

Incomplete outcome data

We assessed four studies to be at high risk of attrition bias (Kasemsuwan 1997; Nawasreh 2001; Tutkun 1995; van Hasselt 1997). Two of these were due to issues regarding participation, with high dropout rates - over 25% in the short time periods within the trials (Kasemsuwan 1997; van Hasselt 1997). It was also noted that Nawasreh 2001 and van Hasselt 1997 had an imbalance of participants between the allocation groups, which could have led to bias. We deemed one study to be at high risk due to a lack of clarity in the statement regarding exclusion of patients - whether this was part of the recruitment criteria or after randomisation (Tutkun 1995).

We assessed eight studies to be low risk, as all or more than 90% of participants appearing in the trial are accounted for in results (Esposito 1990; Gyde 1978; Jamalullah 2016; Kaygusuz 2002; Liu 2003; Mira 1993; Ramos 2003; Siddique 2016). We assessed a further five studies as having unclear risk due to lack of a statement or reasoning (Asmatullah 2014; de Miguel 1999; Fradis 1997; Lorente 1995; van Hasselt 1998a).

Selective reporting

None of the 17 studies had protocols identified through searches of clinical trials registries.

We assessed seven studies to be at high risk of selective reporting bias: three of these studies were due to the methods section not being well presented (Asmatullah 2014; Mira 1993; Nawasreh 2001), three were due to discrepancies in time point outcome reporting (Esposito 1990; Siddique 2016; van Hasselt 1997), and one was due to the study not being published, making it difficult to evaluate the methods fully (van Hasselt 1998a).

We assessed two studies as low risk due to adequate outcome reporting between the methods and results, however no protocols were found (Gyde 1978; Kaygusuz 2002). We assessed the remaining eight studies as having unclear risk of selective reporting (de Miguel 1999; Fradis 1997; Jamalullah 2016; Kasemsuwan 1997; Liu 2003; Lorente 1995; Ramos 2003; Tutkun 1995).

Other potential sources of bias

Funding

Esposito 1990 stated that "the ciprofloxacin tablets and powder used in this study were kindly provided by Bayer Italia Spa, Milan, Italy." Although it was not stated, we assumed one study to have funding from the Christian Blind Mission, as other studies by the same authors were funded through this avenue (van Hasselt 1997). One study specifically stated that "no funding was received from any agency or institution" (Siddique 2016), while the remaining 14 studies provided no information (Asmatullah 2014; de Miguel 1999; Fradis 1997; Gyde 1978; Jamalullah 2016; Kasemsuwan 1997; Kaygusuz 2002; Liu 2003; Lorente 1995; Mira 1993; Nawasreh 2001; Ramos 2003; Tutkun 1995; van Hasselt 1998a).

Declarations of interest

Siddique 2016 stated that "[the] abstract and results of this study were accepted and presented in an oral presentation at the International conference on Medical Education, organised by Association for Excellence in Medical Education (AEME) and held on 07th-09th March 2014 at University of Health Sciences (UHS) Lahore, Pakistan." The remaining studies did not provide any information about conflicts of interest (Asmatullah 2014; de Miguel 1999; Esposito 1990; Fradis 1997; Gyde 1978; Jamalullah 2016; Kasemsuwan 1997; Kaygusuz 2002; Liu 2003; Lorente 1995; Mira 1993; Nawasreh 2001; Ramos 2003; Tutkun 1995; van Hasselt 1997; van Hasselt 1998a).

Effects of interventions

See: **Summary of findings for the main comparison** Topical antibiotics versus placebo/no treatment for chronic suppurative otitis media; **Summary of findings 2** Topical antibiotics on top of systemic antibiotics for chronic suppurative otitis media; **Summary of findings 3** Quinolones versus aminoglycosides for chronic suppurative otitis media

Comparison 1: Topical antibiotics versus placebo or no treatment

One study was included in this comparison: Kasemsuwan 1997 (50 participants), which compared topical ciprofloxacin to saline. See also Summary of findings for the main comparison.

Primary outcomes

Resolution of ear discharge or 'dry ear'

Between one week and up to two weeks

Kasemsuwan 1997 identified that topical antibiotics appeared to be more effective than saline at one to two weeks follow-up (risk ratio (RR) 6.74, 95% confidence interval (CI) 1.82 to 24.99; 35 participants; very low-certainty evidence; Analysis 1.1).

Two weeks to up to four weeks and after four weeks

The study did not report the results per person for this outcome at between two to four weeks or after four weeks.

Health-related quality of life using a validated instrument

This outcome was not reported.

Ear pain (otalgia) or discomfort or local irritation

Kasemsuwan 1997 reports that "no medical side-effects and worsening of audiological measurements related to this topical medication were detected" (very low-certainty evidence).

Secondary outcomes

Hearing

Kasemsuwan 1997 reported "no worsening of audiological outcomes", but specific information relating to hearing levels was not presented (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

Kasemsuwan 1997 reported "no suspected ototoxicity" but it is unclear how this was measured.

Subgroup analysis

With only one study included in the quantitative analysis, subgroup analysis was not possible (very low-certainty evidence).

Comparison 2: Topical antibiotics versus placebo or no treatment (with systemic antibiotics as background treatment)

Four studies (190 participants) were included in this comparison, three of which compared treatment with topical ciprofloxacin drops and systemic ciprofloxacin to systemic ciprofloxacin only (de Miguel 1999; Esposito 1990; Ramos 2003). The remaining study, Mira 1993 (248 participants), compared topical ceftizoxime to placebo ear drops (saline) for seven days with all participants in both treatment arms received intravenous ceftizoxime. None of the primary or secondary outcomes were reported. Two of the studies had reported exactly the same percentages of "cure" across all but one of the intervention arms of the studies (de Miguel 1999; Ramos 2003). We had concerns that these could have been the same set of patients, but the authors clarified that these were entirely different patients (and studies). See Summary of findings 2 for the main comparison.

Primary outcomes

Resolution of ear discharge or 'dry ear'

Between one week and up to two weeks

Ramos 2003 and de Miguel 1999 found that topical and systemic antibiotics resulted in more dry ears compared to the systemic antibiotics only group (RR 1.47, 95% CI 1.20 to 1.80; 150 participants; 2 studies; I^2 = 0%; low-certainty evidence; Analysis 2.1).

Two weeks to up to four weeks

Esposito 1990 found that topical and systemic antibiotics resulted in more dry ears compared to the systemic antibiotics only group (RR 1.88, 95% CI 1.04 to 3.39; 40 participants; Analysis 2.1).

After four weeks

No studies measured the results at this time point.

Health-related quality of life using a validated instrument

None of the studies measured this outcome.

Ear pain (otalgia) or discomfort or local irritation

None of the studies measured this outcome although one study reported that "no side effect was recorded in any patient..." (Esposito 1990).

Secondary outcomes

Hearing

Although three studies reported hearing as an outcome in their methods section (de Miguel 1999; Esposito 1990; Ramos 2003), none of the studies reported results for 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

Three studies reported that they did not suspect ototoxicity in any participants, but it is unclear how this was measured (de Miguel 1999; Esposito 1990; Ramos 2003) (very low-certainty evidence).

de Miguel 1999 reported that the data did not show cochleovestibular dysfunction during treatment or further follow-up. They also stated that all post-treatment audiometries showed a lack of antimicrobial ototoxicity, both for oral and topical routes. However, there was no definition of 'ototoxicity' provided and it may be that they only measured air conduction audiological thresholds rather than bone conduction thresholds as well.

Esposito 1990 stated that "no side effect was recorded in any patient and no worsening of the audiometric function related to the local therapy was observed". Audiometric measurement and vestibular tests were performed before and 24 hours after the end of the therapy in patients receiving topical treatment only.

Ramos 2003 reported a lack of symptoms suggesting vestibular problems, but did not provide details on how this was measured or defined.

Subgroup analysis

No subgroup analysis was completed as there were no differences in any of the identified subgroups.

- High-risk populations - none of the studies reported high-risk populations as defined in our methods.
- Patients with ventilation tubes - none of the studies reported the inclusion of patients with ventilation tubes.
- Diagnosis of CSOM - most of the studies included mixed populations of CSOM along with ear discharge from other causes.
- Duration of ear discharge - only one study reported the duration of discharge.
- Patient age - none of the studies included participants younger than two years of age. Although two studies included children from five years old stratification by age does not appear to have taken place (de Miguel 1999; Ramos 2003).

Comparison 3: Quinolones versus aminoglycosides

Seven studies (734 participants) were included in this comparison (Asmatullah 2014; Fradis 1997; Jamalullah 2016; Kaygusuz 2002; Lorente 1995; Nawasreh 2001; Tutkun 1995). For details of the interventions and comparisons see Table 3. See also Summary of findings 3.

Primary outcome

Resolution of ear discharge or 'dry ear'

Between one week and up to two weeks

Six studies (694 participants) reported this outcome and found that more participants given topical quinolones had resolution of ear discharge at between one to two weeks compared with topical aminoglycosides (RR 1.95, 95% CI 0.88 to 4.29; 694 participants; 6 studies; I^2 = 97%; very low-certainty evidence; Analysis 3.1). However, we noted that the heterogeneity was very high. This was driven by the largest study (Lorente 1995), which had an extremely high resolution rate in both arms: 95% and 94% in the quinolone and aminoglycoside arms respectively compared with an average of 75% and 34% in the quinolone and aminoglycoside arms in the remaining studies. After an investigation of the study details, it was not possible to identify why the results were so different, and so we kept the study in the analysis and used a random-effects model.

Two weeks to up to four weeks

Kaygusuz 2002 found no difference between topical and quinolones compared to aminoglycosides (RR 1.88, 95% CI 1.04 to 3.39; 40 participants; Analysis 3.2).

After four weeks

No studies reported the results per person for this outcome.

Health-related quality of life using a validated instrument

None of the studies measured this outcome.

Ear pain (otalgia) or discomfort or local irritation

Lorente 1995 (308 participants) measured ear pain on a three-point scale. Results were presented as a mean score. No differences between the two groups were identified (very low-certainty evidence).

Secondary outcomes

Hearing

Tutkun 1995 (44 participants) presented mean air and bone conduction hearing levels at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz pre- and post-treatment by treatment group. No standard deviations were presented although the authors assert that "the difference between these two groups was not statistically significant (p>0.01)". Nawasreh 2001 (88 participants) stated that hearing was measured and that neither group showed significant differences. This evidence is of very low certainty.

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

Two studies reported that they had assessed patients for suspected ototoxicity (Lorente 1995; Tutkun 1995). Whilst Lorente 1995 did not present any results, Tutkun 1995 indicated that "There were no side effects, and audiometric evaluation yielded no evidence of ototoxicity as reflected by the pure tone threshold and speech discrimination scores in either group" (very low-certainty evidence).

Subgroup analysis

With the exception of type of antibiotic, no subgroup analysis could be completed:

- High-risk populations - none of the studies reported the inclusion of high-risk populations as defined in our methods.
- Patients with ventilation tubes - none of the studies reported the inclusion of patients with ventilation tubes.
- Diagnosis of CSOM - all of the studies reported patients with 'CSOM'.
- Duration of ear discharge - where given the duration of ear discharge at the start of the study was between three months and two years. There were no studies using a two-week or six-week criteria.
- Patient age - where given, the youngest patients included were nine years of age and no studies stratified participants by age.

Comparison 4: Quinolones versus aminoglycosides/polymixin B ± gramicidin

Three studies were included in this comparison (van Hasselt 1997 (50 participants), van Hasselt 1998a (unclear number of participants) and Siddique 2016 (200 participants)). van Hasselt 1997 and van Hasselt 1998a both compared topical ofloxacin to topical neomycin/polymyxin B, however the unit of randomisation was unclear in both studies and therefore only Siddique 2016, which compared topical ciprofloxacin to topical neomycin/polymixin B and gramicidin, could be included in the analysis.

Primary outcomes

Resolution of ear discharge or 'dry ear'

Between one week and up to two weeks

No studies reported this outcome.

Two weeks to up to four weeks

Siddique 2016 found that treatment marginally favoured the topical quinolones compared to neomycin/polymyxin B and gramicidin for resolution of discharge (RR 1.12, 95% CI 1.03 to 1.22) at two to four weeks (Analysis 3.2).

After four weeks

No studies reported the results per person for this outcome.

Health-related quality of life using a validated instrument

None of the studies measured this outcome.

Ear pain (otalgia) or discomfort or local irritation

A "few" patients experienced local irritation upon the first instillation of topical treatment. No information was given regarding the number or treatment arm of the participants.

Secondary outcomes

Hearing

None of the studies measured 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

None of the studies measured this outcome.

Subgroup analysis

With only one study included in the quantitative analysis, subgroup analysis was not possible.

Comparison 5: Aminoglycosides versus trimethoprim, sulphacetamide and polymyxin B (TSP)

One study was included in this comparison: Gyde 1978 (91 participants) compared a topical aminoglycoside to topical trimethoprim, sulphacetamide and polymyxin B. Participants were randomised by ear and there was no adjustment for the paired nature of this data. Whilst resolution of discharge was assessed at two to four weeks there was no extractable efficacy data.

Primary outcomes

Resolution of ear discharge or 'dry ear'

Between one week and up to two weeks

The study did not report this outcome.

Two weeks to up to four weeks

There were no extractable efficacy data.

After four weeks

The study did not report the results per person for this outcome.

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 reported no signs of local sensitivity or fungal proliferation.

Secondary outcomes

Hearing

The study did not measure this outcome.

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

No side effects were reported.

Suspected ototoxicity

The study reported no signs of ototoxicity. It is unclear how this outcome was measured.

Subgroup analysis

With only one study included in the quantitative analysis, subgroup analysis was not possible.

Comparison 6: Rifampicin versus chloramphenicol

One study was included in this comparison: Liu 2003 (160 participants) compared topical rifampicin to topical chloramphenicol. While resolution of discharge was assessed at one to two weeks there were no extractable efficacy data.

Primary outcomes

Resolution of ear discharge or 'dry ear'

Between one week and up to two weeks

Liu 2003 found that rifampicin resulted in more dry ears compared to chloramphenicol (RR 1.78, 95% CI 1.35 to 2.34) (Analysis 4.1).

Two weeks to up to four weeks

The study did not measure this outcome.

After four weeks

The study did not measure this outcome.

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 reported no signs of local sensitivity or fungal proliferation.

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 reported no signs of ototoxicity. It is unclear how this outcome was measured.

Subgroup analysis

With only one study included in the quantitative analysis, subgroup analysis was not possible.

DISCUSSION

Summary of main results

We found 17 studies reporting on six different comparisons (Asmatullah 2014; de Miguel 1999; Esposito 1990; Fradis 1997; Gyde 1978; Jamalullah 2016; Kasemsuwan 1997; Kaygusuz 2002; Liu 2003; Lorente 1995; Mira 1993; Nawasreh 2001; Ramos 2003; Siddique 2016; Tutkun 1995; van Hasselt 1997; van Hasselt 1998a). Due to the choice of outcome measures used in these studies and the incomplete reporting of results, for many of the comparisons we were not able to find a substantial amount of evidence. Of the

17 studies, one examined the effectiveness of topical antibiotics compared to no treatment (Comparison 1), four examined topical antibiotics compared to no treatment with systemic antibiotics as a background treatment (Comparison 2), and 12 studies directly compared different topical antibiotics (Comparisons 3 to 6).

The following is a summary of the key findings for the comparisons:

Comparison 1: Topical antibiotics versus placebo or no treatment (without background treatment)

We included one study examining topical antibiotics versus no treatment, with no background treatment (Kasemsuwan 1997; 50 participants). This study compared ciprofloxacin drops to saline with resolution of discharge measured at one to two weeks. It was unclear if the resolution of discharge was otoscopically confirmed. Topical antibiotics appeared to be more effective than saline (risk ratio (RR) 6.74, 95% confidence interval (CI) 1.82 to 24.99). However, this study was too small to provide any certainty of the findings (GRADE assessment: very low-certainty evidence). No adverse events, suspected ototoxicity or worsening of audiological measurements were reported and the other outcomes were either not measured or not reported. See Summary of findings for the main comparison for the comparison.

Comparison 2: Topical antibiotics versus placebo or no treatment (with background treatment)

We included two studies examining topical antibiotics versus no treatment, with background treatment (de Miguel 1999; Esposito 1990; 90 participants). Both compared treatment with topical ciprofloxacin drops and systemic ciprofloxacin to systemic ciprofloxacin only. Only one study reported that the resolution of discharge was otoscopically confirmed (de Miguel 1999). Resolution of discharge was measured at one to two weeks and two to four weeks. Treatment marginally favoured the topical and systemic antibiotics group compared to the systemic antibiotics only group for resolution of discharge (RR 1.47, 95% CI 1.20 to 1.80 at one to two weeks and RR 1.88. 95% CI 1.04 to 3.39 at two to four weeks). These studies were too small to provide any certainty of the findings (GRADE assessment: low-certainty evidence). The other outcomes were either not measured or poorly reported. See Summary of findings 2 for the comparison.

Comparison 3: Aminoglycoside versus quinolones

We found seven studies (Asmatullah 2014; Fradis 1997; Jamalullah 2016; Kaygusuz 2002; Lorente 1995; Nawasreh 2001; Tutkun 1995; 734 participants). Five studies used the quinolone ciprofloxacin (Fradis 1997; Kaygusuz 2002; Lorente 1995; Nawasreh 2001; Tutkun 1995). The studies used varying dosages of six (Kaygusuz 2002) or 15 (Fradis 1997; Lorente 1995; Nawasreh 2001; Tutkun 1995) drops per day, and variable concentrations including 0.3% (Kaygusuz 2002; Lorente 1995) and 0.6%, 200 µg/mL (Nawasreh 2001; Tutkun 1995), or did not report the concentration (Fradis 1997). Two studies used the quinolone ofloxacin (Asmatullah 2014; Jamalullah 2016). Both studies had the same dosage of 12 drops per day, whilst Jamalullah 2016 used a 0.6% concentration and Asmatullah 2014 used a 0.3% concentration. Five studies reported that the resolution of discharge was otoscopically confirmed (Asmatullah 2014; Jamalullah 2016; Kaygusuz 2002; Lorente 1995; Tutkun 1995).

We found that resolution of discharge at one to two weeks was almost twice as likely in the quinolones group, although this was not statistically significant (GRADE assessment: very low-certainty evidence). See Summary of findings 3 for the comparison.

Tutkun 1995 (44 participants) presented mean air and bone conduction hearing levels at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz pre- and post-treatment by treatment group. No standard deviations were presented although the authors assert that "the difference between these two groups was not statistically significant (p>0.01)". Nawasreh 2001 (88 participants) stated that hearing was measured and that neither group showed significant differences. Lorente 1995 (308 participants) measured ear pain on a three-point scale. Results were presented as a mean score. There was no difference in hearing levels between the groups.

Comparison 4: Quinolones versus aminoglycosides/polymixin B ± gramicidin

We found three studies for this comparison (van Hasselt 1997 (50 participants); van Hasselt 1998a (unknown number of participants); Siddique 2016 (186 participants). Both van Hasselt 1997 and van Hasselt 1998a used ofloxacin at 0.3% with dosages of three drops per eight hours and six drops per 12 hours respectively and compared this to a combination of neomycin and polymixin B of varying or unclear concentration and dosages. None of the studies reported that the resolution of discharge was otoscopically confirmed. Treatment duration was two weeks for both studies. Siddique 2016 compared ciprofloxacin of unknown concentration with a dosage of three drops per 12 hours with neomycin and polymixin B with gramicidin D of unknown concentration with a dosage of two drops per 12 hours. Treatment duration was unclear but likely lasted four weeks.

Only Siddique 2016 reported resolution of discharge and this was at four weeks post-treatment. More patients experienced resolution of discharge with quinolones at four weeks compared with neomycin and polymixin B with gramicidin D (RR 1.12, 95% CI 1.03 to 1.22).

Comparison 5: Aminoglycosides versus trimethoprim sulphacetamide and polymyxin B

We included only one study examining topical aminoglycosides (gentamicin) versus a combination of trimethoprim sulphacetamide and polymyxin B (Gyde 1978; 91 participants, 100 ears). The study was translated from French and 51% of participants had CSOM (other diagnoses were otitis externa (21%), 'subacute otitis' (16%) and postoperative discharge (12%)). It was not reported whether the resolution of discharge was otoscopically confirmed. Participants were randomised by ear, with no adjustment for the paired nature of the data. Whilst resolution of discharge was assessed at two to four weeks there were no extractable efficacy data.

The study authors reported no signs of ototoxicity, excessive fungal proliferation or any local sensitivity to the ear drops. Health-related quality of life, hearing level and serious complications were not reported.

Comparison 6: Rifampicin versus chloramphenicol

We found one study examining this comparison (Liu 2003; 160 participants), which was translated from Chinese. This study compared topical rifampicin (0.1%, nine drops per day, treatment duration of two weeks) with topical chloramphenicol (0.25%, nine

drops per day, treatment duration of two weeks) with a background treatment of 3% hydrogen peroxide ear wash daily in both arms. It was not reported whether the resolution of discharge was otoscopically confirmed. Topical rifampicin appeared to be more effective than chloramphenicol for resolving ear discharge one to two weeks after completion of treatment (RR 1.78, 95% CI 1.35 to 2.34). However, this study was too small to provide any certainty of the findings (GRADE assessment: very low-certainty evidence). No adverse events, suspected ototoxicity or worsening of audiological measurements were reported and the other outcomes were either not measured or not reported.

Overall completeness and applicability of evidence

The doses used in the studies were in keeping with manufacturers' recommendations and are applicable to the population being studied. The population of patients with CSOM are likely to receive treatment in both primary and secondary care settings.

Whilst the inclusion criteria was ear discharge for more than two weeks, reflecting the World Health Organization (WHO) guidelines for CSOM diagnosis, the majority of studies included patients who had ear discharge for more than six weeks before intervention, which is in keeping with a number of local treatment protocols and the practice of many tertiary-based otolaryngologists. The length of follow-up in most studies was between one to four weeks, meaning that there was limited evidence regarding the long-term effectiveness of topical antibiotics for the resolution of discharge for people with CSOM.

No studies examined children under two years of age. As the peak prevalence of otitis media is in children under two years of age this leaves us with no information on this important patient group. Similarly, no studies included participants classed as 'high-risk' in our protocol, including Indigenous populations and immunocompromised patients. Patients in these high-risk groups can be a challenge for clinicians to treat effectively and evidence to support best-practice interventions for these people is needed. The effectiveness of topical antibiotics is likely to be influenced by the sensitivity of the antibiotic to the micro-organisms present. We were unable to carry out a subgroup analysis of the spectrum of antibiotic activity as the data were either not in the included studies or heterogeneity was not observed, which leaves us with no information on this aspect of antibiotic treatment.

Disease-specific health-related quality of life, which is both specific to the disease and important to patients, was not used in the included studies as an outcome measure. There is therefore no information at all on whether the different types of antibiotics used have an impact on patients' quality of life.

Quality of the evidence

The certainty of the evidence for all outcomes in these comparisons was very low (GRADE assessment), due to the small number of participants available for analysis (resulting in large confidence intervals) and limitations in the methods of study conduct and reporting. Accuracy of the diagnosis was also a potential issue throughout the studies included in this review. Of the 17 included studies, only six described the use of otoscopic confirmation of resolution of discharge. This may have impacted on the accuracy of the diagnostic outcome and therefore the response to treatment.

Potential biases in the review process

In most cases the studies did not report enough information for us to further analyse the results. We have had to take readings from graphs using a digital graph reader and impute standard deviations based on the P values reported. They were often only reported as 'P value < 0.05' or 'P value < 0.01' in comparisons where the studies found statistical significance. Our imputations are based on these values (using P value = 0.01 or P value = 0.05) and we are therefore conservative in our estimation of the standard deviations. However, this lack of information about non-significant results could have prevented us from drawing more conclusive results about the lack of difference between groups.

Agreements and disagreements with other studies or reviews

This review is part of a series of reviews on CSOM (Bhutta 2018; Brennan-Jones 2018a; Brennan-Jones 2018b; Chong 2018a; Chong 2018b; Head 2018a; Head 2018b). A companion review looks at the effectiveness of topical antibiotics with steroids for the treatment of CSOM (Brennan-Jones 2018a).

There are few previous reviews or guidelines for CSOM. The 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 Otolaryngologists in 2000 came to a similar conclusion (Hannley 2000).

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

Although we planned subgroup analyses for different participant characteristics (age, high-risk, ventilation tubes), treatment duration and spectrum of antibiotic activity these were not carried out either because the data were not available or heterogeneity was not observed.

AUTHORS' CONCLUSIONS

Implications for practice

We are uncertain about the effectiveness of topical antibiotics (without steroids) in improving resolution of ear discharge in patients with chronic suppurative otitis media (CSOM) because of the limited amount of low-quality evidence available. However, amongst this uncertainty there is some evidence to suggest that the use of topical antibiotics (without steroids) may be effective when compared to placebo, or when used in addition to a systemic antibiotic. There is also uncertainty about the relative effectiveness of different types of antibiotics; it is not possible to determine with any certainty whether or not quinolones are better or worse than aminoglycosides. These two groups of compounds have different adverse effect profiles, but there is insufficient evidence from the included studies to make any comment about these. In general, adverse effects were poorly reported.

Implications for research

The results of this review, current to April 2019, show that there is very low-certainty evidence that, for people with CSOM, treatment with topical antibiotics (without steroids) may be beneficial in improving the short-term resolution of ear discharge when compared to placebo, or when used in addition to a systemic antibiotic. The low certainty of the 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 topical antibiotics (without steroids) for high-risk groups such as immunocompromised patients or Indigenous populations. Potential adverse effects and hearing outcomes were poorly reported and the impact of background treatment with aural toileting and/or systemic antibiotics is also unclear.

Prior to commencing these reviews, we conducted a scoping review that identified three key questions that clinicians, researchers and consumers would like to see answered:

- Are topical antibiotics effective when added to other interventions (e.g. aural toileting, systematic antibiotics)?
- Which topical antibiotic is more effective (when compared to each other)?
- Which type of topical antibiotic is more effective when added to other interventions?

Due to the low certainty of the available evidence these questions cannot yet be addressed with any certainty. There is clearly room for more trials examining the impact of topical antibiotics for people with CSOM, including trials that assess the class of antibiotic and the dosing/duration. Whilst the largest number of studies compared the use of topical quinolones to topical aminoglycosides, the certainty of the evidence is still very low (GRADE) for this comparison.

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.

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 they 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 a 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 World Health Organization (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 for CSOM, using established methods (Kirkham 2017), 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 trials 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]*

Asmatullah 2014

Methods	Two-arm, non-blinded, parallel-group RCT, with 10 days duration of treatment and 2-week duration of follow-up

Participants	**Location:** Pakistan, 1 site
	
	Setting of recruitment and treatment: ENT Department, Hayatabad Medical Complex, Peshawar, January to July 2012
	
	Sample size: 134
	
	• **Number randomised:** 67 in gentamycin, 67 in ofloxacin
	• **Number completed:** 67 in gentamycin, 67 in ofloxacin
	
	Participant (baseline) characteristics:
	
	• Age: gentamycin: 27.57 ± 9.16 years; ofloxacin: 27.76 ± 7.25 years
	• Gender (F/M): 54 (40.3%)/80 (59.7%)
	• Main diagnosis: active tubotympanic type of CSOM
	• 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: unclear
	  * Presence of mucopurulent discharge: not reported
	  * At baseline
	  ☐ 'Severe' otorrhoea: gentamycin: 62.7%, ofloxacin: 70.2%
	  ☐ 'Moderate' otorrhoea: gentamycin: 37.3%, ofloxacin: 29.8%
	  * 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 (mastoid surgery was an exclusion criterion)
	  * Number who had previous antibiotic treatment for CSOM: not reported (these were excluded if 2 weeks prior to trial)
	
	Inclusion criteria:
	
	• Patients above 16 years of any gender having active tubotympanic type of chronic suppurative otitis media
	
	Exclusion criteria:

Asmatullah 2014 *(Continued)*

- Antibiotics in the last 2 weeks
- Those with marginal perforation
- Cholesteatoma
- Aural polyps
- History of mastoid surgery

Interventions	**Intervention (n = 67):** gentamycin 0.3% ear drops, 4 drops 3 times daily, treatment continued for 10 days **Comparator group (n = 67)**: ofloxacin 0.3% ear drops, 4 drops 3 times daily, treatment continued for 10 days **Concurrent treatment:** none listed. No aural toileting methods mentioned.
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge, measured at between 1 week to 2 weeks. Otoscopically confirmed. **Secondary outcomes:** • Not reported
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "All patients were allocated into two groups by randomization done by lottery method." Comment: not enough information to know whether this method was sufficient to generate a sufficiently randomised sequence
Allocation concealment (selection bias)	Unclear risk	Comment: no methods regarding allocation concealment were reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: there is no mention of blinding for any of the outcomes despite the ability to blind the trial (same treatment regimen)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: there is no mention of blinding the treatment outcome. There may have been bias when judging the marginal cases such as the boundary between 'mild' and 'no' discharge.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the description of patient allocation is not clear within the paper. Although the paper does not appear to have lost patients to follow-up, there is no clear statement of this. It is unclear whether only patients included in the outcome were reported.

Asmatullah 2014 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no trial protocol was mentioned in the paper or found on the clinicaltrials.gov website. The levels of discharge were not well defined in the methods section. In addition, there was no defined measuring or indeed mention of adverse events anywhere within the paper.

de Miguel 1999

Methods	Five-arm, non-blinded, parallel-group RCT, with 7-day duration of treatment and 15-day duration of follow-up

Participants	**Location:** Canary Islands, Spain
	
	Setting of recruitment and treatment: general hospital, published in 1999
	
	Sample size: 125
	
	• **Number randomised:** 25 in group A, 25 in group B, 25 in group C, 25 in group D, 25 in group E
	• **Number completed:** 25 in group A, 25 in group B, 25 in group C, 25 in group D, 25 in group E
	
	Participant (baseline) characteristics:
	
	• Age (mean, range): 39.6 years, 6 to 83, but 17/25 of participants were children
	• Gender (F/M): 56 (44.8%)/69 (55.2%)
	• Main diagnosis: chronic otitis media, which comprised of the following groups:
	  * Simple chronic otitis media: no osteitic changes, tympanosclerosis or cholesteatoma (n = 45)
	  * Osteitic chronic otitis media: with changes to the ossicular chain and some permanent alterations in the mucosa (tympanosclerosis or chronic granulomatosis) (n = 32)
	  * Cholesteatomatous chronic otitis media (n = 17)
	  * Post-surgery cases (n = 31)
	• 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 – all patients had otoscopy under microscopy at entry. 51.2% had non-marginal tympanic perforation. The involvement of the ossicular chain in the otological microscopic examination was found in 43.2% of the patients.
	  • Presence of mucopurulent discharge: yes, 113/125 (90.4%), 89/125 (71.2%) with odorous discharge
	  • Duration of symptoms (discharge): not reported
	• Other important effect modifiers:
	  • Alternative diagnosis of ear discharge: cholesteatoma, n = 17, patients with discharge after operation, n = 31 unclear type/reason for operations
	  • Number who have previously had grommets inserted: not reported
	  • Number who have had previous ear surgery: at least 31/125 (24.8%) - reasons and type of surgery not reported
	  • Number who had previous antibiotic treatment for CSOM: 79/125 (63.2%)
	
	Inclusion criteria:
	
	• Patients (adults and children) with chronic otitis media, presenting with chronic otorrhoea as major symptom. Diagnostic criteria not reported.
	
	Exclusion criteria:

de Miguel 1999 *(Continued)*

	• Not reported
Interventions	**Group A (n = 25):** oral ciprofloxacin, 500 mg/12 hours for 7 days **Group B (n = 25):** topical ciprofloxacin 0.2%, 3 eardrops/8 hours for 7 days **Group C (n = 25):** topical ciprofloxacin 0.5%, 3 eardrops/8 hours for 7 days **Group D (n = 25):** topical ciprofloxacin 0.2%, 3 eardrops/8 hours for 7 days PLUS oral ciprofloxacin, 500 mg/12 hours for 7 days simultaneously **Group E (n = 25):** topical polymixin B + neomycin + hydrocortisone, 3 eardrops/8 hours for 7 days **Concurrent treatment:** all patients had aspiration and cleaning of ear secretions before beginning treatment. Analgesics and antipyretics.
Outcomes	**Outcomes of interest in the review:** **Primary outcome:** • Resolution of ear discharge at 1 to 2 weeks. Unclear if otoscopically confirmed. **Secondary outcomes:** • Hearing: hearing tests at time of diagnosis, at 8 days and at 15 days • Suspected ototoxicity
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "125 patients were analysed for two years attending to health system with chronic otorrhea as the mean symptom." Comment: insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized to five therapeutic groups." Comment: insufficient information about allocation concealment method provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information provided about blinding method or use of placebo. The treatment arms involved different dosage forms (oral versus ear drops) – blinding of these interventions is impossible without the use of a placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information provided regarding to who assessed the outcomes. For subjective outcomes (otoscopy examinations, hearing test or adverse events) is probable that the knowledge of treatment group influenced the results
Incomplete outcome data (attrition bias)	Unclear risk	Comment: no dropouts or missing data reported; no statements about missing data

de Miguel 1999 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information to permit judgement of 'low-risk' or 'high-risk'. Protocol for trial not available.

Esposito 1990

Methods	Three-arm, non-blinded, single-centre, parallel-group RCT, with 5 to 10 days of treatment and 24 hours and 14 days follow-up after end of treatment

Participants	**Location:** Naples, Italy
	
	Setting of recruitment and treatment: Clinic of Infectious Diseases and Otolaryngology, University of Naples
	
	Sample size: 60
	
	• **Number randomised:** 20 in each intervention
	• **Number completed:** 20 in each intervention
	
	Participant (baseline) characteristics:
	
	• Age: mean 38 years
	• Gender (F/M): 29 (48%)/31 (52%)
	• Main diagnosis: mild or moderate CSOM in the acute stage
	• High-risk population:
	  * Cleft palate (or other craniofacial malformation): not reported
	  * Down syndrome: not reported
	  * Indigenous groups (Australian Aboriginals/Greenland natives): not reported
	  * Immunocompromised: "no patients had diabetes or any other comorbidities"
	• Diagnosis method:
	  * Confirmation of perforated tympanic membrane: not reported
	  * 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: 38/60 (63%) had at least 5 days of antibiotics and did not respond
	
	Inclusion criteria:
	
	• Mild to moderate CSOM in acute stage without cholesteatoma or mastoiditis
	
	Exclusion criteria:
	
	• Younger than 18 years old

Interventions	**Topical plus systemic ciprofloxacin (n = 20):** 3 drops topical ciprofloxacin 250 µg/mL in saline solution locally twice a day PLUS oral ciprofloxacin 250 mg twice a day **Topical ciprofloxacin (n = 20):** 3 drops topical ciprofloxacin 250 µg/mL in saline solution locally twice a day **Oral ciprofloxacin (n = 20):** oral ciprofloxacin 250 mg twice a day All interventions given for at least 5 days. Those not cured at 5 days carried on up to 10 days.

Esposito 1990 *(Continued)*

	Concurrent treatment: no other treatment or use of aural toileting was mentioned
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge ("dry ear") at 1 week (5 to 11 days) and 2 to 4 weeks (19 to 24 days). Unclear if otoscopically confirmed (papers states "clinically examined"). **Secondary outcomes:** • Suspected ototoxicity (audiometric and vestibular function)
Funding sources	"The ciprofloxacin tablets and powder used in this study were kindly provided by Bayer Italia Spa, Milan, Italy."
Declarations of interest	No information provided
Notes	Topical ciprofloxacin was prepared from ciprofloxacin powder in sterile saline and tested for stability and activity for 10 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Ciprofloxacin was randomly administered according to the following schedules." Comment: randomisation method not clearly specified. 38/60 patients were previously unsuccessfully treated with at least 5 days of antibiotics – unclear how this was distributed across groups. 12/20 in the oral ciprofloxacin only group had pseudomonas versus 8/20 in other groups.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Group A (20 patients), 250mg orally twice a day; group B (20 patients), 3 drops containing 250ug/mL of ciprofloxacin in saline solution locally twice a day; and group C (20 patients), both the previous treatments twice a day." Comment: most likely that participants were not blinded as the routes of administration (oral versus topical) were different among groups and it was not mentioned that placebo was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Patients were clinically examined before, during (every 2 to 3 days) and after the therapy." Comment: not specified who assessed the outcomes and the assessment method was not specifically standardised. "Cure", "improvement" and "failure" seemed to be more of a subjective judgement.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no dropouts were reported. All of the patients randomised are presented in the results of the study.
Selective reporting (reporting bias)	High risk	Comment: there is no protocol for the trial on clinicaltrials.gov or in the EU register of clinical trials. Some of the results mentioned in the methods section are not fully presented in the results section. "Cure" or resolution of discharge is only reported at one

Esposito 1990 *(Continued)*

	time point, most likely 14 days after end of treatment. The other time point, 24 hours after end of treatment (i.e. 6 to 11 days), was not reported.

Fradis 1997

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 in whom it could not be seen due to granulation tissue (microscopic evaluation of the ears)
	  ☐ Podoshin 1998: in 3 patients it was impossible to recognise a perforation due to granulation tissue in the ear and an additional 5 patients had undergone a mastoidectomy
	  * Presence of mucopurulent discharge: yes 100%
	  * Duration of symptoms (discharge): range 1 to 240 months (Fradis: mean 24 months, Podoshin 1998: mean 74 months)
	• 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:
	  ☐ 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 eardrops containing neomycin and polymyxin B
	  ☐ Podoshin 1998: 34 out of 60 were treated with antibiotics prior to initiation of the study, without improvement, of whom 22 were treated with otic drops and 12 additional patients were given antibiotics by mouth.
	
	Inclusion criteria:
	
	• Chronic otitis media (no definition)
	
	Exclusion criteria:

Fradis 1997 *(Continued)*

	• 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 end point)
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's 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

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: insufficient information about the sequence generation is available to determine whether this is a 'high' 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."

Fradis 1997 *(Continued)*

		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.

Gyde 1978

Methods	Two-arm, double-blind, cross-over RCT, with unclear duration of treatment (up to 3 weeks) and 12 months duration of follow-up

Participants	**Location:** Canada, unclear number of sites
	
	Setting of recruitment and treatment: unclear. Outpatient department, published in 1978.
	
	Sample size: 91 people (100 ears)
	
	• **Number randomised:** 50 ears in gentamycin, 50 ears in trimethoprim, sulphacetamide and polymixin B combination (TSP)
	• **Number completed:** 50 ears in gentamycin, 50 ears in TSP
	
	Participant (baseline) characteristics:
	
	• Age: mean group 1: 25.8 years; mean group 2: 32.7 years
	• Gender (F/M): 46 (41%)/66 (59%)
	• Main diagnosis: otorrhoea
	• High-risk population:
	  * 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: unclear
	  * Presence of mucopurulent discharge: not reported
	  * Duration of symptoms (discharge): not reported

Gyde 1978 *(Continued)*

- Other important effect modifiers:
  - Alternative diagnosis of ear discharge: otitis externa: 24 (21%); sub-acute otitis media: 18 (16%); postoperative infections: 13 (12%)
  - 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:

- Adult or child with otorrhoea due to bacterial infection with:
  - External otitis
  - Chronic otitis media
  - Sub-acute otitis media with perforation of ear drum
  - Postoperative infection of the mastoid cavity or after tympanostomy

Exclusion criteria:

- Known allergy to one of the ingredients
- Pregnant/breastfeeding
- Infants less than 2 months old
- Cases of non-bacterial otorrhoea
- Patients given high-dose corticosteroids
- Patients unable to attend follow-up
- Potentially complicated cases (e.g. cholesteatoma)
- Patients who had previously received an ototoxic therapy
- No treatment with antibiotics within 2 weeks of start of the trial

Interventions	**Intervention (n = 50 ears):** trimethoprim (1 mg/mL), sulphacetamide (5 mg/mL) and polymyxin B (10,000 units/mL) (Burroughs Wellcome Ltd), ear drops, 8 drops/12 hours. Duration of treatment: up to 3 weeks (average treatment time for those with 'success' was 16.4 days). **Comparator group (n = 50 ears):** gentamycin (Garamycin), 0.3% (3mg/mL), ear drops, 8 drops/12 hours. Duration of treatment: up to 3 weeks (average treatment time for those with 'success' was 22.8 days). **Concurrent treatment:** aural toileting: dry mopping and suction cleaning before each treatment. No details on method. No further details on any other treatment.
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge or "dry ear" (whether otoscopically confirmed or not) measured at between 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. If this is not available, the pure-tone average of the thresholds measured will be reported. • 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
Funding sources	No information provided

Gyde 1978 *(Continued)*

Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for reporting outcomes of patients with bilateral disease:** it does not appear that any consideration of the correlation of results between ears has been taken into account. If there was a treatment failure 'ears' were transferred to the alternative groups. These results have not been included in the analysis. If an ear was not dry on review at 6 months, treatment for 3 weeks with the alternative treatment was completed with review after 6 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: (translated) "We used the method minimisation technique of Taves to allocate the patients to the treatment groups using the type of infection as the principal criterium." Comment: references are given to support the method of participant selection
Allocation concealment (selection bias)	Low risk	Comment: if the Taves method of minimisation was used correctly, it is unlikely that the allocating physician could have predicted the treatment group to which the patient would have been allocated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blinded study" Comment: no further information provided
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blinded study" Comment: no further information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: it appears that all of the participants who started the trial were accounted for in the results
Selective reporting (reporting bias)	Low risk	Comment: no protocol was identified on the WHO clinical trials registry

Jamalullah 2016

Methods	Two-arm, non-blinded, parallel-group, quasi-randomised controlled trial, with 2-week duration of treatment and follow-up
Participants	**Location:** Pakistan, 1 site **Setting of recruitment and treatment:** Department of Otolaryngology, Pakistan Institute of Medical Sciences, Islamabad, September 2009 to March 2010 **Sample size:** 80 • **Number randomised:** 40 in gentamycin, 40 in ofloxacin • **Number completed:** 40 in gentamycin, 40 in ofloxacin

Jamalullah 2016 *(Continued)*

Participant (baseline) characteristics:

- Age: 28.1 years (averages with SD given for males and females in each treatment group)
- Gender (F/M): 35 (43.8%)/45 (56.2%)
- Main diagnosis: tubotympanic type of CSOM
- 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 (otoscopic/microscopic examination)
  - Presence of mucopurulent discharge: 100%
  - At baseline
    - ☐ Profuse otorrhoea: gentamycin: 67.5%, ofloxacin: 75%
    - ☐ Moderate otorrhoea: gentamycin 32.5%, ofloxacin: 25%
  - Duration of symptoms (discharge): more than 3 months
- Other important effect modifiers:
  - Alternative diagnosis of ear discharge: polypoidal middle ear mucosa (gentamycin: 10%; ofloxacin: 27.5%)
  - 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:

- Adult patients having central perforation of tympanic membrane and symptoms of ear discharge for more than 3 months and/or polypoidal/erythematous middle ear mucosa and they were not on any topical or systemic antibiotics one week prior to 1st visit

Exclusion criteria:

- Features of atticoantral disease including attic perforation, cholesteatoma, polyps, having previous mastoid exploration, lactating mothers, diabetes mellitus and sensitivity to aminoglycosides or quinolones

Interventions	**Intervention (n = 40):** ofloxacin 0.6%, ear drops, 4 drops 3 times daily. Duration of treatment = 2 weeks. **Comparator group (n = 40)**: gentamycin 0.3%, ear drops, 4 drops 3 times daily. Duration of treatment = 2 weeks. **Concurrent treatment:** aural toileting: "aural toilets or all the patients were done before initiating any therapy." No other information about additional treatments was given.
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge ("dry ear"), measured at between 2 to 4 weeks (2 weeks). Otoscopically confirmed. **Secondary outcomes:** • Not reported
Funding sources	No information provided
Declarations of interest	No information provided

Jamalullah 2016 *(Continued)*

Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This randomized controlled trial ..." Comment: no methods of sequence generation were described
Allocation concealment (selection bias)	Unclear risk	Comment: methods of allocation concealment were not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding of participants was attempted despite blinding being a possibility as both of the treatments were topical ear drops and the regimens were the same
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: the paper does not mention any attempts to blind the outcome assessors, despite this being feasible because the outcomes were the presence or absence of ear discharge
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: it appears that all of the patients who started the trial were included in the analysis. There was no mention of any participants being lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol for the paper was found on the WHO clinical trial database (ICTRP). The paper does not mention a protocol. The outcomes listed in the methods section are reported in the results section although there is a greater emphasis on subgroups relating to the severity of initial otorrhoea and type of mucosa (polypoidal or erythematous) in the results. It is unclear if these were pre-determined subgroups or whether the results were analysed in this way post-hoc.

Kasemsuwan 1997

Methods	Two-arm, double-blind, parallel-group RCT, with 7 days duration of treatment and follow-up
Participants	**Location:** Thailand, 1 site **Setting of recruitment and treatment:** Ramathibodi hospital (specialist hospital), Bangkok, October to December 1993 **Sample size:** 50 • **Number randomised:** unclear • **Number completed:** 19 in intervention, 16 in comparison **Participant (baseline) characteristics:** • Age: 21 to 66 years • Gender (F/M): 22 (63%)/13 (37%) • Main diagnosis: mucopurulent otorrhoea

Kasemsuwan 1997 *(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: not reported
- Diagnosis method: microscopic evaluation
  - Confirmation of perforated tympanic membrane: not reported
  - Presence of mucopurulent discharge: not reported
  - Duration of symptoms (discharge): 3 months
- 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:

- Any patient with a perforated tympanic membrane for longer than 3 months
- Any patient with mucopurulent otorrhoea
- **Note:** it is unclear if patients were included if they had a tympanic membrane perforation AND mucopurulent discharge, or if they had a tympanic membrane perforation OR mucopurulent discharge.

Exclusion criteria:

- Cholesteatoma, pregnancy, underlying diseases, receiving antibiotics in the previous 2 weeks and during the study

Interventions	**Intervention (n = 19):** ciprofloxacin in saline solution (250 mg/mL), ear drops, 5 drops, 3 times daily. Duration of treatment = 7 days. **Comparator group (n = 16)**: saline solution, ear drops. 5 drops, 3 times daily. Duration of treatment = 7 days **Concurrent treatment:** on day 1, 4 and 7 ear cleaning was performed. No other information regarding the concurrent treatment was provided.
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge ("dry ear"), measured at between 1 week and 2 weeks (7 days) **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 will be reported. • Adverse effects from treatment • Suspected ototoxicity
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported
Risk of bias	

Kasemsuwan 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "…randomly allocated treatment…" Comment: no information was provided about how the sequence was generated
Allocation concealment (selection bias)	Low risk	Quote: "…They were randomly allocated treatment with either ciprofloxacin in saline solution or solution without antibiotics in a double blind method. The medications were prepared, and given codes which were known only in the pharmaceutical laboratory." Comment: it is implied that the treatment allocation was completed by physicians without knowledge of the randomisation schedule
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: it is implied that the medications were coded, rather than labelled and so the treatment group was not known by the participants or the personnel in the trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: it is implied that the trial was blinded and the personnel assessing the outcome (ear discharge) were unaware of the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: the paper states that 15/50 (30%) participants did not complete the trial due to "lack of attendance". The paper does not provide an analysis of which group they were allocated to or why they did not attend. Given that the trial was for 7 days, this seems to be a very high dropout rate.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol for the trial was identified through clinicaltrials.gov or the Thai registry of clinical trials. Outcomes that were detailed in the methods are presented in the full paper although the results of the audiological assessments are not presented explicitly, just as a single statement stating no difference.

Kaygusuz 2002

Methods	Four-arm, non-blinded, single-centre, parallel-group RCT, with 3 weeks duration of treatment and follow-up
Participants	**Location:** Turkey, 1 site **Setting of recruitment and treatment:** university ENT clinic; no dates (published in 2002) **Sample size:** 80 patients (103 ears) • **Number randomised:** 20 in each intervention group • **Number completed:** 20 in each intervention group **Participant (baseline) characteristics:** • Age: range: 18 to 60, mean 31 ± 11.5 years • Gender (F/M): 31 (39%)/49 (61%) • Main diagnosis: chronic suppurative otitis media (CSOM) with ear discharge without cholesteatoma. Perforation in ear membrane and ear discharge longer than 3 months.

Kaygusuz 2002 *(Continued)*

- High-risk population:
  - 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 (otoscopic examination)
  - Presence of mucopurulent discharge: 100%
  - Duration of symptoms (discharge): longer than 3 months
- 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: 0%
  - Number who had previous antibiotic treatment for CSOM: not reported

Inclusion criteria:

- Patients diagnosed with CSOM with ear discharge without cholesteatoma
- Perforation in ear membrane and ear discharge longer than 3 months

Exclusion criteria:

- Patients < 18 years old
- Previous ear surgery
- Patients with cholesteatoma
- General health problems
- Allergy to aminoglycoside and fluoroquinolone antibiotics

Interventions	**Topical ciprofloxacin (n = 20):** 0.3% ciprofloxacin hydrochloride eardrops, 2 drops, 3 times in a day, treatment duration = 21 days **Topical tobramycin (n = 20)**: 0.3% tobramycin eardrops, 2 drops, 3 times in a day, treatment duration = 21 days **Topical ciprofloxacin + dexamethasone (n = 20)**: 0.3% ciprofloxacin hydrochloride PLUS 0.1% dexamethasone combination eardrops, 2 drops, 3 times in a day, treatment duration = 21 days **Topical tobramycin + dexamethasone (n = 20)**: 0.3% tobramycin PLUS 0.1% dexamethasone combination ear drops, 2 drops, 3 times in a day, treatment duration = 21 days **Concurrent treatment:** daily aspiration during exam for 3 weeks
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge "dry ear", measured at between 2 to 4 weeks. Otoscopically confirmed. **Secondary outcomes:** • Not reported
Funding sources	No information provided
Declarations of interest	No information provided
Notes	Part of a 4-arm trial with the following treatment groups: • Topical ciprofloxacin • Topical tobramycin

Kaygusuz 2002 *(Continued)*

- Topical ciprofloxacin + dexamethasone
- Topical tobramycin + dexamethasone

Only the first 2 arms are presented in this review

Unit of randomisation: person

Methods for including patients with bilateral disease: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no clear statement regarding "randomized". No description about randomisation method.
Allocation concealment (selection bias)	Unclear risk	Comment: there is no information about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: there is no clear statement regarding whether the study was blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: there is no clear statement regarding whether the study was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	Comment: there was no study protocol mentioned within the paper and no protocol was found on clinicaltrials.gov All of the outcomes mentioned in the methods section are reported in the results

Liu 2003

Methods	Two-arm, blinding not described, parallel-group RCT, with 2-week duration of treatment and follow-up
Participants	**Location:** China, 1 site **Setting of recruitment and treatment:** outpatient department, department of Otolaryngology, Wenzhou Second People's Hospital, published in 2003 **Sample size:** 160 • **Number randomised:** 87 in rifampicin, 73 in chloramphenicol • **Number completed:** 87 in rifampicin, 73 in chloramphenicol **Participant (baseline) characteristics:** • Age: mean 30 years (range: 12 to 65 years) • Gender (F/M): 58 (38.7%)/92 (61.3%). Note: only 150 of 160 recruited patients are accounted for • Main diagnosis: "patients who were diagnosed with chronic suppurative otitis media in the out-patient department." No definition was provided.

Liu 2003 *(Continued)*

- 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: unclear
  - Confirmation of perforated tympanic membrane: not reported
  - 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:

- Not reported

Exclusion criteria:

- Not reported

Interventions	**Group A (n = 87):** rifampicin (0.1%) eye drops, through the ear canal, 3 drops, 3 times a day. Duration of treatment: 2 weeks. **Group B (n = 73):** chloramphenicol (0.25%) eye drops, through the ear canal, 3 drops, 3 times a day. Duration of treatment: 2 weeks. **Concurrent treatment:** aural toileting, "wash the ear canal with 3% H_2O_2 solution and dry the ear" before administration of ear drops
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** Complete resolution of ear discharge measured at 2 weeks: Quote: "Criteria for assessment of outcomes: • Cured: otorrhea disappeared, mucosal hyperemia of the tympanic membrane and tympanic cavity disappeared • Significantly effective: no complaints of otorrhea, no visible purulence in the ear canal and tympanic cavity, and nonvisible or slight hyperemia of the tympanic membrane and the tympanic canal • Non-effective: otorrhea persisted after 2 weeks of treatment, purulence in the external ear and tympanic cavity, and hyperemia of the tympanic membrane" The outcome was presented as the number of patients whose treatment was considered curative, significantly effective, or non-effective, respectively **Secondary outcomes:** • Not reported
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person

Liu 2003 *(Continued)*

Methods for including patients with bilateral disease: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "We randomly selected 160 patients who were diagnosed with chronic suppurative otitis media in outpatient department (male 92, female 58, age 16 to 65, mean 30). These patients were divided into rifampicin group (group A, 87 patients) and chloramphenicol group (group B, 73 patients). The two group showed no significant difference in terms of gender, age, and course of disease." Comment: it is not clear whether or not the patients were randomised
Allocation concealment (selection bias)	Unclear risk	Quote: "We randomly selected 160 patients who were diagnosed with chronic suppurative otitis media in outpatient department (male 92, female 58, age 16 to 65, mean 30). These patients were divided into rifampicin group (group A, 87 patients) and chloramphenicol group (group B, 73 patients). The two group showed no significant difference in terms of gender, age, and course of disease." Comment: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: not mentioned. Given the different colour of the 2 different eye drops, blinding would be difficult to achieve.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: attrition not reported. It seems that no participant was lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Comment: a protocol for this trial is not available

Lorente 1995

Methods	Two-arm, double-blinded, multicentre, parallel-group RCT, with 8 days duration of treatment and 30 days duration of follow-up
Participants	**Location:** Spain, 4 centres **Setting of recruitment and treatment:** hospital ENT clinics, Barcelona, no dates (published in 1995) **Sample size:** 308 • **Number randomised:** unclear • **Number completed:** 159 in ciprofloxacin, 149 in gentamicin **Participant (baseline) characteristics:** • Age: 42.23 ± 13.92 years • Gender (F/M): 140 (45.5%)/168 (54.5%)

Lorente 1995 *(Continued)*

- Main diagnosis: CSOM (purulent discharge for more than 3 months and perforated tympanic membrane)
- 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 (no method is given)
  - Presence of mucopurulent discharge: yes (no method is given). Mild discharge: 22%; moderate discharge: 56%; severe discharge: 21%
  - Duration of symptoms (discharge): 3 months
- 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:

- Patients age 18 to 65 years
- Chronic otitis media in suppurative phase with purulent discharge for more than 3 months with a perforated ear drum

Exclusion criteria:

- Cholesteatoma
- Pregnant/breastfeeding
- Severe renal or hepatic insufficiency
- Antibiotic treatment in previous 48 hours
- Bilateral hearing loss > 60 dB
- Otomycosis

Interventions	**Intervention (n = 159):** ciprofloxacin 0.3% (3 mg/mL), ear drops, 5 drops, 3 times a day, duration of treatment = 8 days **Comparator group (n = 149):** gentamicin 0.3% (3 mg/mL), ear drops, 5 drops, 3 times a day, duration of treatment = 8 days **Concurrent treatment:** not reported
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Complete resolution of ear discharge, measured at between 1 week to 2 weeks (8 days) and after 4 weeks (30 days). Otoscopically confirmed. • Adverse effects: ear pain, itching, stinging (measured on a 4-point scale: 0 = none to 3 = severe) **Secondary outcomes:** • Hearing • Suspected ototoxicity
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person

Lorente 1995 *(Continued)*

Methods for including patients with bilateral disease: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: the study indicates that it was "randomised" but does not provide any further details
Allocation concealment (selection bias)	Unclear risk	Comment: the study does not provide any details about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: the study indicates that it is "double-blind" but does not provide any details on how blinding of participants and healthcare professionals was ensured
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: the study indicates that it is "double-blind" but does not indicate if this includes those people who assessed the outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the paper does not mention that any participants were lost to follow-up. The paper presents the number of people available for analysis at the end of the trial but does not specifically state how many were randomised to treatment. In a trial of 300 participants for 30 days it would be unusual to have no participants withdrawing from treatment.
Selective reporting (reporting bias)	Unclear risk	Comment: no protocol could be identified on clinicaltrials.gov or in the European clinical trials registry. Although the outcomes as presented in the methods section are presented in the results section, the level of reporting is not always clear. The hearing results just show that there was no significant difference between the groups.

Mira 1993

Methods	Two-arm, single-blinded, parallel-group RCT, with 7 days duration of treatment and 21 days follow-up
Participants	**Location:** Italy, 1 site **Setting of recruitment and treatment:** Department of Otolaryngology, published in 1993 **Sample size:** 248 • **Number randomised:** 128 in intervention, 120 in comparison • **Number completed:** 127 in intervention, 120 in comparison **Participant (baseline) characteristics:** • Age: mean 42.6 ± 13.7 (range 14 to 79) • Gender (F/M): 124 (50%)/124 (50%) • Main diagnosis: recurrence of chronic suppurative otitis media or suppuration following mastoidectomy or tympanoplasty

Mira 1993 *(Continued)*

- 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: unclear
  - Presence of mucopurulent discharge: unclear
  - Duration of symptoms (discharge): not reported
- Other important effect modifiers:
  - Alternative diagnosis of ear discharge:
    - Suppuration following tympanoplasty: 26/248 (10.5%)
    - Suppuration following mastoidectomy: 26/248 (10.5%)
  - Number who have previously had grommets inserted: not reported
  - Number who have had previous ear surgery: at least 52/248 (21%)
  - Number who had previous antibiotic treatment for CSOM: not reported

Inclusion criteria:

- Age ≥ 14 years
- Recurrence of chronic suppurative otitis media or suppuration following mastoidectomy or tympanoplasty

Exclusion criteria:

- Ascertained or suspected hypersensitivity to cephalosporins and/or penicillins
- External otitis
- Cholesteatoma
- Concomitant serious diseases (neoplasias, renal or hepatic insufficiency)

Interventions	**Intervention (n = 128):** ceftizoxime 2 g dissolved in 4 mL of saline twice per day for 7 days. Method of administration: 2 mL of solution was instilled into the auditory canal while the patient was supine and keeping their head turned to one side. The patient remained in this position for 3 to 5 minutes, after which they released the excess liquid by turning their head to the opposite side. The remaining part of the supplied solution was then also instilled and the canal was padded with an ear gauze. Morning treatment: ear pad was removed after 2 hours Evening treatment: ear pad kept in situ overnight and removed the next morning **Comparator group (n = 120):** saline solution – same method as per intervention arm above **Concurrent treatment:** at the first visit a specialist aspirated local secretions All patients received systemic antibiotics 2 g daily of ceftizoxime by intramuscular route (1 vial every 12 hours) for 7 days
Outcomes	Ear discharge was reported but not in a way that we could use in this review
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported

Risk of bias

Mira 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was a single-blind randomised investigation." Comment: there is no information about the method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: there is no information regarding allocation concealment. It is not clear whether the healthcare professionals could have influenced the allocation to treatment group
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The study was a single-blind randomised investigation." Comment: although the study indicates that the study was "single-blinded" it does not provide details of who was blinded to treatment. It is assumed that it was the participants who were blinded to treatment. The saline placebo was used at the same volume and with the same method of application as the antibiotic ear drops.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The study was a single-blind randomised investigation." Comment: it is assumed that the single blinding was blinding of the participants. In this case the outcome assessors would have known the treatment to which the participants were allocated when assessing outcomes. This could have led to bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: it appears that only 1 participant in the topical antibiotics group did not complete the trial (1/128; 0.7%)
Selective reporting (reporting bias)	High risk	Comment: a protocol was not available through clinicaltrials.gov or the European Clinical Trials Registry. The outcomes as reported in the methods section are not all well presented in the results section. The methods sections reports some information about the scales used to measure symptom scores but it is not clear which symptoms were measured. Similarly the methods section gives definitions of the outcomes 'recovered', 'improved' and 'unchanged or worsened' but these are not presented in the results. The results are given descriptively without any information about precision.

Nawasreh 2001

Methods	Two-arm, non-blinded, parallel-group RCT, with 10-day duration of treatment and follow-up
Participants	**Location:** Jordan, 1 site **Setting of recruitment and treatment:** unclear setting, January to August 1999 **Sample size:** 88 at the end of the trial • **Number randomised:** unclear • **Number completed:** 48 in ciprofloxacin, 40 in gentamycin **Participant (baseline) characteristics:** • Age: mean 30 years (range 9 to 62 years) • Gender (F/M): 42 (48%)/46 (52%)

Nawasreh 2001 *(Continued)*

- Main diagnosis: chronic suppurative otitis media (persistent perforation of the tympanic membrane) and intermittent mucopurulent heavy discharge for more than 1 year
  - 88% with "tubotympanic CSOM" and 12% with "atticoantral CSOM", i.e. at greater risk of cholesteatoma
- 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: unclear
  - Presence of mucopurulent discharge: unclear
  - Duration of symptoms (discharge): 1 year
- 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:

- "All patients included in the study were examined carefully and diagnosed as having chronic suppurative otitis media before the start of treatment"
- Included patients stopped taking any medication at least 10 days prior to starting treatment

Exclusion criteria:

- History of allergy to fluoroquinolone derivatives or aminoglycosides
- Under 9 years of age
- Past history of general health problems

Interventions	**Intervention (n = 48):** ciprofloxacin in distilled water (200 µg/mL), ear drops, 5 drops, 3 times per day. Treatment duration = 10 days **Comparator group (n = 40):** gentamicin sulphate (5 mg/mL) ear drops, 5 drops, 3 times per day. Treatment duration = 10 days **Concurrent treatment:** none listed. No mention of aural toileting.
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge ("dry ear"), measured at between 1 week to 2 weeks (10 days) **Secondary outcomes:** • Hearing (measured as change in hearing threshold from baseline or at endpoint)
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported
Risk of bias	

Nawasreh 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "…[patients] were randomly placed…." Comment: the abstract mentions that randomisation occurred but there is no mention of randomisation or methods for randomisation in the full paper. The full paper describes the patients as "divided" between the 2 groups. It is unclear if the groups were evenly distributed as there were 40 in one group and 48 in the other but baseline characteristics between the groups were not provided.
Allocation concealment (selection bias)	Unclear risk	Comment: there is no information within the paper about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: it does not appear that personnel or participants were blinded to treatment group, although both groups had the same treatment regimen so this would have been possible
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: it does not appear that any efforts were made to keep the outcome assessors blind to the treatment group
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Patients who failed to use the topical solution regularly or who took other medication during the study period were excluded." Comment: there is no information about how many people were in these categories or into which treatment group they had been allocated to show whether there was a difference between the groups that could have led to bias in the results. There is an imbalance in participants between the groups. There were nearly 20% fewer participants in the gentamicin group.
Selective reporting (reporting bias)	High risk	Comment: no trial protocol could be identified in clinicaltrials.gov. Some of the results that were identified in the methods section were not well presented in the paper (e.g. hearing, where there is only a statement that gives the basic significant difference between the start and end of treatment in each group, rather than a between treatment group comparison). Only 10-day treatment results are presented, not 1-, 5- and 7-day treatment results.

Ramos 2003

Methods	Five-arm, open-label, parallel-group RCT, with 7-day duration of treatment and 10 days of follow-up. Follow-up to 3 days after finishing the treatment
Participants	**Location:** Spain **Setting of recruitment and treatment:** 3 ENT departments of 3 tertiary hospitals **Sample size:** 300 patients • **Number randomised:** 50 in each group • **Number completed:** 50 in each group **Participant (baseline) characteristics:** • Age (mean, range): 5 to 73, n = 36 (12%) were children (< 14 years)

Ramos 2003 *(Continued)*

- Gender (F/M): 134 females (44.7%)/166 males (55.3%)
- Main diagnosis: chronic ear discharge, which comprised of the following groups
  - Simple chronic otitis media (n = 128): no lesions of the ossicular chain, erosion of the tympanic frame, absence of tympanosclerosis and no evidence of cholesteatoma
  - Chronic otitis media with osteolysis (OMCO) (n = 57), including osteolytic lesions and alterations of the mucosa of medium type, type of pansclerosis, granulomatous lesions, atelectasis or marginal perforation, without signs of cholesteatoma
  - Chronic cholesteatoma (n = 42): signs of infection of middle cholesteatoma
  - Chronic otorrhoea in operated ears (n = 73): radical mastoidectomy (n = 40), tympanoplasty infection (n = 21), transtympanic grommets (n = 12)
- High-risk population:
  - 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*:* all had otoscopic examination at baseline: 62.3% had perforation confirmed (marginal perforation: 1.43% non-marginal perforation; 42% attic perforation)
  - Presence of mucopurulent discharge: otoscopic examination
  - Duration of symptoms (discharge): "for more of 6 weeks or sporadically with 3 or more episodes in the last year"
- Other important effect modifiers:
  - Alternative diagnosis of ear discharge: cholesteatoma, n = 42 (see above)
  - Number who have previously had grommets inserted: 12
  - Number who have had previous ear surgery: 73
  - Number who had previous antibiotic treatment for CSOM: 65.6% (n = 197)

Inclusion criteria:

- Chronic otorrhoea, meaning that those cases presenting permanent, unilateral or bilateral, otorrhoea for more than 6 weeks, or sporadically, as long as it has manifested 3 or more episodes in the last year, regardless of the origin and morphological changes

Exclusion criteria:

- Pregnant women
- Patients with renal and/or hepatic impairment
- Patients who had undergone topical or systemic antibiotic treatment during the 48 hours prior to the start of the study
- Patients with mycotic infections
- Patients who had concomitant treatment with theophylline or antacids, which include magnesium hydroxide or aluminium hydroxide in its formulation

Interventions	**Group A (n = 50):** oral ciprofloxacin 500 mg 12-hourly PLUS topical ciprofloxacin 0.2% 0.5 mL 8-hourly for 7 days **Group B (n = 50):** topical ciprofloxacin 0.3% PLUS fluocinolone 0.5 mL 8-hourly for 7 days **Group C (n = 50):** topical ciprofloxacin 0.5%, 0.5 mL 8-hourly for 7 days **Group D (n = 50):** topical ciprofloxacin 0.2%, 0.5 mL 8-hourly for 7 days **Group E (n = 50):** topical polymyxin 10,000 IU, neomycin 0.0035 g, hydrocortisone 0.00025 g, 8-hourly for 7 days **Group F (n = 50):** oral ciprofloxacin 500 mg twice 12-hourly for 7 days **Concurrent treatment:** not reported

Ramos 2003 *(Continued)*

Outcomes	**Outcomes of interest in the review:**
	
	Primary outcome:
	
	• Resolution of ear discharge ('dry ear'), unsure whether measured otoscopically, confirmed at 1 to 2 weeks
	
	Secondary outcomes
	
	• Hearing: hearing tests at time of diagnosis, at 8 days and at 15 days
	• Suspected ototoxicity
	  * Diagnosed with audiogram (specific definition not stated, but study reports 0/125 patients had ototoxicity from treatment) (not definition of ototoxicity)
	  * Balance problems/dizziness/vertigo not reported
	  * Tinnitus not reported

Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly allocated into 6 groups." Comment: insufficient information about the sequence generation. In addition, the study stated that children were not randomised to oral ciprofloxacin; it is unclear how this was done.
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomly allocated into 6 groups." Comment: insufficient information about allocation concealment. There is no information about how they maintained allocation concealment but did not randomise children to ciprofloxacin.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information provided about blinding method or use of placebo. The treatment arms involved different dosage forms (oral versus ear drops) – blinding of these interventions is impossible without the use of placebo.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no information provided regarding who assessed the outcomes. For subjective outcomes (otoscopy examinations) the knowledge of treatment group may influence the results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 patients on oral treatment were reported as withdrawn due to gastrointestinal adverse events. It is unclear in which group this was and whether these patients were counted in the percentages reported. The percentage of withdrawals is small.
Selective reporting (reporting bias)	Unclear risk	Comment: an audiogram was performed at baseline and the end of treatment, but not reported

Siddique 2016

Methods	Two-arm, unblinded, parallel-group RCT, with unclear duration of treatment (probably 4 weeks) and 4-week follow-up

Participants	**Location:** Pakistan, 1 site
	
	Setting of recruitment and treatment: specialist/tertiary military hospital, Peshawar, January to December 2013
	
	Sample size: 200
	
	• **Number randomised:** 200, but unclear how many to each group
	• **Number completed:** 93 in intervention group, 93 in comparison group
	
	Participant (baseline) characteristics:
	
	• Age: mean 38 years (range 12 to 70 years)
	• Gender (F/M): 34 (18%)/152 (81.7%)
	• Main diagnosis: tubotympanic type of CSOM (persistent or recurrent infections ascending via the Eustachian tube to the middle ear thereby causing infection and subsequent perforation in pars tensa)
	• High-risk population:
	  * Cleft palate (or other craniofacial malformation): not reported
	  * Down syndrome: not reported
	  * Indigenous groups (Australian Aboriginals/Greenland natives): not reported
	  * Immunocompromised: 0%
	• Diagnosis method:
	  * Confirmation of perforated tympanic membrane: unclear
	  * Presence of mucopurulent discharge: unclear
	  * Baseline discharge
	  ☐ Middle ear only: ciprofloxacin: 4%; neomycin: 5%
	  ☐ Partially filling external auditory meatus: ciprofloxacin: 12%; neomycin: 24%
	  ☐ Full external auditory meatus: ciprofloxacin: 84%; neomycin: 71%
	  * Duration of symptoms (discharge): unclear
	• 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:
	
	• Patients above 12 years irrespective of gender, with a diagnosis of tubotympanic type of CSOM defined as: "persistent or recurrent infections ascending via the Eustachian tube to the middle ear thereby causing infection and subsequent perforation in pars tensa"
	
	Exclusion criteria:
	
	• Immunocompromised patients
	• Diabetic patients
	• Patients having hypersensitivity to neomycin or quinolone
	• Patients with any other ENT pathologies like tonsillitis, symptomatic DNS or sinusitis
	• Pregnant females
	• Patients with cholesteatoma or "Atticoantral or tympanomastoid type CSOM, involving predominantly the attic and antral region of the middle ear cleft"

Interventions	**Intervention (n = 93):** 'standard dosage' ciprofloxacin (Cipotec ear drops), 3 drops/12 hours. Unclear treatment duration (probably 4 weeks).

Siddique 2016 *(Continued)*

	Comparator group (n = 93): 'standard dosage' neomycin (Neosporin ear drops), 2 drops/12 hours. Unclear treatment duration (probably 4 weeks). **Concurrent treatment:** there is no information about the use of aural toileting or any additional treatments
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge ("dry ear"), measured at between 2 to 4 weeks. Unclear if otoscopically confirmed. • Ear pain, discomfort, local irritation **Secondary outcomes:** • Serious complications • Suspected ototoxicity
Funding sources	"No funding was received from any agency or institution"
Declarations of interest	"Abstract and results of this study were accepted and presented in an oral presentation at the International conference on Medical Education, organised by Association for Excellence in Medical Education (AEME) and held on 07th-09th March 2014 at University of Health Sciences (UHS) Lahore, Pakistan" No other conflicts were mentioned
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** 15 patients (8%) had bilateral disease but how these cases were handled is not stated. The denominator in the trials is the person so it is assumed that no double counting occurred

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quotes: "Randomized clinical trial" and "patients… assigned to one or the other group based on consecutive non-probability sampling." Comment: it is unclear what the actual process for the 'non-probability' sampling was and how it ensured that the allocation was random
Allocation concealment (selection bias)	Unclear risk	Quote: "patients… assigned to one or the other group based on consecutive non-probability sampling." Comment: it is not clear how much impact the investigators had in terms of allocating people to treatment groups
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: it does not appear that participants or personnel were blinded to treatment group. The treatment groups had different treatment regimens.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: it does not appear that the outcome assessors were blinded to treatment group although this would have been feasible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 200 patients included in the study 14 were lost to follow up."

Siddique 2016 *(Continued)*

		Comment: the rate of loss to follow-up is low (7%) but there is no explanation of why patients were lost to follow-up and to which groups they had been allocated. Due to the small numbers this is unlikely to have influenced the results.
Selective reporting (reporting bias)	High risk	Comment: no trial protocol was identified on clinicaltrials.gov or the WHO clinical trials registry site. Comment: whilst the methods state that the amount of ear discharge at both 2 weeks and 4 weeks was measured, only the amount of ear discharge at 4 weeks is reported.

Tutkun 1995

Methods	Two-arm, non-blinded, single-centre, parallel-group RCT, with 10 days duration of treatment and follow-up

Participants	**Location:** Turkey, 1 site
	
	Setting of recruitment and treatment: tertiary medical centre, university hospital, Istanbul; November 1993 to June 1994
	
	Sample size: 44
	
	• **Number randomised:** unclear
	• **Number completed:** 24 in ciprofloxacin group, 20 in gentamicin group
	
	Participant (baseline) characteristics:
	
	• Age: mean 28 years (range 9 to 65 years)
	• Gender (F/M): 21 (48%)/23 (52%)
	• Main diagnosis: chronic otitis media with purulent otorrhoea lasting for more than a year
	• High-risk population:
	  * 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 (otoscope)
	  * Presence of mucopurulent discharge: yes, purulent discharge for more than 1 year
	  * Duration of symptoms (discharge): more than 1 year
	• 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:
	
	• History of purulent otorrhoea lasting more than 1 year
	• Patients who were examined carefully and diagnosed with CSOM
	
	Exclusion criteria:
	
	• History of allergy to fluoroquinolone derivatives or aminoglycosides
	• Age < 9 years
	• History of general health problems
	• Did not use the topical solutions regularly

Tutkun 1995 *(Continued)*

	• Taken any other medication during the study period
Interventions	**Intervention (n = 24):** ciprofloxacin hydrochloride 200 µg/mL (0.02%), ear drop, 5 drops (equivalent volume unknown), 3 times daily, duration of 10 days (solution prepared by dissolving ciprofloxacin HCL in distilled water) **Comparator group (n = 21):** gentamicin sulfate 5 mg/mL, ear drops, 5 drops, 3 times daily, duration of 10 days **Concurrent treatment:** not reported All patients were free of any medications for at least 10 days before the treatment and were advised not to take any other medications during the course of the study
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge ("dry ear"), measured at 1 to 2 weeks. Otoscopically confirmed. **Secondary outcomes:** • Hearing measured as the pure-tone average of air conduction thresholds across 4 frequencies tested (500 Hz, 1000 Hz, 2000 Hz and 4000 Hz), of the affected ear • Serious complications, including intracranial complications (such as otitic meningitis, lateral sinus thrombosis and cerebellar abscess) and extra cranial complications (such as mastoid abscess, postauricular fistula and facial palsy), and death
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly divided into two groups." Comment: specific method not reported
Allocation concealment (selection bias)	Unclear risk	Comment: no method reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no blinding or placebo mentioned. No other information on whether there was other concurrent treatment such as aural toileting, except that "taking any other medication… were excluded". The treatment regimens were the same for both groups.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no blinding or placebo mentioned. The treatment regimens were the same for both groups.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Patients who did not use the topical solutions regularly and those who had taken any other medication during the study period were also excluded…"

Tutkun 1995 *(Continued)*

		Comment: it is unclear whether this statement referred to recruitment criteria or exclusion of patients after randomisation. There is no information regarding how many patients this related to, nor whether the patients who were excluded were different to those who completed. The study reported the results of 24 patients in the ciprofloxacin group and 20 patients in the gentamicin group It is unclear if there were dropouts from the intervention arm.
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol was identified on clinicaltrials.gov or the European Clinical Trials registry. All of the outcomes listed in the methods section of the report are also presented in the results section. Standard deviations are not provided for continuous outcomes. Insufficient information to judge.

van Hasselt 1997

Methods	Three-arm, non-blinded, parallel-group RCT, with 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 and 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 group, 30 in neomycin/polymyxin B group and 28 in acetic acid/spirit group
	
	Participant (baseline) characteristics:
	
	• Age: not specified - "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
	• 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)

van Hasselt 1997 *(Continued)*

	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:** for 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, 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 patients had bilateral disease in the ofloxacin, neomycin and antiseptic acid groups respectively. The costs of treatment were DM 10.00 for ofloxacin ear drops, DM 0.60 for neomycin/polymyxin B ear drops 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: original report 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 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 most participants.
Allocation concealment (selection bias)	Unclear risk	Comment: there is no mention of allocation concealment

van Hasselt 1997 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: there is 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 results of outcome could not be found. There is no protocol available on the WHO clinical trial registry.

van Hasselt 1998a

Methods	Four-arm, double-blind, parallel-group RCT, with 2-week duration of treatment and 8-week duration of follow-up

Participants	**Location:** Malawi, rural, unclear number of sites
	
	Setting of recruitment and treatment: community-based, study presented in 1998
	
	Sample size: 107 children (151 ears)
	
	• **Number randomised:** unclear
	• **Number completed:** unclear
	
	Participant (baseline) characteristics:
	
	• Age: not specified - "mainly children"
	• Gender (F/M): not reported
	• Main diagnosis: CSOM for more than 2 months
	• High-risk population:
	  * 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: not reported
	  * Presence of mucopurulent discharge: not reported
	  * Duration of symptoms (discharge): 2 months

van Hasselt 1998a *(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:

- CSOM for more than 2 months

Exclusion criteria:

- Uncooperative with suction cleaning

Interventions	**Intervention 1:** neomycin/polymyxin-B, ear drops, no information on concentration, 6 drops/7 days. Duration of treatment = 2 weeks. **Intervention 2:** neomycin/polymyxin-B, ear drops, no information on concentration, 6 drops/12 hours. Duration of treatment = 2 weeks. **Intervention 3:** ofloxacin 0.3%, ear drops, 6 drops/7 days. Duration of treatment = 2 weeks. **Intervention 4:** ofloxacin 0.3%, ear drops, 6 drops/12 hours. Duration of treatment = 2 weeks. **Concurrent treatment:** weekly suction cleaning in all groups (no information about methods used). No other information.
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Resolution of ear discharge or "dry ear" measured at between 1 week to 2 weeks, 2 to 4 weeks and after 4 weeks. Unclear if otoscopically confirmed. **Secondary outcomes:** • Not reported
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** unclear **Methods for reporting outcomes of patients with bilateral disease:** counting bilateral ears separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomised" Comment: no information about sequence generation. A lack of baseline characteristics makes it difficult to determine whether there was bias due to the randomisation sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no information about allocation concealment

van Hasselt 1998a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Double-blind" Comment: authors state that the trial was double-blind but the treatment regimens were not the same (once weekly versus twice daily) and there was no mention of placebo used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Double-blind" Comment: authors state that the trial was double-blind but the treatment regimens were not the same (once weekly versus twice daily) and there was no mention of placebo used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: the number of "defaulting ears" was 15% at 8 weeks, however it is not possible to determine whether the people that "defaulted" were evenly balanced across the different treatment groups. No reasons are provided for dropouts.
Selective reporting (reporting bias)	High risk	Comment: the study was not published and was only reported as a conference presentation. It is not possible to evaluate the methods fully due to lack of information presented. No protocol was available on the WHO clinical trials registry.

CSOM: chronic suppurative otitis media; F: female; HPMC: hydroxypropyl methyl-cellulose; M: male; RCT: randomised controlled trial; WHO: World Health Organization

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

Study	Reason for exclusion
Abbott 2016	POPULATION: not CSOM (acute otitis media without perforation)
Alper 2000	POPULATION: animal study (monkeys)
Baba 1980	INTERVENTION: comparison of antibiotics within same class and spectrum of activity (cefroxadine versus cephalexin); cefroxadine is a withdrawn drug DURATION: only 6 days of follow-up
Baba 1982b	POPULATION: acute suppurative otitis media, including acute otitis media
Baba 1983	POPULATION: acute suppurative otitis media
Baba 1983b	POPULATION: acute suppurative otitis media
Baba 1986	STUDY DESIGN: not a RCT (all patients received same treatment, aztreonam)
Baba 1987	POPULATION: acute suppurative otitis media
Baba 2008	STUDY DESIGN: not a RCT (all patients received the same intervention)
Berman 1990	POPULATION: middle ear effusion, not CSOM
Blekher 1967	INTERVENTION: not interventions of interest
Block 2000	POPULATION: not CSOM (acute otitis media without perforation of tympanic membrane)

Study	Reason for exclusion
Bluestone 2001	STUDY DESIGN: not a RCT (systematic review)
Boesorire 2000	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Brook 1979	STUDY DESIGN: not a RCT - (alternative treatment) aminoglycosides only added when Gram-negative organisms present in large numbers
Brook 1980	STUDY DESIGN: not a RCT (all patients received the same intervention, additional intervention only added based on bacteriological findings)
Bross Soriano 1996	POPULATION: AOM; patients with CSOM were excluded
Browning 1983	INTERVENTION: standard antibiotics were not given, the choice was dependent on cultures
Browning 1988	COMPARISON: variety of topical antibiotics + 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
Connolly 1997	INTERVENTION: compared method of administration, i.e. delivery system (spray versus drops) of neomycin-dexamethasone
Couzos 2003	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Crowther 1991	COMPARISON: topical antibiotic + variety of steroids (see CSOM-4)
Deguchi 1985	STUDY DESIGN: not a RCT
Deguchi 1986	STUDY DESIGN: not a RCT
Deitmer 2002	STUDY DESIGN: not a RCT
Dellamonica 1995	INTERVENTION: within-class comparison (cephalosporin)
Dohar 2002	STUDY DESIGN: not a RCT (short review)
Eason 1986	COMPARISON: systemic antibiotics versus none (see CSOM-2), antiseptics versus none (see CSOM-5), aural toilet versus none (see CSOM-7)
Esposito 1992	COMPARISON: topical versus systemic antibiotics (see CSOM-3)
Esposito 2000	STUDY DESIGN: not a RCT (all patients had the same intervention - ceftazidime)
Fliss 1990	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Fombeur 1994	STUDY DESIGN: not a RCT (no mention of randomisation); INTERVENTION: high-dose versus low-dose ciprofloxacin
Fraysse 1988	INTERVENTION: fenspiride (a bronchodilator/anti-inflammatory agent) is not an intervention under investigation
Garcia-Rodriguez 1993	POPULATION: mixture of patients, less than half had CSOM. Patients were not stratified by diagnosis
Gehanno 1997	STUDY DESIGN: not a RCT (all patients had the same intervention)

Study	Reason for exclusion
Gendeh 2001	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Ghosh 2012	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Granath 2007	POPULATION: not CSOM (patients with recurrent AOM with discharge through tympanostomy tube)
Gupta 2015	COMPARISON: antibiotic versus antiseptic (see CSOM-6)
Gyde 1981	POPULATION: less than 50% (27/68) had CSOM
Gyde 1982	POPULATION: less than 50% had CSOM
Harris 2016	STUDY DESIGN: not a RCT (systematic review)
Helmi 2000	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Hemlin 1997	POPULATION: unilateral or bilateral secretory otitis media (COME); INTERVENTION: systemic corticosteroids
Hwang 2015	STUDY DESIGN: not a RCT (case control study)
I-HEAR-BETA	COMPARISON: systemic antibiotic versus none (see CSOM-2), topical antiseptic versus none (see CSOM-5), topical antiseptic versus topical antibiotic (see CSOM-6)
Indudharan 2005	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
ISRCTN12149720	INTERVENTION: antimicrobial peptide OP145
ISRCTN84220089	INTERVENTION: antimicrobial peptide OP145
ISRCTN86106121	INTERVENTION: not an intervention of interest to the review (oral zinc sulphate)
Jahn 1984	STUDY DESIGN: not a RCT
Jang 2004	STUDY DESIGN: not a RCT (mentioned use of a "control group", no mention of randomisation)
Jaya 2003	COMPARISON: topical antibiotic versus topical antiseptic (see CSOM-6)
Jiang 2016	INTERVENTION: comparison of 2 agents of the same class of antibiotics (erythromycin versus azithromycin) used in addition to a traditional Chinese medicine product
Kadar 2003	STUDY DESIGN: not a RCT
Kashiwamura 2004	STUDY DESIGN: cohort (no comparison group); POPULATION: less than 50% with CSOM
Kenna 1986	STUDY DESIGN: not a RCT - cohort study (no comparison group)
Khanna 2000	INTERVENTION: culture sensitivity-based prescribing
Khon 2012	POPULATION: not CSOM - either diffuse otitis externa or acute otitis externa; STUDY DESIGN: no evidence of randomisation
Kiris 1998	COMAPRISON: daily aural toilet versus singular aural toilet (see CSOM-7)
Kothari 1969	STUDY DESIGN: not a RCT (no comparison)

Study	Reason for exclusion
Kovacic 1999	STUDY DESIGN: not a RCT (compared ofloxacin in patients who had previous ear surgery versus no previous ear surgery)
Kurilin 1976	STUDY DESIGN: not a RCT (no mention of randomised controlled study design or control group included for comparison)
Lancaster 1999	STUDY DESIGN: not a RCT (cross-sectional survey)
Lancaster 2003	STUDY DESIGN: not a RCT (compared compliance)
Lang 1992	STUDY DESIGN: not a RCT (case series)
Lautala 1983	STUDY DESIGN: not a RCT (case series)
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)
Li 2004	INTERVENTION: not an intervention of interest to the review (self-prepared Chinese herbal medicine ear drops)
Loock 2012	COMPARISON: variety of topical antiseptics (see CSOM-5), topical antibiotic versus topical antiseptic (see CSOM-6)
Lorentzen 1978	POPULATION: AOM with intact or spontaneously erupted tympanic membrane; INTERVENTION: surgery
Macfadyen 2005	COMPARISON: topical antibiotic versus topical antiseptic (see CSOM-6)
Manolidis 2004	STUDY DESIGN: not a RCT (review)
Mendelman 1992	POPULATION: acute suppurative otitis media (symptoms of 7 days or less)
Merifield 1993	STUDY DESIGN: not a RCT (case series)
Mesure 1973	POPULATION: in clinical trial part of study (part 2) only 1 case of chronic otitis media
Minja 2006	COMPARISON: systemic antibiotic versus none (see CSOM-2) and topical antiseptic versus none (see CSOM-5)
Miro 2000	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Mora 2012	INTERVENTION: polyvalent bacterial lysate (antigens)
Morgon 1976	STUDY DESIGN: single-arm study
NCT02592096	INTERVENTION: phase I dose finding trial - compared different concentrations of pazufloxacin
NCT02817347	INTERVENTION: phase II trial - compared different concentrations of piperacillin against tazobactam plus dexamethasone
Nwokoye 2015	COMPARISON: variety of systemic antibiotics (see CSOM-2)

Study	Reason for exclusion
Onali 2018	COMPARISON: systemic antibiotic versus none (see CSOM-2)
Otwombe 2003	STUDY DESIGN: systematic review, not a RCT
Panchasara 2015	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Papastavros 1989	COMPARISON: topical antiseptic versus none (see CSOM-5)
Picozzi 1983	COMPARISON: topical antibiotic + steroid versus none (see CSOM-4)
Picozzi 1984	COMPARISON: systemic metronidazole versus placebo in people who already had gentamicin plus hydrocortisone ear drops (see CSOM-2)
Poliakova 1991	STUDY DESIGN: not a RCT
Povedano 1995	COMPARISON: systemic versus topical antibiotics (see CSOM-3)
Principi 1995	POPULATION: acute and recurrent otitis media
Quick 1973	POPULATION: not CSOM (included acute tonsillitis, acute pharyngitis, acute sinusitis, acute otitis media, chronic sinusitis and peritonsillar)
Quick 1975	POPULATION: not CSOM (only 6/145 patients had otitis media)
Renukananda 2014	COMPARISON: systemic antibiotics added onto topical antibiotics (see CSOM-2)
Rotimi 1990	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Saez-Llorens 2005	POPULATION: AOM
Sanchez Gonzales 2001	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Shkil' 1964	INTERVENTION: no comparison of interest (antiseptic arms used a number of different agents - unclear which)
Singhal 1992	STUDY DESIGN: not a RCT (no comparison group)
Smith 1996	COMPARISON: aural toilet versus no treatment (see CSOM-7)
Somekh 2000	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Stenstrom 1991	POPULATION: acute otitis media, not CSOM
Subramaniam 2001	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
Sultan 2017	STUDY DESIGN: not a RCT - single intervention (oral levofloxacin) studied
Sumitsawan 1995	STUDY DESIGN: not a RCT - single intervention (ofloxacin drops) studied
Supiyaphun 1995	STUDY DESIGN: not a RCT (cohort - all patients received same treatment)
Tachibana 1986	STUDY DESIGN: not a RCT (all patients received same treatment)
Thomsen 1976	STUDY DESIGN: not a RCT; POPULATION: acute suppurative otitis media

Study	Reason for exclusion
Tong 1996	COMPARISON: steroids added onto topical antibiotics (see CSOM-4)
van der Veen 2007	COMPARISON: systemic antibiotics versus none (see CSOM-2)
van Dongen 2014	POPULATION: 1) inclusion of minimum 2 weeks (review defined exclusion of 6 weeks perioperatively); 2) max duration of otorrhoea was 1 week
van Hasselt 1998b	COMPARISON: povidone iodine added in hydroxypropyl methylcellulose ear drops (see CSOM-5)
Vishwakarma 2015	COMPARISON: topical antiseptic versus topical antibiotic (see CSOM-6)
Wilde 1995	INTERVENTION: different ways of administering the same ear drops (ribbon gauze versus drops)
Wintermeyer 1997	STUDY DESIGN: not a RCT (cohort)
Wright 2009	STUDY DESIGN: not a RCT (review)
Xu 1999	INTERVENTION: not a comparison of interest - antibiotics versus Chinese medicine
Yuen 1994	COMPARISON: systemic versus topical antibiotics (see CSOM-3)

AOM: acute otitis media; CSOM: chronic suppurative otitis media; RCT: randomised controlled trial

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

Abdul 2005

Methods	Unclear, "comparative study"
Participants	Active chronic suppurative otitis media
Interventions	Local ciprofloxacin versus aluminium acetate 3.5% versus no treatment
Outcomes	Unclear
Notes	Unable to locate paper. It is not clear if there was a control arm from the title of the paper.

Abes 1998

Methods	Randomised controlled clinical trial; single-blinded
Participants	Patients 9 to 54 years old with CSOM (3 weeks)
Interventions	Experimental intervention: ofloxacin 0.3% otic solution, 5 drops twice daily for 2 to 4 weeks Control intervention: polymixin otic solution, 3 to 5 drops to the affected ear 3 times daily for 2 to 4 weeks
Outcomes	Cure rate; resolution of ear discharge; bacterial eradication rate; adverse drug event
Notes	Concealment of allocation is not clear Data from Abes 2003

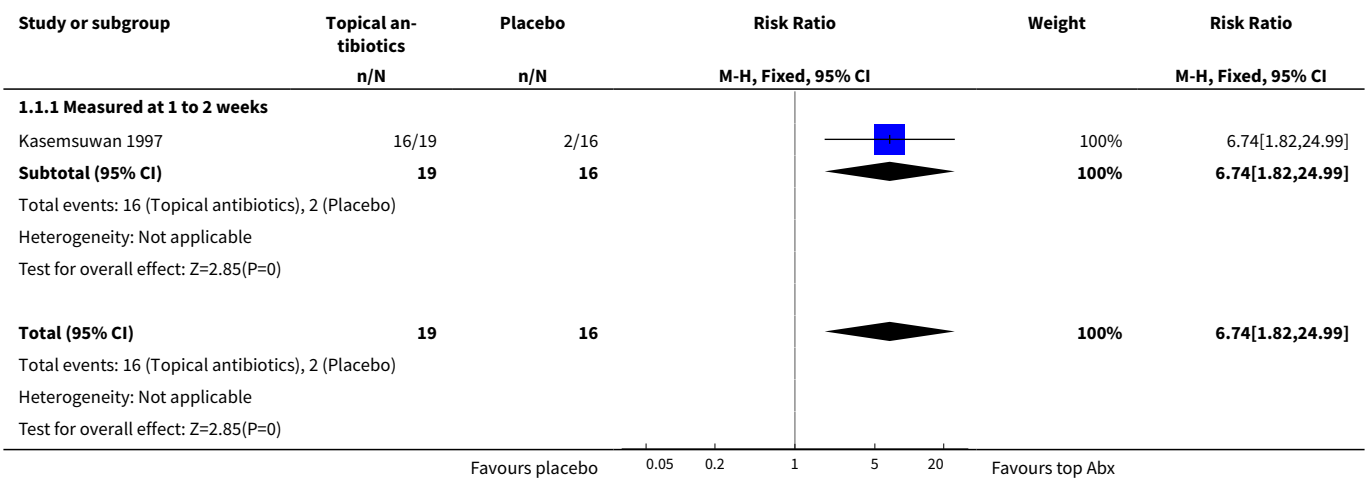
CSOM: chronic suppurative otitis media

DATA AND ANALYSES

Comparison 1. Topical ciprofloxacin versus placebo (aural toileting in both arms)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge	1	35	Risk Ratio (M-H, Fixed, 95% CI)	6.74 [1.82, 24.99]
1.1 Measured at 1 to 2 weeks	1	35	Risk Ratio (M-H, Fixed, 95% CI)	6.74 [1.82, 24.99]

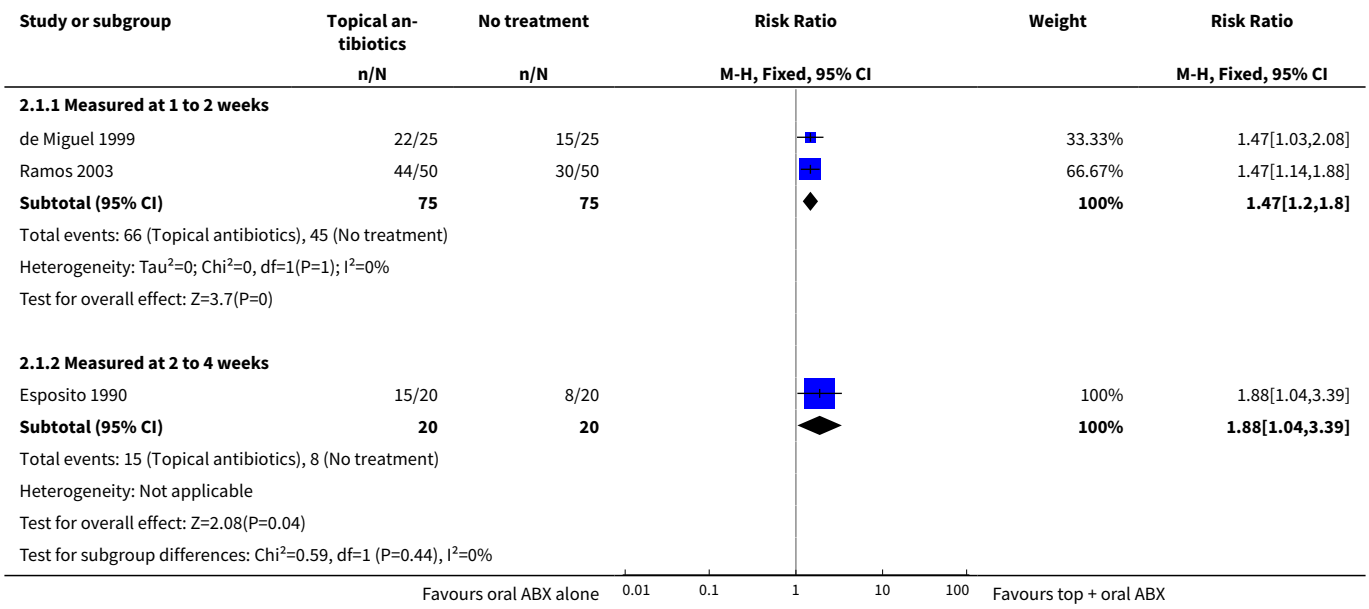
Analysis 1.1. Comparison 1 Topical ciprofloxacin versus placebo (aural toileting in both arms), Outcome 1 Resolution of ear discharge.



Comparison 2. Topical ciprofloxacin added on to oral ciprofloxacin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Measured at 1 to 2 weeks	2	150	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.20, 1.80]
1.2 Measured at 2 to 4 weeks	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.04, 3.39]

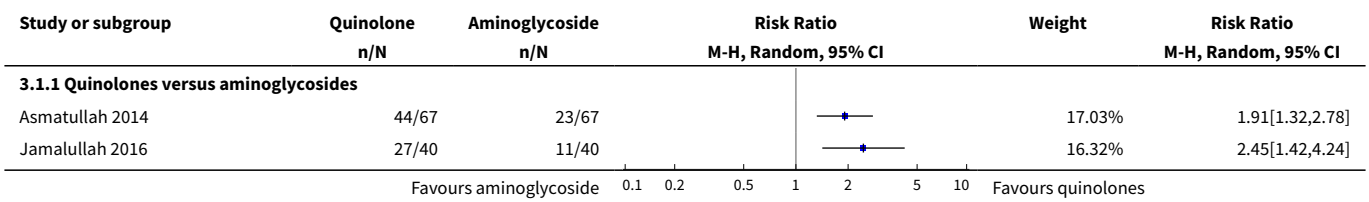
Analysis 2.1. Comparison 2 Topical ciprofloxacin added on to oral ciprofloxacin, Outcome 1 Resolution of ear discharge.

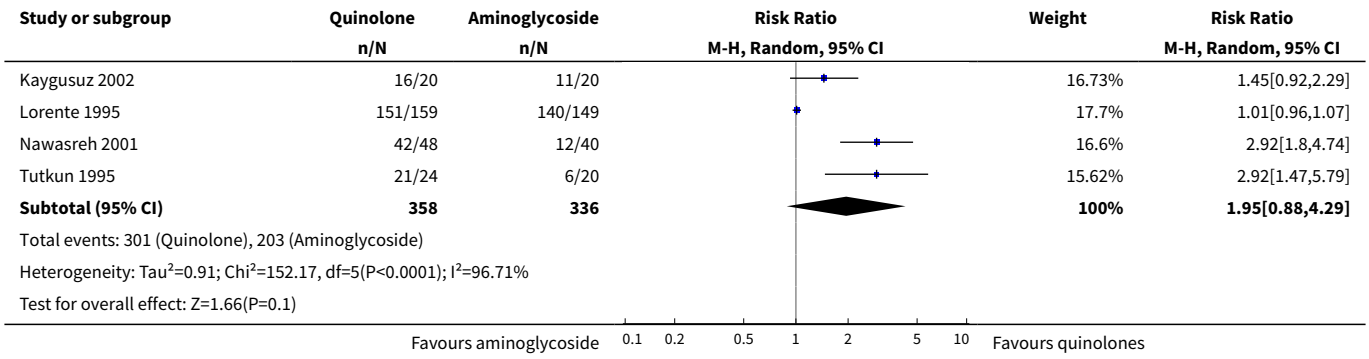


Comparison 3. Quinolones versus others

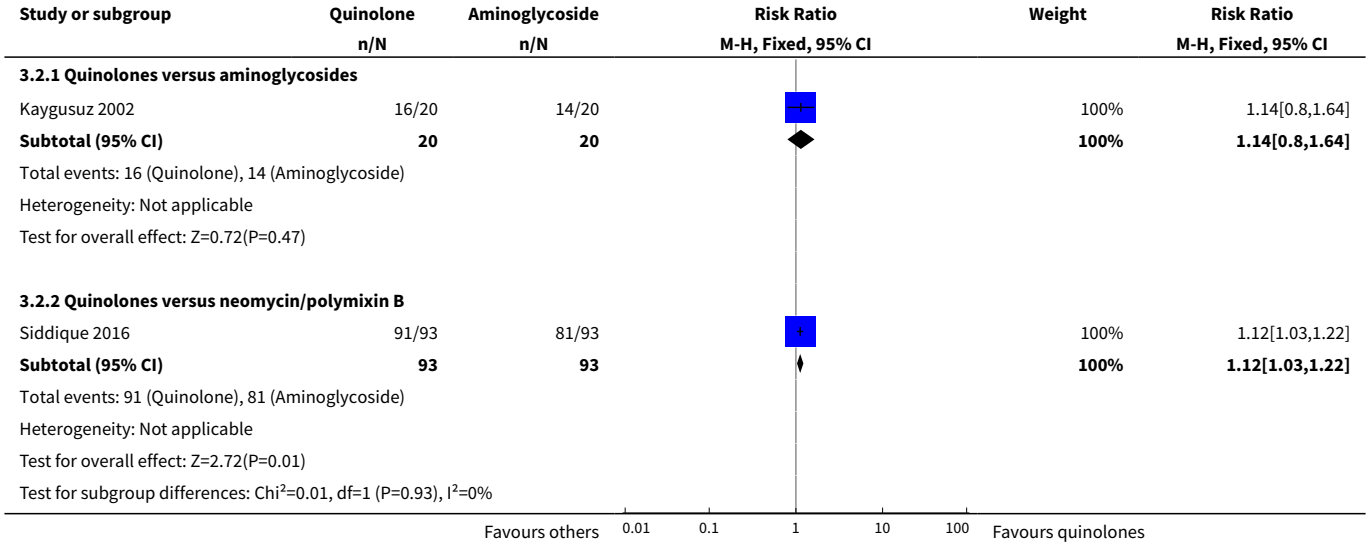
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge (1 to 2 weeks)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Quinolones versus aminoglycosides	6	694	Risk Ratio (M-H, Random, 95% CI)	1.95 [0.88, 4.29]
2 Resolution of ear discharge (2 to 4 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Quinolones versus aminoglycosides	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.80, 1.64]
2.2 Quinolones versus neomycin/polymixin B	1	186	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.03, 1.22]

Analysis 3.1. Comparison 3 Quinolones versus others, Outcome 1 Resolution of ear discharge (1 to 2 weeks).





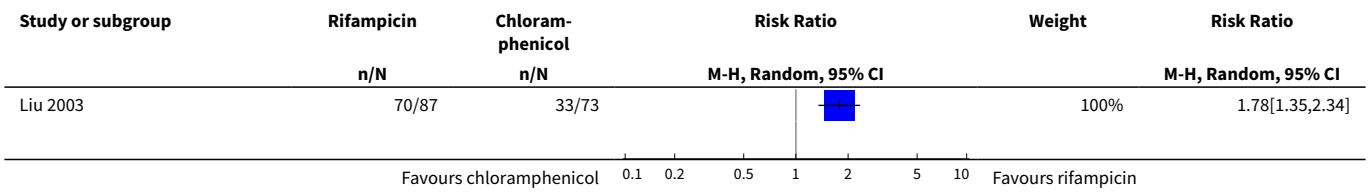
Analysis 3.2. Comparison 3 Quinolones versus others, Outcome 2 Resolution of ear discharge (2 to 4 weeks).

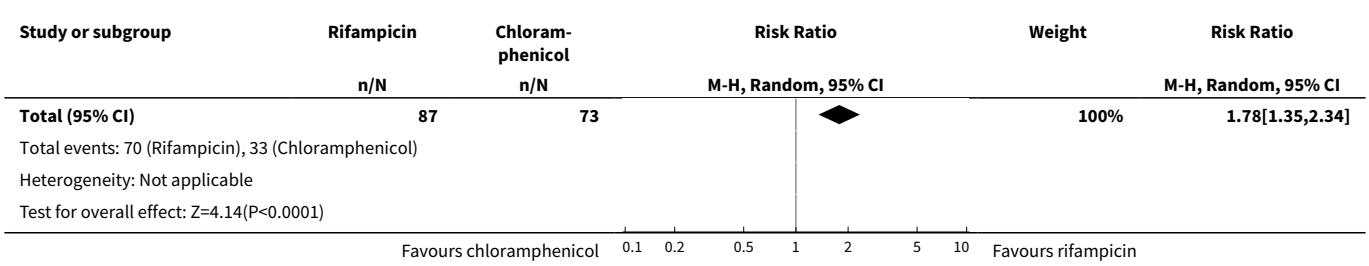


Comparison 4. Rifampicin versus chloramphenicol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Resolution of ear discharge (1 to 2 weeks)	1	160	Risk Ratio (M-H, Random, 95% CI)	1.78 [1.35, 2.34]

Analysis 4.1. Comparison 4 Rifampicin versus chloramphenicol, Outcome 1 Resolution of ear discharge (1 to 2 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
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 2018b).
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 2018a).
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

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

Monobactams	Aztreonam	Parenteral

Table 3. Summary of study characteristics

Ref ID (no. participants)	Setting	Population	Intervention 1	Intervention 2	Treatment duration	Follow-up	Background Treatment	Notes
Topical antibiotics versus placebo/no treatment (no background or aural toileting)								
Kasemsuwan 1997 (n = 50)	Specialist hospital, Thailand	Mucopurulent otorrhoea with perforated tympanic membrane (CSOM)	Ciprofloxacin 250 mg/mL, 5 drops per 8 hours	Saline, 5 drops per 8 hours	1 week	1 week	Aural toilet on day 1, 4 and 7	Randomised by person
Topical antibiotic versus placebo/no treatment (systemic antibiotic as background treatment)								
de Miguel 1999 (n = 50)	General hospital, Spain	Simple chronic otitis media (36%), osteitic chronic otitis media (25.6%), cholesteatomas chronic otitis media (13.6%), post surgery cases (24.8%)	Topical ciprofloxacin 0.2%, 3 drops per 8 hours and oral ciprofloxacin, 500 mg per 12 hours	No treatment	7 days	15 days	Aural toileting before beginning treatment, analgesics and antipyretics. Oral ciprofloxacin, 500 mg per 12 hours	Part of 5-arm trial Randomised by person
Esposito 1990 (n = 40)	University clinic, Italy	Mild or moderate CSOM in acute stage	Ciprofloxacin 250 µg/mL, 3 drops per 12 hours	No treatment	5 to 10 days	2 weeks	Oral ciprofloxacin, 250mg per 12 hours	Part of 3-arm trial Randomised by person
Mira 1993 (n = 50)	University clinic, Italy	Recurrence of CSOM or suppuration following mastoidecto-	Ceftizoxime 500 µg/mL, 2 x 2 mL washes per 12 hours	Saline, 2 x 2 mL washes per 12 hours	1 week	3 weeks	Systemic ceftizoxime by intramuscular route every 12 hours Aural toilet at first visit	Randomised by person

Table 3. Summary of study characteristics *(Continued)*

		my or tympanoplasty						
Ramos 2003 (n = 100)	ENT departments, Spain	Simple chronic otitis media (42.7%), chronic otitis media with osteolysis (19%), chronic cholesteatoma (14%), chronic otorrhoea in operated ears 24.3%)	Ciprofloxacin 0.2%, 0.5 mL per 8 hours	No treatment	1 week	10 days	Oral ciprofloxacin, 500 mg per 12 hours	Part of a 6-arm trial Randomised by person
Quinolones versus aminoglycosides								
Asmatullah 2014 (n = 134)	ENT department, Pakistan	Active tubotympanic type CSOM	Ofloxacin 0.3%, 12 drops per day	Gentamycin 0.3%, 12 drops per day	10 days	2 weeks	None mentioned	Randomised by person
Fradis 1997 (n = 40)	Outpatient clinic, Israel	Chronic otitis media	Ciprofloxacin (no conc), 15 drops per day	Tobramycin (no conc), 15 drops per day	3 weeks	3 weeks	None mentioned	Part of 3-arm trial Randomised by ear
Kaygusuz 2002 (n = 40)	University ENT clinic, Turkey	CSOM	Ciprofloxacin 0.3%, 6 drops per day	Tobramycin 0.3%, 6 drops per day	3 weeks	3 weeks	Daily aspiration	Translated from Turkish Part of 4-arm trial Randomised by person.
Nawasreh 2001 (n = 88)	Unclear setting, Jordan	CSOM and intermittent mucopurulent heavy discharge for more than 1 year	Ciprofloxacin 200 µg/mL (0.02%), 15 drops per day	Gentamicin 5 mg/mL, 15 drops per day	10 days	2 weeks	None mentioned	Randomised by person

Table 3. Summary of study characteristics *(Continued)*

Lorente 1995 (n = 308)	Hospital ENT clinics, Spain	CSOM (purulent discharge > 3 months and perforated membrane)	Ciprofloxacin 0.3%, 15 drops per day	Gentamycin 0.3%, 15 drops per day	8 days	30 days	Unclear	Translated from Spanish Assume this is same as Sabater paper Randomised by person
Tutkun 1995 (n = 44)	University hospital, Turkey	CSOM and purulent discharge for more than 1 year	Ciprofloxacin 200 µg/mL (0.02%), 15 drops per day	Gentamicin 5 mg/mL, 15 drops per day	10 days	10 days	None mentioned	Randomised by person
Jamalullah 2016 (n = 80)	Otolaryngology department, Pakistan	CSOM (tubotympanic type)	Ofloxacin 0.6%, 12 drops per day	Gentamycin 0.3%, 12 drops per day	2 weeks	2 weeks	One aural toilet at start	Randomised by person
Quinolones versus others								
Siddique 2016 (n = 200)	Specialist hospital, Pakistan	Tubotympanic type of CSOM	Ciprofloxacin (no conc), 3 drops per 12 hours	Neomycin/polymixin/gramicidin-D (no conc), 2 drops per 12 hours	Unclear (probably 4 weeks)	4 weeks	No information	Randomised by person
van Hasselt 1997 (n = 50)	Rural setting, Malawi	Children with CSOM	Ofloxacin 0.3%, 3 drops per 8 hours	Neomycin 0.5%/polymixin B 0.1%, 3 drops per 8 hours	2 weeks	2 weeks	Aural toilet at start and weekly	Part of a 3-arm trial Only presented as an internal report Unclear unit of randomisation, results reported by ear
van Hasselt 1998a (n = unclear)	Rural setting, Malawi	"Mainly children" with CSOM	Ofloxacin 0.3%, 6 drops per 12 hours	Neomycin/polymixin B (no conc), 6 drops per 12 hours	2 weeks	8 weeks	Aural toilet at start and weekly	Only a presentation given at a conference available Unclear unit of randomisation, results presented by ear Part of 4-arm trial - once weekly arms have not been included.

Table 3. Summary of study characteristics *(Continued)*

Aminoglycosides versus trimethoprim, sulphacetamide and polymixin B (TSP)								
Gyde 1978 (n = 91)	Outpatient clinic, Canada	Otitis externa (21%), CSOM (51%), subacute otitis (16%), postoperative infection (21%)	Trimethoprim, sulphacetamide and polymyxin B, 16 drops per day	Gentamicin 0.3%, 16 drops per day	Mean: 16 days	12 months	Not reported	Translated from French Randomised by person but reported by ear Semi cross-over trial
Rifampicin versus chloramphenicol								
Liu 2003 (n = 160)	Outpatient department, China	CSOM	Rifampicin 0.1%, 9 drops per day	Chloramphenicol 0.25%, 9 drops per day	2 weeks	2 weeks	3% hydrogen peroxide ear wash daily	Translated from Chinese Randomised by person

CSOM: chronic suppurative otitis media

Table 4. Resolution of ear discharge outcome

Reference	Unit of randomisation	Reported	Definition	Otoscopically confirmed?	Time points	Notes
Asmatullah 2014	Person	Person	"no discharge"	Yes	1 to 2 weeks (10 days)	—
de Miguel 1999	Person	Person	"global index of clinic microbiological cure"	Yes	1 to 2 weeks (7 days)	—
Esposito 1990	Person	Person	"cured" (no definition but assumed to be no discharge)	Unclear, paper states "clinically examined"	1 week to 2 weeks (6 to 11 days) and 2 to 4 weeks (19 to 24 days)	1 to 2 weeks examined but not reported
Fradis 1997	Ear	Ear	"clinical success as defined as cessation of otorrhea and eradication of the microorganisms in the post treatment culture"	Unclear	2 to 4 weeks (21 days)	Unclear how many patients had bilateral ear disease in each group
Gyde 1978	Person	Ear	"dry ear" and a negative culture at 3 weeks or a real improvement in at 3 weeks and the cessation of discharge at 6 weeks	Unclear	2 to 4 weeks (3 weeks) and after 4 weeks (6 weeks)	Semi crossover trial. It does not appear that any consideration of the correlation of results between ears has been taken into account. If there was a treatment failure 'ears' were transferred to the alternative groups. These results have not been included in the analysis. If the ear was not dry on review at 6 months, treatment for 3 weeks with the alternative

Table 4. Resolution of ear discharge outcome *(Continued)*

						treatment was completed with review after 6 months
Jamalullah 2016	Person	Person	"absence" of aural discharge	Yes	2 to 4 weeks (2 weeks)	—
Kasemsuwan 1997	Person	Person	"cure"	Unclear	1 to 2 weeks (7 days)	—
Kaygusuz 2002	Person	Ear	Assessed using 3-point scale (2 points = no drainage)	Yes	2 to 4 weeks (day 14 and 21)	Unclear method of allocation, unsure if random selection of study ear
Liu 2003	Person	Person	"Cured: otorrhea disappeared, mucosal hyperaemia of the tympanic membrane and tympanic cavity disappeared. Significantly effective: no complaints of otorrhea, no visible purulence in the ear canal and tympanic cavity, and nonvisible or slight hyperaemia of the tympanic membrane and the tympanic canal"	Unclear	1 to 2 weeks (2 weeks)	—
Lorente 1995	Person	Person	"Complete resolution of ear discharge"	Yes	1 to 2 weeks (8 days) and after 4 weeks (30 days)	—
Mira 1993	Person	Person	Not reported in a way that could be used in the review	N/A	N/A	Paper plotted the time course of otorrhoea (quantity) on a scale of 0 to 3 at 3, 7 and 21 days
Nawasreh 2001	Person	Person	"cessation of otorrhea"	Yes	1 to 2 weeks (10 days)	—
Ramos 2003	Person	Person	"cured" according to "indices de curacion"	Unclear	1 to 2 weeks (10 days)	—
Siddique 2016	Person	Person	"absence of discharge from middle ear cavity and no inflammation/congestion in middle ear mucosa and tympanic membrane"	Unclear	2 to 4 weeks (4 weeks)	15 patients (8%) had bilateral disease but how these cases were handled is not stated. The denominator in the

Table 4. Resolution of ear discharge outcome *(Continued)*

						trials is the person so it is assumed that no double counting occurred.
Tutkun 1995	Person	Person	"cessation of otorrhea"	Yes	1 to 2 weeks (10 days)	—
van Hasselt 1997	Unclear, most likely person	Ear	"dry ear"	Unclear	1 to 2 weeks (1 week) and after 4 weeks (> 2 weeks)	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 patients had bilateral disease in the ofloxacin, neomycin and antiseptic acid groups respectively.
van Hasselt 1998a	Unclear	Ear	"inactive ear" - completely dry middle ear	Unclear	1 to 2 weeks (1 week), 2 to 4 weeks (2 weeks) and after 4 weeks (8 weeks)	Counting bilateral ears separately

N/A: not applicable

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	1 exp Otitis Media/ 2 ("otitis media" or OME).ab,ti.	1 exp otitis media/ 2 ("otitis media" or OME).ab,ti. 3 exp eardrum perforation/

(Continued)

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

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.

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

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.

21 (earach* adj3 (chronic or persist* or recurr* or repeat*)).ab,ti.

22 17 or 18 or 19 or 20 or 21

(Continued)

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 S7 TX perforat* or hole or ruptur* S6 S4 OR S5 S5 TX "ear drum*" or eardrum* or tympanic S4 (MH "Tympanic Membrane")	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 or disease*))):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 13 ((earach* and (chronic or persist* or recurr* or repeat*))):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER

(Continued)

	S3 (MH "Tympanic Membrane Perforation") S2 TX "otitis media" or OME S1 (MH "Otitis Media+")	14 #10 OR #11 OR #12 OR #13 AND INREGISTER

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 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	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)

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

(Continued)

- 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 (%)
	• 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:

(Continued)

	• *[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' • 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).

CONTRIBUTIONS OF AUTHORS

Christopher G Brennan-Jones: clinical guidance at all stages of the review; reviewed the analyses; wrote, reviewed and edited the text of the review.

Lee Yee Chong: scoped the review, designed and wrote the protocol. Screened the search results and selected studies, carried out data extraction, 'Risk of bias' assessment and statistical analyses, reviewed and edited the text of the review.

Karen Head: scoped the review, designed and wrote the protocol. Screened the search results and selected studies, carried out data extraction, 'Risk of bias' assessment and statistical analyses, wrote 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.

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.

DECLARATIONS OF INTEREST

Christopher G Brennan-Jones: Dr Brennan-Jones's research team is primarily funded by the Australian NHMRC and the WA Department of Health. He sits on the national Technical Advisory Group responsible for developing treatment guidelines for otitis media in Australia.

Karen Head: none known.

Lee Yee Chong: 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.

Mahmood F Bhutta: Dr 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).

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