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## Topical antibiotics with steroids for chronic suppurative otitis media (Review)

Brennan-Jones CG, Chong LY, Head K, Burton MJ, Schilder AGM, Bhutta MF

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## [Intervention Review]

# Topical antibiotics with steroids for chronic suppurative otitis media

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## ABSTRACT

### Background

Chronic suppurative otitis media (CSOM) is a chronic inflammation and often polymicrobial 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. Topical antibiotics 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 steroids, antiseptics or ear cleaning (aural toileting). Antibiotics are commonly prescribed in combined preparations with steroids.

### Objectives

To assess the effects of adding a topical steroid to topical antibiotics in the treatment of people with chronic suppurative otitis media (CSOM).

### Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Register; Central Register of Controlled Trials (CENTRAL 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Ovid MEDLINE; Ovid Embase; CINAHL; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials.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 16 March 2020.

### 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 combination of a topical antibiotic agent(s) of any class and a topical corticosteroid (steroid) 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 and steroid compared to a) placebo or no intervention and b) another topical antibiotic.

### 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; ear pain (otalgia) or discomfort or local irritation. Secondary outcomes included hearing, serious complications and ototoxicity.

## Main results

We included 17 studies addressing 11 treatment comparisons. A total of 1901 participants were included, with one study (40 ears) not reporting the number of participants recruited, which we therefore could not account for. No studies reported health-related quality of life. The main comparisons were:

### 1. Topical antibiotics with steroids versus placebo or no treatment

Three studies (210 participants) compared a topical antibiotic-steroid to saline or no treatment. Resolution of discharge was not reported at between one to two weeks. One study (50 'high-risk' children) reported results at more than four weeks by ear and we could not adjust the results to by person. The study reported that 58% (of 41 ears) resolved with topical antibiotics compared with 50% (of 26 ears) with no treatment, but the evidence is very uncertain. One study (123 participants) noted minor side effects in 16% of participants in both the intervention and placebo groups (very low-certainty evidence). One study (123 participants) reported no change in bone-conduction hearing thresholds and reported no difference in tinnitus or balance problems between groups (very low-certainty evidence). One study (50 participants) reported serious complications, but it was not clear which group these patients were from, or whether the complications occurred pre- or post-treatment. One study (123 participants) reported that no side effects occurred in any participants (very low-certainty evidence).

### 2. Topical antibiotics with steroids versus topical antibiotics (same antibiotics) only

Four studies (475 participants) were included in this comparison. Three studies (340 participants) compared topical antibiotic-steroid combinations to topical antibiotics alone. The evidence suggests little or no difference in resolution of discharge at one to two weeks: 82.7% versus 76.6% (risk ratio (RR) 1.08, 95% confidence interval (CI) 0.96 to 1.21; 335 participants; 3 studies (4 study arms); low-certainty evidence). No results for resolution of discharge after four weeks were reported. One study (110 participants) reported local itchiness but as there was only one episode in each group it is uncertain whether there is a difference (very low-certainty evidence). Three studies (395 participants) investigated suspected ototoxicity but it was not possible to determine whether there were differences between the groups for this outcome (very low-certainty evidence). No study reported serious complications.

### 3. Topical antibiotics with steroids compared to topical antibiotics alone (different antibiotics)

Nine studies (981 participants plus 40 ears) evaluated a range of comparisons of topical non-quinolone antibiotic-steroid combinations versus topical quinolone antibiotics alone. Resolution of discharge may be greater with quinolone topical antibiotics alone at between one to two weeks compared with non-quinolone topical antibiotics with steroids: 82.1% versus 63.2% (RR 0.77, 95% CI 0.71 to 0.84; 7 studies; 903 participants, low-certainty evidence). Results for resolution of ear discharge after four weeks were not reported. One study (52 participants) reported usable data on ear pain, two studies (419 participants) reported hearing outcomes and one study (52 participants) reported balance problems. It was not possible to determine whether there were significant differences between the groups for these outcomes (very low-certainty evidence). Two studies (149 participants) reported no serious complications (very low-certainty evidence).

## Authors' conclusions

We are uncertain about the effectiveness of topical antibiotics with steroids in improving the resolution of ear discharge in patients with CSOM because of the limited amount of low-certainty evidence available. Amongst this uncertainty, we found no evidence that the addition of steroids to topical antibiotics affects the resolution of ear discharge. There is also low-certainty evidence that some types of topical antibiotics (without steroids) may be better than topical antibiotic/steroid combinations in improving resolution of discharge. 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

### Benefits and risks of combining antibiotics and steroids as drops, sprays, ointments or creams to treat chronic suppurative otitis media (persistent or recurring ear infection with discharge)

#### Why this is important

Chronic suppurative otitis media (CSOM) is an inflammation and infection of the middle ear that lasts for two weeks or more. People with CSOM usually experience recurrent or persistent ear discharge – pus that leaks out from a hole in the eardrum – and hearing loss.

CSOM is commonly treated with a combination of antibiotics (medicines that fight bacterial infections) and steroids (anti-inflammation medicines) as a topical treatment (that is, in the form of drops, sprays, ointments or creams put directly into the ear). To find out how effective this combination is, and whether it causes unwanted effects, we reviewed the evidence from research studies.

## How we identified and assessed the evidence

We searched for all relevant studies in the medical literature, compared the results and summarised the evidence from all the studies. We also assessed how certain the evidence was, considering factors such as study size and the way studies were conducted. Based on our assessments, we categorised the evidence as being of very low, low, moderate or high certainty.

## What we found

We found 17 studies on over 1901 people with CSOM. People were followed for between 10 days and 20 weeks after treatment was completed.

The studies covered a range of antibiotic plus steroid combinations, and compared them with either no treatment, a fake treatment (placebo), the same antibiotic without steroids or different antibiotics without steroids. Here we report findings from the three main comparisons:

*Topical antibiotics plus steroids compared against placebo (fake treatment) or no treatment (three studies, 210 people)*

We do not know whether antibiotics plus steroids are better or worse than placebo or no treatment for:

- stopping ear discharge at three time points (one to two weeks; two to four weeks; or after four weeks); or
- hearing; or
- causing unwanted effects (such as ear pain or serious complications).

This is because either no studies considered these outcomes or the evidence was of very low certainty.

*Topical antibiotics plus steroids compared against the same topical antibiotic used alone (four studies, 475 people)*

Topical antibiotics plus steroids may make little or no difference to stopping ear discharge after one to two weeks (low-certainty evidence).

We do not know whether antibiotics plus steroids are better or worse than the same topical antibiotic used alone for:

- stopping ear discharge at three time points (one to two weeks; two to four weeks; or after four weeks); or
- hearing; or
- causing unwanted effects (such as ear pain or serious complications).

This is because either no studies considered these outcomes or the evidence was of very low certainty.

*Topical antibiotics other than quinolones (a family of antibiotics) plus steroids compared to topical quinolone antibiotics used alone (nine studies, at least 981 people plus an additional 40 ears)*

Non-quinolone antibiotics plus steroids may not be as effective as quinolone antibiotics used alone at stopping ear discharge after one to two weeks (low-certainty evidence).

We do not know whether non-quinolone antibiotics plus steroids are better or worse for:

- stopping ear discharge at three time points (one to two weeks; two to four weeks; or after four weeks); or
- hearing; or
- causing unwanted effects (such as ear pain or serious complications).

This is because either no studies considered these outcomes or the evidence was of very low certainty.

Across the different comparisons, no studies reported on health-related quality of life.

## What this means

Steroids combined with non-quinolone antibiotics may not be as good as quinolone antibiotics alone to stop ear discharge after one to two weeks (low-certainty evidence).

Too few robust studies have been conducted for us to know whether:

- topical antibiotics plus steroids are better or worse than no treatment or a placebo;

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- adding steroids to a topical antibiotic affects the antibiotic's effectiveness or has an impact on unwanted effects.

**How-up-to date is this review?**

The evidence in this Cochrane Review is current to March 2020.

## SUMMARY OF FINDINGS

### Summary of findings 1. Topical antibiotics with steroids compared to placebo/no treatment for chronic suppurative otitis media

#### Topical antibiotics with steroids compared to placebo/no treatment for chronic suppurative otitis media

**Patient or population:** people (of any age) with chronic suppurative otitis media

**Setting:** various; Solomon Islands community study (one study); United Kingdom medical study (two studies)

**Intervention:** topical antibiotics with steroids

**Comparison:** placebo/no treatment

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Without topical antibiotics with steroids	With topical antibiotics with steroids	Difference		
Resolution of ear discharge at between 1 and up to 2 weeks	None of the studies reported this outcome at this time point.						
Resolution of ear discharge after 4 weeks  Assessed with: otoscopically confirmed  Follow-up: 6 weeks	—	50 (1 RCT)	None of the studies reported this outcome by the individual.  One study conducted in 'high-risk' children reported this outcome by ear at 6 weeks and found that 58% of 41 ears were improved with topical antibiotics (framycetin sulphate, dexamethasone and gramicidin) with steroids compared with 50% of 26 ears with no topical treatment (Eason 1986).			⊕⊕⊕⊕ very low <sup>1</sup>	It is very unclear if there is a difference between the groups in resolution of ear discharge after 4 weeks.
Health-related quality of life	None of the studies reported this outcome.						
Ear pain (otalgia) or discomfort or local irritation  Assessed with: self-assessed  Follow-up: 4 to 6 weeks	—	123 (1 RCT)	None of the studies reported this outcome quantitatively although one study noted that "side effects occurred in 16% of patients in both active and placebo management groups and were minor" (Browning 1988).			⊕⊕⊕⊕ very low <sup>2</sup>	It is very unclear if there is a difference between the groups in ear pain.
Hearing	—	123 (1 RCT)	Browning 1988 reported hearing outcomes but it was unclear what the outcomes were for participants in this specific trial, as the results of participants from previous trials were also included.			⊕⊕⊕⊕ very low <sup>2</sup>	It is very unclear if there is a difference



Assessed with: bone conduction					between the groups in hearing.
Follow-up: 4 to 6 weeks					
Serious complications (including intracranial complications, extracranial complications and death)	—	173 (2 RCTs)	<a href="#">Browning 1988</a> reported that no side effects occurred in any participants, which would include the defined serious complications. <a href="#">Eason 1986</a> reported one case of mastoiditis and one case of meningitis with focal encephalitis. It is not clear which group these patients were from, or whether the complications occurred pre- or post-treatment.	⊕⊕⊕⊕ <b>very low<sup>2</sup></b>	It is very unclear if there is a difference between the groups in serious complications.
Assessed with: self-reported					
Follow-up: 4 to 6 weeks					
Suspected ototoxicity	—	123 (1 RCT)	One study reported that "in the majority there was no change in [bone conduction] thresholds and if a change did occur it was as likely to reflect an improvement as a deterioration...". The study also reported "no increased incidence of otological symptoms, in particular of tinnitus or vertigo, was detected in patients complying to antibiotic-steroid ear drops compared with the pre-management incidence or against that in patients after placebo management" ( <a href="#">Browning 1988</a> ).	⊕⊕⊕⊕ <b>very low<sup>2</sup></b>	It is very unclear if there is a difference between the groups in suspected ototoxicity.
Assessed with: bone conduction					
Follow-up: 4 to 6 weeks					

\***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

<sup>1</sup>Downgraded to very low certainty: downgraded by two levels due to study limitations (risk of bias) because there were concerns about randomisation and lack of blinding and unclear risk of bias for allocation concealment, selective reporting and incomplete outcome data. Downgraded by two levels due to imprecision as there was one small study (50 participants) with results only presented narratively. Downgraded by one level due to indirectness due to the study being conducted in children who were considered to be a 'high-risk' population, which makes it difficult to know whether these results could be reapplied to different populations.

<sup>2</sup>Downgraded to very low certainty: downgraded by two levels due to study limitations (risk of bias) because there were concerns in all of the risk of bias domains across the studies. Downgraded by two levels due to imprecision as the results were from two small studies (173 participants), only presented narratively and, for [Eason 1986](#), it is not clear to which group the events could be attributed or if they occurred before or after treatment. Downgraded by one level due to suspected publication bias as unpublished studies were identified for other comparisons.

## Summary of findings 2. Topical antibiotics with steroids compared to topical antibiotics alone (same antibiotics) for chronic suppurative otitis media

### Topical antibiotics with steroids compared to topical antibiotics alone (same antibiotics) for chronic suppurative otitis media

**Patient or population:** people (of any age) with chronic suppurative otitis media or ear discharge

**Setting:** outpatient ENT clinics in India, Turkey and Spain

**Intervention:** topical antibiotics with steroids

**Comparison:** topical antibiotics alone (same antibiotics)

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			With topical antibiotics alone	With topical antibiotics with steroids	Difference		
Resolution of ear discharge at between 1 to 2 weeks  Assessed with: two otoscopically confirmed, one method unclear  Follow-up: range 10 days to 3 weeks	RR 1.08 (0.96 to 1.21)	(335; 3 RCTs; <a href="#">Kaygusuz 2002</a> ; <a href="#">Panchasara 2015</a> ; <a href="#">Ramos 2003</a> )	Study population  76.6%	82.7% (73.5 to 92.6)	6.1% more (3.1 fewer to 16.1 more)	⊕⊕⊕⊕ <b>low</b> <sup>1</sup>	Topical antibiotics with steroids may result in little to no difference in resolution of ear discharge at 1 to 2 weeks compared with topical antibiotics alone.
Resolution of ear discharge after 4 weeks	None of the studies reported this outcome at this time point.						
Health-related quality of life	None of the studies reported this outcome.						
Ear pain (otalgia) or discomfort or local irritation  Assessed with: self-reported	(RR 0.98, 95% CI 0.06 to 15.28)	105 (1 RCT; <a href="#">Panchasara 2015</a> )	1.9%	1.9% (0.1% to 29.4%)	0% (no difference) (1.8 fewer to 27.5 more)	⊕⊕⊕⊕ <b>very low</b> <sup>2</sup>	It is very unclear if there is a difference between the groups in ear pain/discomfort/local irritation.

Hearing Assessed with: bone conduction Follow-up: 4 weeks	—	135 participants; 152 ears (1 RCT; <a href="#">Indudharan 2005</a> )	One study stated that "28.85% (15/52) treated with gentamicin and 30.23% (13/43) with gentamicin with betamethasone had a bone conduction threshold shift of 5 dB or more, respectively. The deterioration in bone conduction was not statistically significant ( $p > 0.05$ ) whether gentamicin or gentamicin with betamethasone was used" and that "average bone conduction threshold was decreased by 7.70 dB with gentamicin and 8.75 dB with gentamicin with betamethasone ( $p > 0.05$ ) in our study, but it is impossible to distinguish whether this is due to bacterial toxins or the aminoglycoside or if it is due to the subjective nature of the test". It was not clear in the study whether the results were reported by person or by ear ( <a href="#">Indudharan 2005</a> ).	⊕⊕⊕⊕ <b>very low</b> <sup>3</sup>	It is very unclear if there is a difference between the groups in hearing.
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 Assessed with: self-reported Follow-up: range 10 days to 4 weeks	—	395 (3 RCT; <a href="#">Indudharan 2005</a> ; <a href="#">Panchasara 2015</a> ; <a href="#">Ramos 2003</a> )	<a href="#">Panchasara 2015</a> (110 participants) stated that one participant in both the intervention and control group reported vertigo, whereas <a href="#">Ramos 2003</a> (150 participants) stated that no people from either group reported dizziness. <a href="#">Indudharan 2005</a> (135 participants) reported that only 95 had pre- and post-treatment pure-tone audiograms, but it was not clear if this was by person or by ear. Of these, 13/43 in the intervention group and 15/52 in the control group showed deterioration in bone conduction thresholds of 5 dB or more across 3 frequencies tested (at 500 Hz, 1000 Hz and 2000 Hz). No participants complained of tinnitus following treatment. One participant in the intervention group and no participants in the control group complained of vertigo following treatment.	⊕⊕⊕⊕ <b>very low</b> <sup>3</sup>	It is very unclear if there is a difference between the two groups with respect to suspected ototoxicity.

\***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

<sup>1</sup>Downgraded to low certainty: downgraded by one level due to study limitations (risk of bias) because there were concerns about randomisation, unclear allocation concealment and lack of blinding in two of three studies. Downgraded by one level due to suspected publication bias as unpublished studies were identified for other comparisons.

<sup>2</sup>Downgraded to very low certainty: downgraded by two levels due to imprecision as only included one small study (105 participants) with the confidence intervals both crossing the lines of minimally important benefit and harm. Downgraded by one level due to suspected publication bias as unpublished studies were identified for other comparisons.

<sup>3</sup>Downgraded to very low certainty: downgraded by two levels due to study limitations (risk of bias) because there was a high risk of bias for randomisation, allocation concealment and blinding. Downgraded by one level due to imprecision as numeric results were presented in different ways. Downgraded by one level due to suspected publication bias as unpublished studies were identified for other comparisons.

### Summary of findings 3. Topical antibiotics with steroids compared to topical antibiotics alone for chronic suppurative otitis media

#### Topical antibiotics with steroids compared to topical antibiotics alone for chronic suppurative otitis media

**Patient or population:** people (of any age) with chronic suppurative otitis media or ear discharge  
**Setting:** nine included studies across a range of settings (community, outpatient clinic, general hospital)  
**Intervention:** non-quinolone topical antibiotics with steroids  
**Comparison:** quinolone topical antibiotics alone

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Topical antibiotics (quinolones) alone	Topical antibiotics (non-quinolones) with steroids	Difference		
Resolution of ear discharge at between 1 to 2 weeks  Assessed with: three otoscopically confirmed, four method unclear  Follow-up: range 10 days to 20 weeks	RR 0.77 (0.71 to 0.84)	903 participants (7 RCTs <sup>1</sup> ; Boesoirie 2000 unpublished; Gendeh 2001 unpublished; Helmi 2000 unpublished; Leach 2008; Miro 2000; Ramos 2003; Subramaniam 2001 unpublished)	Study population  82.1%	  63.2% (58.3 to 69.0)	  18.9% fewer (23.8 fewer to 13.1 fewer)	⊕⊕⊕⊖ <b>low</b> <sup>2</sup>	Quinolone topical antibiotics alone may increase the number of people with resolution of ear discharge at between one to two weeks compared with non-quinolone topical antibiotics with steroids.
Resolution of ear discharge after 4 weeks	None of the studies reported this outcome at this time point.						

Health-related quality of life	None of the studies reported this outcome.				
Ear pain or discomfort at 14 weeks Assessed with: self-reported Follow-up: 14 weeks	RR 1.08 (0.07 to 16.36)	52 (1 RCT; Tong 1996)	Study population 3.7%      4.0%      0.3% more (0.3 to 60.6)      (3.4 fewer to 56.9 more)	⊕⊕⊕⊕ <b>very low</b> <sup>3</sup>	The effect of non-quinolone topical antibiotics with steroids on ear pain or discomfort at 14 weeks compared with quinolone topical antibiotics alone is very uncertain.
Hearing Assessed with: air conduction hearing threshold Follow-up: range 10 days to 20 weeks	—	419 (2 RCTs; Leach 2008; Miro 2000)	Three studies reported that hearing was measured. Leach 2008 (97 participants) reported that "of 73 children who had hearing loss assessed, the mean hearing threshold was 38 dB for 41 children in the ciprofloxacin group and 35 dB for 32 children in the framycetin-gramicidin-dexamethasone group, mean difference 3 dB; (95% CI: 1 to 6). The proportion of children with a hearing threshold greater than 25 dB was 93% overall and was similar for both treatment groups RD 10%; (95% CI: 2 to 22)." Miro 2000 (322 participants) reported one case of sensorineural hearing loss in the group receiving non-quinolone topical antibiotics PLUS steroids.	⊕⊕⊕⊕ <b>very low</b> <sup>4</sup>	It is very unclear if there is a difference between the groups in hearing.
Serious complications (including intracranial complications, extracranial complications and death) Assessed with: self-reported Follow-up: range 10 to 20 weeks	—	149 (2 RCTs; Leach 2008; Tong 1996)	Two studies (149 participants) reported enough information to determine that no serious complications occurred in any participants during the study.	⊕⊕⊕⊕ <b>very low</b> <sup>5</sup>	It is very uncertain if there is a difference between the groups in serious complications.
Suspected ototoxicity: dizziness/vertigo/balance Assessed with: self-reported Follow-up: 14 weeks	RR 0.46 (0.04 to 4.80)	52 (1 RCT; Tong 1996)	Study population 8.0%      3.7%      4.3% fewer (0.3 to 38.4)      (7.7 fewer to 30.4 more)	⊕⊕⊕⊕ <b>very low</b> <sup>3</sup>	It is very uncertain if there is a difference between the two groups with respect to suspected ototoxicity.

**\*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

<sup>1</sup>Neomycin-polymixin B-steroid combinations were used in four studies; framycetin-gramicidin-dexamethasone combination was used in three studies. There were no detected differences in the results in the subgroup analysis.

<sup>2</sup>Downgraded to low certainty: downgraded by one level due to concerns about study limitations (risk of bias). Six of seven studies were classified as having unclear risk of randomisation bias and all as having unclear or high risk of allocation concealment bias; four of nine studies were at high risk of bias for blinding. Downgraded by one level due to concerns about publication bias (four studies were identified through a systematic review and no peer-reviewed results were available).

<sup>3</sup>Downgraded to very low certainty: downgraded by one level due to study limitations (risk of bias) because there were concerns about incomplete outcome data and selective outcome reporting. Downgraded by two levels due to imprecision (small study with 52 participants and very wide confidence intervals). Downgraded by one level due to concerns about publication bias.

<sup>4</sup>Downgraded to very low certainty: downgraded by one level due to study limitations (risk of bias) because one study was assessed to be at high risk of bias due to lack of blinding. Downgraded by one level due to imprecision as numeric results were presented in different ways making them difficult to interpret. Downgraded by one level due to suspected publication bias as unpublished studies were identified for other comparisons.

<sup>5</sup>Downgraded to very low certainty: downgraded by one level due to study limitations (risk of bias) because one study was assessed to be at high risk of bias for incomplete outcome data and selective reporting. Downgraded by two levels due to imprecision as there was only one small study (142 participants) and no events were reported. Downgraded by one level due to suspected publication bias as unpublished studies were identified for other comparisons.

## BACKGROUND

This is one of a suite of Cochrane Reviews evaluating the comparative effectiveness of non-surgical interventions for CSOM using topical antibiotics, topical antibiotics with corticosteroids (hereafter referred to as steroids), systemic antibiotics, topical antiseptics and aural toileting (ear cleaning) methods ([Table 1](#)).

This review compares the effectiveness of topical antibiotics (with steroids) against other non-surgical interventions (topical antibiotics, systemic antibiotics, topical antiseptics and aural toileting) or topical steroids alone or placebo/no treatment for CSOM.

### Description of the condition

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

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

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

### Definition of disease

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

In accordance with a consensus statement, here we use CSOM only to refer to tympanic membrane perforation, with intermittent or continuous ear discharge ([Gates 2002](#)). We have used a duration

of otorrhoea of two weeks as an inclusion criterion, in accordance with the definition used by the World Health Organization, but we have used subgroup analyses to explore whether this is a factor that affects observed treatment effectiveness ([WHO 2004](#)).

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

### At-risk populations

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

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

### Treatment

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



## Description of the intervention

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

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

Topical steroids are added to some topical antibiotic preparations. These formulations are usually in the form of ear drops and are generally recommended to be administered three or four times daily over a period of 7 to 10 days. Commonly used combinations are ciprofloxacin with dexamethasone, gentamicin with hydrocortisone and neomycin, and polymyxin b with hydrocortisone.

## How the intervention might work

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

Some antibiotics (such as aminoglycosides) can 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). Clinically relevant ototoxicity or vestibulotoxicity (damage to the vestibular system) from topical aminoglycosides in the treatment of CSOM is likely to be rare. However, expert opinion on the use of potentially ototoxic antibiotics varies by country; some countries do not recommend their use or may limit the use of topical aminoglycosides, others do not specifically limit its use and others may provide guidance on its use (Gilbert 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.

The addition of topical steroids to topical antibiotics may reduce the degree of inflammation in the outer or middle ear, which has been postulated to also improve penetration of the antibiotic agent

and reduce allergic sensitivity to the antibiotic component of ear drops (Indudharan 2005). However, it is unclear whether this results in observable benefit in terms of resolution of ear discharge or prevention of recurrence (Kutz 2013).

Although different types of steroids may have different potencies they share the main mechanism of action of reducing inflammation; we therefore expected a class effect for different topical steroids.

## Why it is important to do this review

Topical antibiotics are widely recommended as the first-line treatment for CSOM; however, there are variations in practice and opinions as to whether preparations with additional topical steroids should be used (Brennan-Jones 2015; CKS 2016; DOGG 2010; IMA 2014; WHO 2004).

In countries such as the USA and UK most commercial antibiotic eardrop preparations are combined with steroids and these formulations are the option used most often. However, in Australia opinion about the addition of steroids varies. The latest guidance recommends the use of antibiotic drops (without steroids) as the first-line treatment (DOGG 2010). A *BMJ* review of evidence (which included studies up to 2010) concluded that "there is a lack of good evidence to support the benefit of topical antibiotics plus topical steroids with confidence" (Morris 2012). New trials are likely to have been conducted since 2010 and it is important to systematically evaluate and update the available evidence in this area.

## OBJECTIVES

To assess the effects of adding a topical steroid to topical antibiotics in the treatment of people with chronic suppurative otitis media (CSOM).

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included studies with the following design characteristics:

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

We excluded studies with the following design characteristics:

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



## Types of participants

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

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

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

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

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

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

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

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

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

## Types of interventions

### Intervention

We have included any combinations of topical antibiotic plus topical steroids, whether formulated as a single formulation or applied separately.

### Duration

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

### Dose

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

For the other active interventions used as comparators (topical antibiotics, systemic antibiotics, topical antiseptics and aural toileting), we applied the same definitions used in other reviews in terms of types of agent, method of application, dose and duration ([Table 3](#)). We also included studies that used topical steroids as the comparator, regardless of whether it was the same type of steroid used in the intervention arm, as long as it was using a similar type of application method as the intervention arm.

## Comparisons

The following were the comparators:

- Placebo or no intervention (topical antibiotic plus steroid versus placebo or no intervention).
- Systemic antibiotics (topical antibiotic plus steroid versus systemic antibiotics).
- Topical antiseptics (topical antibiotic plus steroid versus topical antiseptics).
- Aural toileting (topical antibiotic plus steroid versus aural toileting).
- Topical antibiotics (topical antibiotic A plus steroid versus topical antibiotic A, or topical antibiotic A plus steroid versus topical antibiotic B).
- Topical steroids (topical antibiotic plus steroid versus topical steroid).
- Another topical antibiotic plus topical steroid (topical antibiotic A plus steroid versus topical antibiotic B plus steroid).
- Topical antibiotics plus steroid versus topical antibiotics plus oral antibiotics.

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

- **Topical antibiotics with steroids 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 with steroids 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 with steroids as an add-on therapy to other systemic or topical antibiotics:** this included studies where all participants in both treatment groups also received a systemic or topical antibiotic that was a different type to the antibiotic under investigation, with or without aural toileting or antiseptics.

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

- topical antibiotic plus topical steroid as a single therapy (main treatment) versus placebo or no intervention;
- topical antibiotic plus topical steroid versus topical antibiotics alone (of the same class), where no other 'add-on' treatments are used; and
- topical antibiotic plus topical steroid versus topical antibiotics alone (of any), where no other 'add-on' treatments are used.

## 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 16 March 2020.

### Electronic searches

The Information Specialist searched:

- the Cochrane ENT Register (searched via the Cochrane Register of Studies to 16 March 2020);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (searched via the Cochrane Register of Studies Web to 16 March 2020);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 16 March 2020);
- Ovid EMBASE (1974 to 16 March 2020);
- EBSCO CINAHL (1982 to 16 March 2020);
- LILACS (Latin American and Caribbean Health Science Information database), [lilacs.bvsalud.org](http://lilacs.bvsalud.org) (search to 16 March 2020);
- Web of Knowledge, Web of Science (1945 to 16 March 2020);
- ClinicalTrials.gov, [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (search via the Cochrane Register of Studies to 16 March 2020);

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search to 16 March 2020).

We also searched:

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

The search strategies for major databases are detailed in [Appendix 1](#). The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. The strategies were designed to identify all relevant studies for a suite of reviews on various interventions for chronic suppurative otitis media (Bhutta 2018; Brennan-Jones 2018a; Brennan-Jones 2018; Chong 2018a; Chong 2018b; Head 2018a; Head 2018b). Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011).

### Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, the Information Specialist searched Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Information Specialist also ran non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

We did not perform a separate search for adverse effects. We considered adverse effects described in 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 ear discharge (where known);
- number people who may have been at higher risk of CSOM, including those with cleft palate or Down syndrome;
- ethnicity of participants including the number who were from Indigenous populations;
- number who had previously had ventilation tubes (grommets) inserted (and, where known, the number who had tubes still in place);
- number who had previous ear surgery;
- number who had previous treatments for CSOM (non-responders, recurrent versus new cases).

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

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

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

- For continuous data: the mean values, standard deviations and number of patients for each treatment group. Where endpoint data were not available, we extracted the values for change from baseline. We analysed data from disease-specific quality of life scales such as COMOT-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 patients, we extracted the data with the highest incidence to prevent double counting.

### **Extracting data from figures**

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

### **Assessment of risk of bias in included studies**

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

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

### **Measures of treatment effect**

We summarised the effects of dichotomous outcomes (e.g. proportion of patients with complete resolution of ear discharge) as risk ratios (RR) with confidence intervals (CIs). For the key outcomes that are presented in the 'Summary of findings' table, we expressed the results as absolute numbers based on the pooled results and compared to the assumed risk. We also calculated the number needed to treat to benefit (NNTB) using the pooled results. The assumed baseline risk was typically either (a) the median of the risks of the control groups in the included studies, this being used to represent a 'medium-risk population' or, alternatively, (b) the average risk of the control groups in the included studies, which is used as the 'study population' ([Handbook 2011](#)). If a large number of studies were available, and where appropriate, we 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 randomise by patient and those with bilateral CSOM received the same intervention for both ears. In some studies the results may be reported as a separate outcome for each ear (the total number of ears is used as the denominator in the analysis). The correlation of response between the left ear and right ear when given the same treatment was expected to be very high, and if both ears were counted in the analysis this was effectively a form of double counting, which may be especially problematic in smaller studies if the number of people with bilateral CSOM was unequal. We did not exclude these studies, but we only reported the results if the paper presented the data in such a way that we could include the data from each participant only once (one data point per participant) or if we had enough information to reliably estimate the effective sample size or inflated standard errors as presented in chapter 16.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). If this was not possible we attempted to contact the authors for more information. If there was no response from the authors, then we did not include data from these studies in the analysis.

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

## Dealing with missing data

We attempted to contact the study authors via email whenever the outcome of interest was not reported but the methods of the

study had suggested that the outcome had been measured. We did the same if not all of the data required for the meta-analysis was 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<sup>2</sup> test (with a significance level set at P value < 0.10) and the I<sup>2</sup> statistic, which calculated the percentage of variability that is due to heterogeneity rather than chance, with I<sup>2</sup> values over 50% suggesting substantial heterogeneity (Handbook 2011).

## Assessment of reporting biases

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

### *Outcome reporting bias (within-study reporting bias)*

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

### *Publication bias (between-study reporting bias)*

We intended to create funnel plots if sufficient studies (more than 10) were available for an outcome. If we had observed asymmetry of the funnel plot, we would have conducted a more formal investigation using the methods proposed by Egger 1997. Where we identified unpublished studies the results were included but we considered the impact of the inclusion of these studies on the overall result using subgroup analysis.

## Data synthesis

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



methods. We analysed time-to-event data using the generic inverse variance method.

For continuous outcomes, if all the data were from the same scale, we pooled 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 measure, we did not pool change and endpoint data.

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

### Subgroup analysis and investigation of heterogeneity

We subgrouped studies where most participants (80% or more) met the criteria stated below in order to determine whether the effect of the intervention was different compared to other patients. Due to the risks of reporting and publication bias with unplanned subgroup analyses of trials, we only analysed subgroups reported in studies if these were prespecified and stratified at randomisation.

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

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

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

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

For this review, effect modifiers included:

- Diagnosis of CSOM:** it was likely that some studies would include patients with chronic ear discharge but who had not had a diagnosis of CSOM. Therefore, we subgrouped studies where most patients (80% or more) met the criteria for CSOM diagnosis in order to determine whether the effect of the intervention was different compared to patients where the precise diagnosis was unknown and inclusion into the study was based purely on chronic ear discharge symptoms.
- Duration of ear discharge:** there is uncertainty about whether the duration of ear discharge prior to treatment has an impact on the effectiveness of treatment and whether more established

disease (i.e. discharge for more than six weeks) is more refractory to treatment compared with discharge of a shorter duration (i.e. less than six weeks).

- Patient age:** patients who were younger than two years old versus patients up to six years old versus adults. Patients under two years are widely considered to be more difficult to treat.

We presented the results as subgroups regardless of the presence of statistical heterogeneity based on these 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 the comparison arm was topical antiseptic, we subgrouped by the type of antiseptic used in the comparison arm (e.g. iodines, alcohols, acids). This was because different types of antiseptics have different mechanisms of action and therefore the treatment effects and adverse effect profiles were likely to be different.
- When the comparison arm was aural toileting, we subgrouped based on the main type of aural toileting method (dry mopping, irrigation, microsuction). This was because different aural toileting methods were expected to have different treatment effects and adverse effects due to their intensity (e.g. microsuction is thought to be more a more intense method than dry mopping).

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 cannot 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.

A class effect for topical steroids was expected and no subgroup analysis based on the type of steroids used was conducted.

### 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.
- Unpublished data: the impact of including data from unpublished studies within the review.

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

### GRADE and 'Summary of findings' table

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

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

- study limitations (risk of bias);

- inconsistency;
- indirectness of evidence;
- imprecision;
- publication bias.

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

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

## RESULTS

### Description of studies

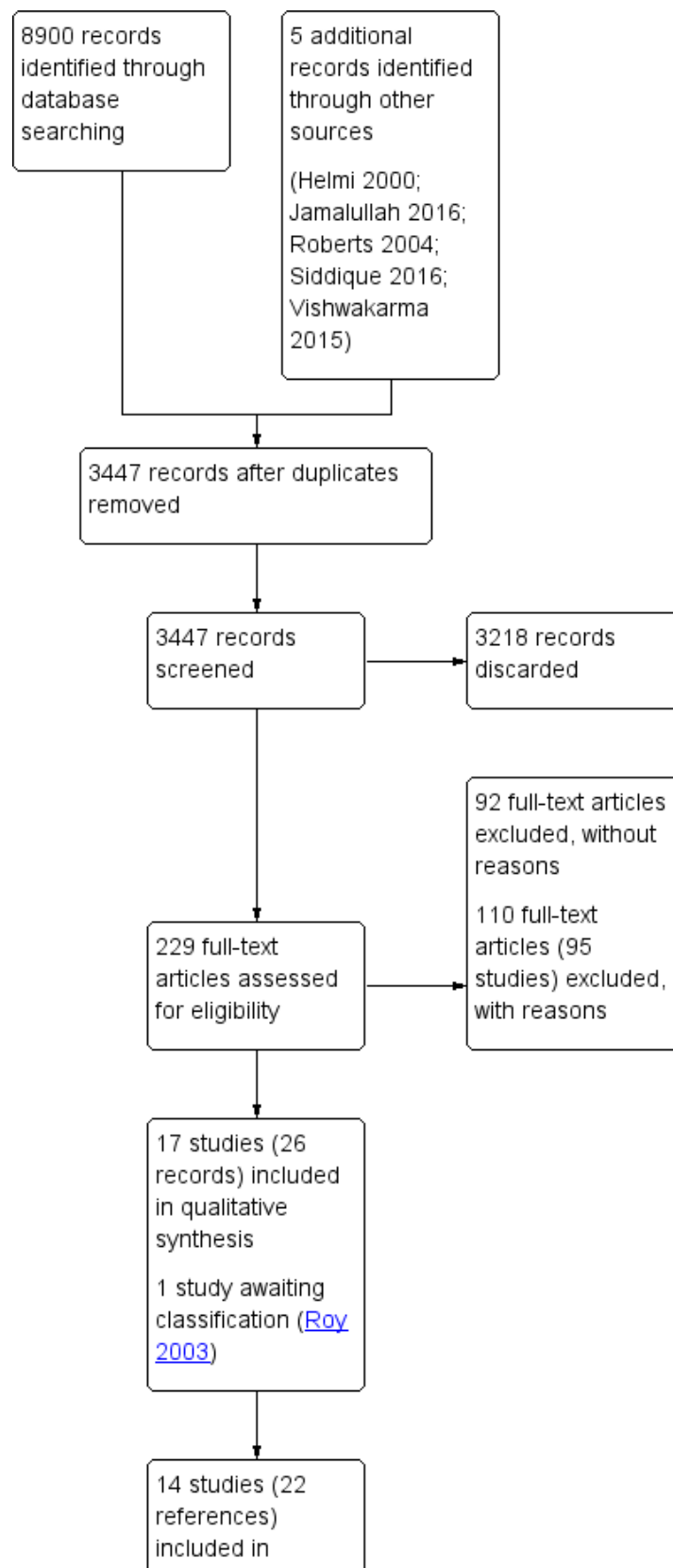
#### Results of the search

The searches retrieved a total of 8900 references and we identified five additional references from other sources. This was reduced to 3447 after removal of duplicates. We screened the titles and abstracts and subsequently removed 3218 references. We assessed 229 full-text articles for eligibility of which we excluded 202 references. We excluded 110 of these references (95 studies) with reasons recorded in the review (see [Excluded studies](#)).

We included 26 references (17 studies). There is one study awaiting classification ([Roy 2003](#)). 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 in  
quantitative  
synthesis  
(meta-analysis)

### Included studies

We included 17 studies ([Boesoire 2000 unpublished](#); [Browning 1988](#); [Couzos 2003](#); [Crowther 1991](#); [Eason 1986](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Indudharan 2005](#); [Kaygusuz 2002](#); [Lazo Saenz 2000](#); [Leach 2008](#); [Miro 2000](#); [Panchasara 2015](#); [Picozzi 1983](#); [Ramos 2003](#); [Subramaniam 2001 unpublished](#); [Tong 1996](#)). There were two studies by Indudharan, which probably reported on the same set of patients due to the identical research method, similar timings, location and baseline data. We attempted to contact the authors but they could not be reached. We therefore reported the data as though they were the same study ([Indudharan 2005](#)).

Four of the included studies were identified through the [Abes 2003](#) systematic review ([Boesoire 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Subramaniam 2001 unpublished](#)). We were not able to find published results for these studies and so all data were extracted from the systematic review.

[Table 4](#) provides a summary of the included studies.

### Study design

Ten studies were two-arm trials ([Browning 1988](#); [Couzos 2003](#); [Crowther 1991](#); [Indudharan 2005](#); [Lazo Saenz 2000](#); [Leach 2008](#); [Miro 2000](#); [Panchasara 2015](#); [Picozzi 1983](#); [Tong 1996](#)). One study was part of a five-arm trial ([Eason 1986](#)), however we only included three study arms (topical antibiotics plus steroids, topical antiseptics and no treatment, with all arms receiving aural toileting). Another study was part of a six-arm trial ([Ramos 2003](#)), and we used all six arms in the review across different comparisons ([Table 4](#)). One study was part of a four-arm trial ([Kaygusuz 2002](#)), with all four arms presented in this review. Information on the number of arms could not be found for the four unpublished studies ([Boesoire 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Subramaniam 2001 unpublished](#)).

Sixteen studies indicated that they were 'randomised controlled trials' and one was 'quasi-randomised' ([Indudharan 2005](#)). All studies were of parallel-group design. Seven were from single centres ([Browning 1988](#); [Crowther 1991](#); [Kaygusuz 2002](#); [Lazo Saenz 2000](#); [Panchasara 2015](#); [Picozzi 1983](#); [Tong 1996](#)). Six were multicentre studies ([Couzos 2003](#); [Eason 1986](#); [Indudharan 2005](#); [Leach 2008](#); [Ramos 2003](#)). It was unclear in how many centres the remaining studies were conducted ([Boesoire 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Subramaniam 2001 unpublished](#)).

### Sample size

A total of 1901 participants were included in the studies, with another 40 ears (from one study; [Lazo Saenz 2000](#)) that could not be accounted for in the participant numbers as data were only available for number of ears. It was difficult to interpret

total participant numbers because the unpublished studies did not report the number randomised and so we have included the number that were reported in the analysis. The sample size by study ranged from 37 to 322, with a median of 92 participants per trial.

### Unit of randomisation

It is not often clear how the investigators allocated treatment to the individual ears, and typically correlation of response between ears of the individual appears not to have been considered.

The individual (rather than the ear) was randomised to treatment group in 12 studies ([Browning 1988](#); [Couzos 2003](#); [Crowther 1991](#); [Eason 1986](#); [Indudharan 2005](#); [Kaygusuz 2002](#); [Leach 2008](#); [Miro 2000](#); [Panchasara 2015](#); [Picozzi 1983](#); [Ramos 2003](#); [Tong 1996](#)). Of these 12 studies:

- Nine studies reported results by individual:
  - Two studies reported that for patients with bilateral disease one ear was chosen as the study ear ([Browning 1988](#); [Couzos 2003](#)).
  - Two studies stated the number of bilateral patients, but not how these cases were assessed ([Leach 2008](#); [Panchasara 2015](#)).
  - Five studies did not state whether there were any bilateral patients or how these cases were assessed ([Crowther 1991](#); [Kaygusuz 2002](#); [Miro 2000](#); [Picozzi 1983](#); [Ramos 2003](#)).
- Three studies reported results by separately by ear ([Eason 1986](#); [Indudharan 2005](#); [Tong 1996](#)).

It was unclear whether people or ears were randomised in the five remaining studies ([Boesoire 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Lazo Saenz 2000](#); [Subramaniam 2001 unpublished](#)).

### Location

The studies were conducted in 10 countries: Australia, Hong Kong, India, Indonesia, Malaysia, Mexico, the Solomon Islands, Spain, Turkey and the United Kingdom (see [Table 4](#)).

### Setting of trial

In the clinical settings, two studies were in general hospitals ([Crowther 1991](#); [Indudharan 2005](#)), four were in specialist hospitals ([Kaygusuz 2002](#); [Lazo Saenz 2000](#); [Ramos 2003](#); [Tong 1996](#)), and two were in outpatient departments ([Browning 1988](#); [Panchasara 2015](#)). Three studies were completed in community settings ([Couzos 2003](#); [Eason 1986](#); [Leach 2008](#)).

Six studies did not report the setting ([Boesoire 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Miro 2000](#); [Picozzi 1983](#); [Subramaniam 2001 unpublished](#)).



Where it was reported, two studies were conducted in the 1980s (Crowther 1991; Eason 1986), four were conducted in the 1990s (Indudharan 2005; Lazo Saenz 2000; Miro 2000; Tong 1996), and two were conducted in the 2000s (Couzou 2003; Leach 2008). The remaining studies did not provide details of when they conducted the study.

## Population

### Age and sex

Three studies did not have any available patient characteristics (Gendeh 2001 unpublished; Picozzi 1983; Tong 1996). The Tong 1996 study stated that participants were "unselected for age, race, sex".

Three exclusively investigated **children**: Couzos 2003 (1 to 14 years), Eason 1986 (mean  $5.4 \pm 3.1$  years) and Leach 2008 (mean 7.7 years), with the latter study stratifying randomisation for those younger than six and those who were six or older.

Six studies included both **adults and children** (Boesoirie 2000 unpublished; Couzos 2003; Helmi 2000 unpublished; Indudharan 2005; Ramos 2003; Subramaniam 2001 unpublished). Two studies included only **adults** (Browning 1988; Panchasara 2015), and a further four studies did not state whether they included both adults and children, but the mean ages given were between 31 and 48 years, indicating mainly adults (Crowther 1991; Kaygusuz 2002; Lazo Saenz 2000; Miro 2000).

One study did not disclose information on sex, with the authors reporting no significant difference between them (Couzos 2003). The 10 studies that provided patient characteristics reported that they included both males and females (Browning 1988; Crowther 1991; Eason 1986; Indudharan 2005; Kaygusuz 2002; Lazo Saenz 2000; Leach 2008; Miro 2000; Panchasara 2015; Ramos 2003). Of the 1305 participants reportedly included in all arms of the studies, 600 (46%) were female, with the percentage of females in studies ranging from 36.6% to 72%.

### High-risk

Three studies reported that they included participants from **Indigenous groups** in their studies: two studies only included Indigenous Australian Aboriginals (Couzos 2003; Leach 2008). The last study included participants from the Solomon Islands (Eason 1986), which we considered to be a 'high-risk' Indigenous group. The paper stated that the incidence of CSOM in the population was 3.8% for under 15-year olds.

None of the other studies reported the inclusion of any of the 'high-risk' populations as defined in our inclusion criteria (cleft palate, Down syndrome, Indigenous groups, immunocompromised patients).

### Diagnosis

CSOM was the main diagnosis for inclusion in 15 studies (Boesoirie 2000 unpublished; Browning 1988; Couzos 2003; Crowther 1991; Eason 1986; Helmi 2000 unpublished; Indudharan 2005; Kaygusuz 2002; Lazo Saenz 2000; Leach 2008; Miro 2000; Panchasara 2015; Picozzi 1983; Subramaniam 2001 unpublished; Tong 1996). In the remaining two studies, Gendeh 2001 unpublished included participants with both CSOM and otitis externa, but only the results for CSOM are reported, and Ramos 2003 included patients with

chronic ear discharge, but on a breakdown of the participants more than 50% had CSOM and so we included the results of the study.

Two studies included only a subgroup of CSOM patients. Leach 2008 only included children with active CSOM despite treatment with framycetin-gramicidin-dexamethasone combination (Sofradex) for an unclear duration, which represents a population that is potentially more recalcitrant than a general population with CSOM. Panchasara 2015 only included patients with CSOM who had a culture that was sensitive to ofloxacin, which means that the participants may be more likely to respond better to ofloxacin treatment than the general population.

Nine studies provided the diagnostic method for confirmation of tympanic membrane perforation or presence of mucopurulent discharge via otoscopy or microscopic examination (Browning 1988; Couzos 2003; Crowther 1991; Eason 1986; Kaygusuz 2002; Leach 2008; Miro 2000; Panchasara 2015; Ramos 2003). An additional two studies confirmed perforation of the tympanic membrane but did not provide a method (Indudharan 2005; Tong 1996). The diagnostic method was not reported in one study (Picozzi 1983) and was unclear in one study (Lazo Saenz 2000). No details were available in the four unpublished studies (Boesoirie 2000 unpublished; Gendeh 2001 unpublished; Helmi 2000 unpublished; Subramaniam 2001 unpublished).

### Duration of ear discharge

Eight studies reported the duration of symptoms/mucopurulent discharge for diagnosis, with one study including patients with ear discharge for more than two weeks (Couzos 2003), one study more than three weeks (Boesoirie 2000 unpublished), one study more than six weeks or sporadically with more than three episodes in the last year (Ramos 2003), two studies more than three months (Eason 1986; Kaygusuz 2002), one study with a mean 46 weeks (Browning 1988), and one study with one month to 40 years (Indudharan 2005). An additional study had a median of six to seven years since first CSOM, and a median of 15 days (range 1 to 365) for the current episode (Miro 2000). Six studies did not provide inclusion criteria or details of the average duration of ear discharge at the start of the study (Crowther 1991; Lazo Saenz 2000; Leach 2008; Panchasara 2015; Picozzi 1983; Tong 1996). No details were available for three unpublished studies (Gendeh 2001 unpublished; Helmi 2000 unpublished; Subramaniam 2001 unpublished).

### Other important effect modifiers

One study reported the previous use of grommets (Ramos 2003: 12 participants; 4%), two studies provided alternative diagnoses (Crowther 1991: 33.3% had a mastoid cavity; Ramos 2003: 14% had cholesteatoma) and two studies reported the number having previous surgery (Miro 2000: 79 participants; 34.1%; Ramos 2003: 73 participants; 24.3%). Three studies reported the number having previous antibiotic treatment for CSOM (Leach 2008: 97 participants; 100%; Miro 2000: 103 participants; 44.4%; Ramos 2003: 197 participants; 65.6%).

Nine studies did not report on any important effect modifiers (Browning 1988; Couzos 2003; Eason 1986; Indudharan 2005; Kaygusuz 2002; Lazo Saenz 2000; Panchasara 2015; Picozzi 1983; Tong 1996). No details were available for four unpublished studies (Boesoirie 2000 unpublished; Gendeh 2001 unpublished; Helmi 2000 unpublished; Subramaniam 2001 unpublished).

## Intervention

Details of the interventions, background treatment and treatment durations for each of the included studies are summarised in [Table 4](#).

### Topical antibiotics plus steroids

Nine studies used the steroid hydrocortisone, with six of these using a neomycin-polymixin-hydrocortisone combination ([Boesoirie 2000 unpublished](#); [Helmi 2000 unpublished](#); [Miro 2000](#); [Ramos 2003](#); [Subramaniam 2001 unpublished](#); [Tong 1996](#)), while the remaining three studies used gentamicin plus hydrocortisone ([Browning 1988](#); [Crowther 1991](#); [Picozzi 1983](#)).

Six studies used the steroid dexamethasone, with four using a framycetin-gramicidin-dexamethasone combination known as Sofradex ([Couzos 2003](#); [Eason 1986](#); [Gendeh 2001 unpublished](#); [Leach 2008](#)), one study using ciprofloxacin plus dexamethasone ([Kaygusuz 2002](#)), and the other using ofloxacin plus dexamethasone ([Panchasara 2015](#)).

One study used the steroid betamethasone in combination with gentamicin ([Indudharan 2005](#)). Another study used fludrocortisone, using a neomycin-polymixin B-fludrocortisone with lidocaine combination ([Lazo Saenz 2000](#)). Another arm of the Ramos study used the steroid fluocinolone in combination with ciprofloxacin ([Ramos 2003](#)).

### Background treatment

Eleven studies used aural toileting at different frequencies: prior to treatment ([Crowther 1991](#)), at entry to study (with alcohol and antiseptics) ([Indudharan 2005](#)), at baseline ([Miro 2000](#)), placebo therapy patients had "regular" aural toileting with cotton buds ([Browning 1988](#)), prior to instillation ([Picozzi 1983](#)), once daily ([Kaygusuz 2002](#); [Panchasara 2015](#)), twice daily, with povidone-iodine antiseptic ([Couzos 2003](#)), four times daily (except no treatment group) ([Eason 1986](#); [Leach 2008](#)), and on days 1, 7 and 14 ([Tong 1996](#)). Six studies gave no details of background treatment ([Boesoirie 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Lazo Saenz 2000](#); [Ramos 2003](#); [Subramaniam 2001 unpublished](#)).

### Duration of intervention

Ten studies had a duration of intervention of two weeks or less ([Boesoirie 2000 unpublished](#); [Couzos 2003](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Lazo Saenz 2000](#); [Miro 2000](#); [Panchasara 2015](#); [Ramos 2003](#); [Subramaniam 2001 unpublished](#); [Tong 1996](#)). Three studies treated for between two and four weeks ([Crowther 1991](#); [Indudharan 2005](#); [Kaygusuz 2002](#)). Four studies treated for four weeks or more ([Browning 1988](#); [Eason 1986](#); [Leach 2008](#); [Picozzi 1983](#)).

### Comparisons

Three studies compared the use of topical antibiotic plus steroid versus **placebo or no intervention**:

- [Browning 1988](#) (123 participants): gentamycin plus hydrocortisone versus placebo.
- [Eason 1986](#) (50 participants, 67 ears): framycetin-gramicidin-dexamethasone (Sofradex) versus no treatment.
- [Picozzi 1983](#) (37 participants): gentamicin plus hydrocortisone versus placebo.

Twelve studies (16 comparison pairs) compared the use of topical antibiotic plus steroid versus **topical antibiotic**, with or without background treatment:

- Four studies (five comparison pairs) used the **same antibiotic** in both treatment arms with the addition of steroids in one arm.
  - \* All four studies had no background treatment.
    - ☐ Two studies compared aminoglycoside plus steroids versus aminoglycoside:
      - [Indudharan 2005](#) (135 participants, 152 ears): gentamycin plus betamethasone versus gentamycin.
      - [Kaygusuz 2002](#) (40 participants): tobramycin plus dexamethasone versus tobramycin.
    - ☐ Three studies compared quinolone plus steroids versus quinolone:
      - [Kaygusuz 2002](#) (40 participants): ciprofloxacin plus dexamethasone versus ciprofloxacin.
      - [Ramos 2003](#) (150 participants): ciprofloxacin plus fluocinolone versus ciprofloxacin.
      - [Panchasara 2015](#) (110 participants): ofloxacin plus dexamethasone versus ofloxacin.
- Ten studies used topical antibiotics with steroids in one arm compared against a different type of topical antibiotics alone in the other arm.
  - \* Nine studies had no background treatment.
    - ☐ Six studies compared neomycin-polymixin plus steroid versus quinolone:
      - [Boesoirie 2000 unpublished](#) (92 participants): neomycin-polymixin B plus hydrocortisone versus ofloxacin.
      - [Helmi 2000 unpublished](#) (138 participants): neomycin-polymixin B plus hydrocortisone versus ofloxacin.
      - [Tong 1996](#) (52 participants): neomycin-polymixin B plus hydrocortisone versus ofloxacin.
      - [Miro 2000](#) (322 participants): neomycin-polymixin B plus hydrocortisone versus ciprofloxacin.
      - [Ramos 2003](#) (150 participants): neomycin-polymixin B plus hydrocortisone versus ciprofloxacin.
      - [Lazo Saenz 2000](#) (40 ears): neomycin-polymixin B plus fludrocortisone versus ciprofloxacin.
    - ☐ Three studies compared framycetin-gramicidin-dexamethasone combination (Sofradex) versus quinolone:
      - [Gendeh 2001 unpublished](#) (70 participants): framycetin-gramicidin-dexamethasone versus ofloxacin.
      - [Leach 2008](#) (97 participants): framycetin-gramicidin-dexamethasone versus ciprofloxacin.
      - [Subramaniam 2001 unpublished](#) (60 participants): framycetin-gramicidin-dexamethasone versus ofloxacin.
  - \* One study had an antiseptic background:
    - ☐ [Couzos 2003](#) (147 participants): framycetin, gramicidin and dexamethasone plus povidone iodine versus ciprofloxacin plus povidone iodine.

One study compared the use of topical antibiotic plus steroid versus **topical steroid alone**:

- [Crowther 1991](#) (64 participants): gentamicin plus hydrocortisone versus betamethasone.

One study compared the use of topical antibiotic plus steroid versus **topical antiseptics**:

- [Eason 1986](#) (55 participants, 73 ears): framycetin-gramicidin-dexamethasone with steroids versus boric acid.

One study (two comparison arms; 150 participants) compared the use of topical antibiotic plus steroid versus **systemic (oral) antibiotics**:

- Comparing quinolone plus steroid versus systemic quinolone:
  - \* [Ramos 2003](#) (100 participants): ciprofloxacin plus fluocinolone versus oral ciprofloxacin.
- Comparing neomycin-polymixin B plus steroid versus systemic quinolone:
  - \* [Ramos 2003](#) (100 participants): neomycin-polymixin B plus hydrocortisone versus oral ciprofloxacin.

One study (two comparison arms; 150 participants) compared topical antibiotics plus steroid versus **topical antibiotics plus oral antibiotics**:

- Comparing quinolone plus steroid versus systemic quinolone:
  - \* [Ramos 2003](#) (100 participants): ciprofloxacin plus fluocinolone versus oral plus topical ciprofloxacin.
- Comparing neomycin-polymixin B plus steroid versus systemic quinolone:
  - \* [Ramos 2003](#) (100 participants): neomycin-polymixin B plus hydrocortisone versus oral plus topical ciprofloxacin.

One study compared the use of topical antibiotic A plus steroid A versus **topical antibiotic B plus steroid B**:

- [Ramos 2003](#) (100 participants): ciprofloxacin plus fluocinolone versus neomycin-polymixin B plus hydrocortisone.

No studies compared topical antibiotic plus steroid versus aural toileting.

## Outcomes

### Resolution of ear discharge

The definitions, methods and timing of assessment differed between studies and these are summarised in [Table 5](#).

Four studies reported the results by ear ([Eason 1986](#); [Indudharan 2005](#); [Lazo Saenz 2000](#); [Tong 1996](#)). As three studies stated that counting of bilateral ears was done separately ([Eason 1986](#); [Indudharan 2005](#); [Tong 1996](#)), and another was also randomised by ear ([Lazo Saenz 2000](#)), it was difficult to interpret the number of participants in each arm for these studies.

### 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

Six studies measured adverse effects associated with treatment. One study described subjective assessment of headache, local itchiness and 'other', with one case of local itchiness reported in each group ([Panchasara 2015](#)). Another study stated that "side

effects occurred in 16 per cent of patients in both active and placebo management groups and were minor" ([Browning 1988](#)). [Couzos 2003](#) reported "minor adverse reactions" in 3/55 of the ciprofloxacin group and 2/56 of the framycetin, gramicidin and dexamethasone (Sofradex) group, but provided no definitions. One study had a participant drop out due to a "burning sensation" ([Crowther 1991](#)). [Miro 2000](#) stated that 9/165 in the polymyxin B, neomycin and hydrocortisone group and 7/153 in the ciprofloxacin group experienced this outcome, but it was not clearly reported as there was a risk of double counting. Local itchiness was reported as a complication by one participant in each group in [Tong 1996](#).

The results presented show that in [Gendeh 2001 unpublished](#), 21/34 participants had resolution of otalgia in the group receiving topical antibiotics with steroids and 32/36 had resolution of otalgia in the group receiving topical quinolone antibiotics alone. This indicates that 13/34 (38%) had unresolved otalgia in the topical antibiotics with steroids arm and 4/36 (11%) in the topical antibiotics alone arm.

Similarly for [Subramaniam 2001 unpublished](#), it is reported that 32/40 and 34/39 had resolution of otalgia in the topical antibiotics with steroids and topical quinolone antibiotics alone arms, respectively. In other words, 8/40 (20%) had unresolved otalgia in the arm receiving topical antibiotics with steroids and 5/39 (13%) had unresolved otalgia in the topical antibiotics alone arm.

One study listed this as a measured outcome but did not provide further details ([Leach 2008](#) (pain only)). The remaining eight studies did not report this outcome ([Boesoirie 2000 unpublished](#); [Eason 1986](#); [Helmi 2000 unpublished](#); [Indudharan 2005](#); [Kaygusuz 2002](#); [Lazo Saenz 2000](#); [Picozzi 1983](#); [Ramos 2003](#)).

### Hearing

Six studies indicated that they measured hearing pre- and post-treatment: one measured a change in hearing threshold from individual baseline air-bone gap audiometry to a pre-treatment mean but did not report the results ([Lazo Saenz 2000](#)); two stated when measurement occurred but gave no details of how it was done ([Leach 2008](#): 4.5 to 8 months after randomisation; [Ramos 2003](#): at time of diagnosis, at 8 days and at 15 days). In [Leach 2008](#), there was a mean difference of 3 dB (95% confidence interval (CI) of 1 to 6; 97 participants) between the study groups, however the proportion of children with a hearing threshold greater than 25 dB was 93% overall and was similar for both treatment groups. One study, which used bone conduction hearing tests, reported that "in the majority there was no change in [bone conduction] thresholds and if a change did occur it was as likely to reflect an improvement as a deterioration..." ([Browning 1988](#)). Another study reported one case of sensorineural hearing loss in the polymyxin B, neomycin and hydrocortisone group, which evolved from a normal audiogram at visit 1 to hearing loss at all frequencies at visit 3 ([Miro 2000](#)). Another study also stated that "28.85% (15/52) treated with gentamicin and 30.23% (13/43) with gentamicin with betamethasone had a bone conduction threshold shift of 5 dB or more, respectively. The deterioration in bone conduction was not statistically significant ( $p > 0.05$ ) whether gentamicin or gentamicin with betamethasone was used" and that "average bone conduction threshold was decreased by 7.70 dB with gentamicin and 8.75 dB with gentamicin with betamethasone ( $p$

> 0.05) in our study, but it is impossible to distinguish whether this is due to bacterial toxins or the aminoglycoside or if it is due to the subjective nature of the test" (Indudharan 2005). For Couzos 2003, there were non-significant ( $P = 0.59$ ) improvements reported in median air-conduction hearing thresholds for both the quinolone topical antibiotic group (1.9 dB) and the non-quinolone topical antibiotic and steroids group (1.3 dB). Another study reported this outcome but provided no information regarding the methods used, including whether air or bone conduction methods were used and the frequencies of testing (Tong 1996). All results were reported narratively. The remaining nine studies did not report this outcome (Boesoire 2000 unpublished; Crowther 1991; Eason 1986; Gendeh 2001 unpublished; Helmi 2000 unpublished; Kaygusuz 2002; Panchasara 2015; Picozzi 1983; Subramaniam 2001 unpublished).

#### **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, two studies reported that no side effects occurred in any participants, which would include the defined serious complications (Browning 1988; Tong 1996). Another study stated that "no child was withdrawn because of increased severity of disease" (Leach 2008). However, an additional study stated that "suppurative complications were limited to one case of mastoiditis and one of meningitis with focal encephalitis" but it was unclear whether this was detected pre-randomisation or during/after treatment (Eason 1986). The remaining 13 studies did not report on this outcome (Boesoire 2000 unpublished; Couzos 2003; Crowther 1991; Gendeh 2001 unpublished; Helmi 2000 unpublished; Indudharan 2005; Kaygusuz 2002; Lazo Saenz 2000; Miro 2000; Panchasara 2015; Picozzi 1983; Ramos 2003; Subramaniam 2001 unpublished).

#### **Suspected ototoxicity**

Six studies reported on this outcome. One study adequately measured suspected ototoxicity as the number of people with the following symptoms: sensorineural hearing loss as a pure-tone audiogram measuring deterioration in bone conduction threshold across three frequencies as measured at four weeks; tinnitus measured at four weeks and vertigo measured at four weeks (Indudharan 2005). This study reported "deterioration in bone conduction threshold of 5 dB or more at frequencies 500, 1000 and 2000 Hz compared to pre-treatment PTA implied ototoxicity", which was present in 13/43 in the gentamicin with betamethasone group and 15/52 in the gentamicin alone group, but it was not clear if this was by person or by ear (Indudharan 2005). In this study there were no complaints of tinnitus but one case of dizziness/vertigo/balance complaint, however it was unclear in which group this occurred. Another study did not report on balance, dizziness, vertigo or tinnitus, but diagnosed suspected ototoxicity with an audiogram (no specific definition) with 0/125 patients having ototoxicity from treatment (Ramos 2003). One study provided subjective assessment of vertigo, which one participant from each group experienced (Panchasara 2015). Browning 1988 stated that "no increased incidence of otological symptoms, in particular of

tinnitus or vertigo, was detected in patients complying to antibiotic-steroid ear drops compared with the pre-management incidence or against that in patients after placebo management." Another study reported "transient dizziness" in 2/55 in the ciprofloxacin group and 1/56 in the framycetin, gramicidin and dexamethasone (Sofradex) group (Couzos 2003). Vertigo was reported in 1/25 in the group receiving antibiotics at 14 weeks and 2/27 in the group receiving topical antibiotics alone in Tong 1996. The remaining 11 studies did not report this outcome (Boesoire 2000 unpublished; Crowther 1991; Eason 1986; Gendeh 2001 unpublished; Helmi 2000 unpublished; Kaygusuz 2002; Lazo Saenz 2000; Leach 2008; Miro 2000; Picozzi 1983; Subramaniam 2001 unpublished).

#### **Excluded studies**

We excluded 110 papers (96 studies) after reviewing the full text. Further details for the reasons for exclusion can be found in the [Characteristics of excluded studies](#) table. The following are the main reasons for exclusion:

We excluded 24 studies (33 references) because the comparisons were not appropriate for this review, but were relevant to another review in this suite of CSOM Cochrane Reviews (Asmatullah 2014; De Miguel 1999; Esposito 1990; Esposito 1992; Fradis 1997; Gupta 2015; Gyde 1978; I-HEAR-BETA; Jamallullah 2016; Jaya 2003; Kasemsuwan 1997; Liu 2003; Loock 2012; Lorente 1995; Macfadyen 2005; Mira 1993; Nawasreh 2001; Povedano 1995; Tutkun 1995; van Hasselt 1997; van Hasselt 1998; Vishwakarma 2015; Yuen 1994).

We excluded 29 studies (30 references) on the basis of their study design (Baba 1986; Baba 2008; Brook 1979; Brook 1980; Deguchi 1985; Deguchi 1986; Deitmer 2002; Esposito 2000; Gehanno 1997; Hwang 2015; Jahn 1984; Jang 2004; Kadar 2003; Kenna 1986; Kothari 1969; Kovacic 1999; Kurilin 1976; Lancaster 1999; Lancaster 2003; Lang 1992; Lautala 1983; Merifield 1993; Morgon 1976; Poliakova 1991; Singhal 1992; Sumitsawan 1995; Supiyaphun 1995; Tachibana 1986; Wintermeyer 1997).

We excluded 22 studies (24 references) due to the population characteristics included in their study (Abbott 2016; 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; IRCT20130427013136N6; IRCT2016082313136N4; Mesure 1973; Principi 1995; Quick 1973; Quick 1975; Saez-Llorens 2005; Stenstrom 1991; van Dongen 2014).

We excluded 14 studies (15 references) because the intervention was outside our protocol (Browning 1983; Connolly 1997; Dellamonica 1995; Frayse 1988; ISRCTN12149720; ISRCTN84220089; Jiang 2016; Khanna 2000; Mora 2012; NCT02592096; NCT02817347; Wilde 1995; Xu 1999).

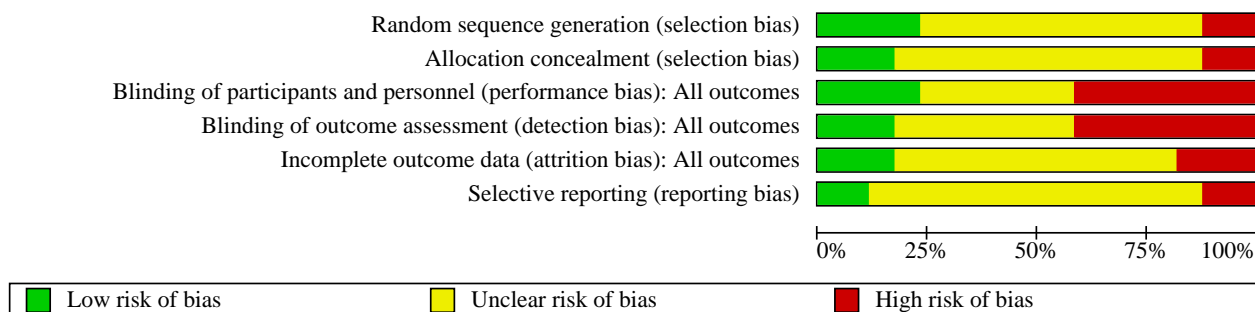
Seven studies (eight references) had multiple reasons for exclusion (Baba 1980; Fombeur 1994; Hemlin 1997; Kashiwamura 2004; Khon 2012; Lorentzen 1978; Thomsen 1976).

#### **Risk of bias in included studies**

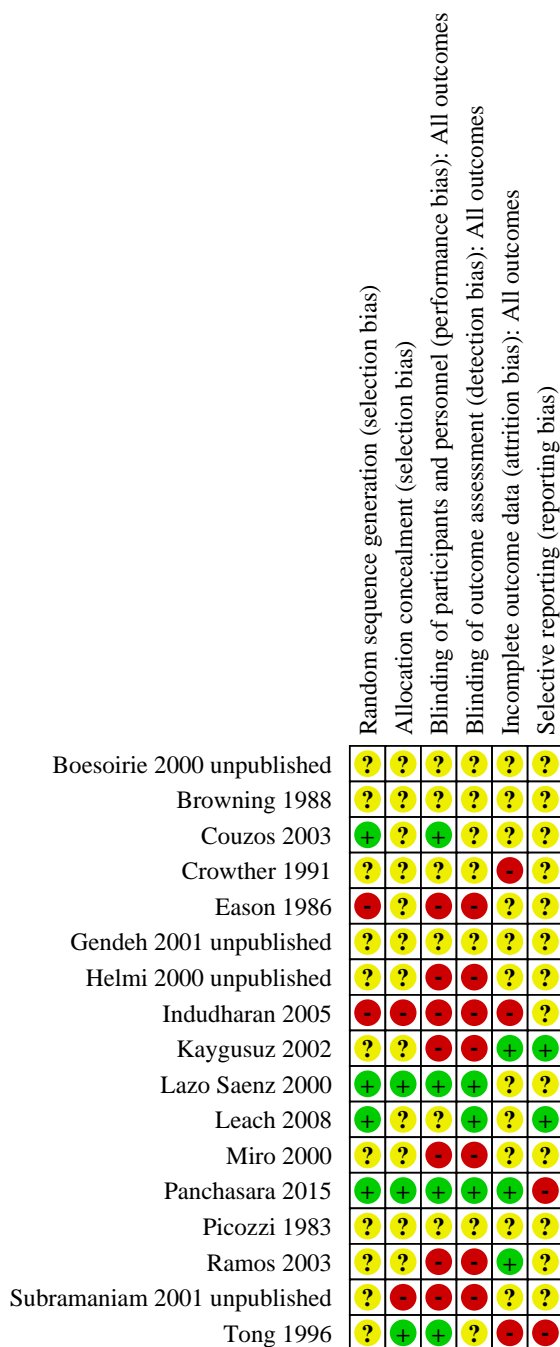
See [Figure 2](#) for the 'Risk of bias' graph (our judgements about each risk of bias item presented as percentages across all included studies) and [Figure 3](#) for the 'Risk of bias' summary (our judgements about each risk of bias item for each included study).



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



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



## Allocation

### Randomisation

We assessed two studies to be at high risk of selection bias with regards to randomisation ([Eason 1986](#); [Indudharan 2005](#)). For [Eason 1986](#), this was due to insufficient information about the sequence generation method and a larger number of patients in

the more effective treatment groups. For [Indudharan 2005](#), this was due to it being a quasi-randomised trial. We assessed four studies as being at low risk, with adequate sequence generation ([Couzos 2003](#); [Lazo Saenz 2000](#); [Leach 2008](#); [Panchasara 2015](#)). We assessed the remaining 11 studies as being at 'unclear risk' because they did not provide enough information ([Boesoirie 2000 unpublished](#); [Browning 1988](#); [Crowther 1991](#); [Gendeh 2001 unpublished](#); [Helmi](#)

2000 unpublished; Kaygusuz 2002; Miro 2000; Picozzi 1983; Ramos 2003; Subramaniam 2001 unpublished; Tong 1996).

### Allocation concealment

We assessed two studies to be at high risk of selection bias with regards to allocation concealment (Indudharan 2005; Subramaniam 2001 unpublished). Indudharan 2005 used allocation occurring as alternates, making it possible to predict what intervention the patient would receive before enrolment. Subramaniam 2001 unpublished stated "no concealment of allocation, open label".

We assessed three studies as being at low risk as we deemed the allocation to be adequately concealed (Lazo Saenz 2000; Panchasara 2015; Tong 1996). We assessed the remaining 12 studies as being at 'unclear risk' because they did not provide enough information (Boesoirie 2000 unpublished; Browning 1988; Couzos 2003; Crowther 1991; Eason 1986; Gendeh 2001 unpublished; Helmi 2000 unpublished; Kaygusuz 2002; Leach 2008; Miro 2000; Picozzi 1983; Ramos 2003).

### Blinding

#### Performance bias

We assessed seven studies to be at high risk of performance bias (Eason 1986; Helmi 2000 unpublished; Indudharan 2005; Kaygusuz 2002; Miro 2000; Ramos 2003; Subramaniam 2001 unpublished). Eason 1986 and Ramos 2003 had treatment arms involving different forms of administration (e.g. oral versus ear drops), making blinding impossible without the use of a placebo. Helmi 2000 unpublished and Subramaniam 2001 unpublished, were described as "open label". Indudharan 2005 was not a blinded study due to the alternate allocation of patients and having no mention of masking the treatment option. Kaygusuz 2002 had no clear statement regarding whether the study was blinded and Miro 2000 had no blinding.

We assessed four studies as at low risk of performance bias, with participants and personnel unlikely to distinguish treatment (Couzos 2003; Lazo Saenz 2000; Panchasara 2015; Tong 1996). We assessed the remaining six studies as at 'unclear risk' because they did not provide enough information (Boesoirie 2000 unpublished; Browning 1988; Crowther 1991; Gendeh 2001 unpublished; Leach 2008; Picozzi 1983).

#### Detection bias

We assessed seven studies to be at high risk of detection bias (Eason 1986; Helmi 2000 unpublished; Indudharan 2005; Kaygusuz 2002; Miro 2000; Ramos 2003; Subramaniam 2001 unpublished). Helmi 2000 unpublished and Subramaniam 2001 unpublished were described as "open label". Eason 1986 provided no statement of who the assessor was (e.g. patients or medical team) and there was no use of otoscopic examination to determine outcome success. Indudharan 2005 gave no description of blinding and used subjective analysis of the main outcome of interest that is described as "ear becoming dry". Kaygusuz 2002 provided no clear statement regarding whether the study was blinded. In Miro 2000 no blinding of assessors was mentioned, except for ototoxicity evaluation, which was not reported. Ramos 2003 provided no information regarding who assessed the subjective outcomes (otoscopy examinations).

We assessed three studies as at low risk of detection bias because outcomes with defined characteristics were assessed clinically (Lazo Saenz 2000; Leach 2008; Panchasara 2015). We assessed the remaining seven studies as at unclear risk because they did not provide enough information (Boesoirie 2000 unpublished; Browning 1988; Couzos 2003; Crowther 1991; Gendeh 2001 unpublished; Picozzi 1983; Tong 1996).

### Incomplete outcome data

We assessed three studies to be at high risk of attrition bias (Crowther 1991; Indudharan 2005; Tong 1996). Crowther 1991 had a high level of dropout without reasons and adherence to treatment only needed to be 75% to be included in the analysis. Indudharan 2005 reported a large proportion of patients being excluded or lost to follow-up. Tong 1996 had an imbalance of patients excluded between treatment arms, which could have affected the results, and there was doubt as to when the exclusions occurred.

We assessed three studies as being at low risk as no or a small percentage of patients were lost to follow-up and these were balanced between arms (Kaygusuz 2002; Panchasara 2015; Ramos 2003). We assessed the remaining 11 studies as at 'unclear risk' because they did not provide enough information (Boesoirie 2000 unpublished; Browning 1988; Couzos 2003; Eason 1986; Gendeh 2001 unpublished; Helmi 2000 unpublished; Lazo Saenz 2000; Leach 2008; Miro 2000; Picozzi 1983; Subramaniam 2001 unpublished).

### Selective reporting

Only one of the 17 studies had a protocol that we could identify through searches of clinical trials registries (Panchasara 2015). We assessed two studies to be at high risk of selective reporting bias because hearing was not reported in the papers (Panchasara 2015; Tong 1996). We assessed two studies as being at low risk due to adequate outcome reporting between the methods and results (Kaygusuz 2002; Leach 2008). We assessed the remaining 13 studies as having an unclear risk of selective reporting bias (Boesoirie 2000 unpublished; Browning 1988; Couzos 2003; Crowther 1991; Eason 1986; Gendeh 2001 unpublished; Helmi 2000 unpublished; Indudharan 2005; Lazo Saenz 2000; Miro 2000; Picozzi 1983; Ramos 2003; Subramaniam 2001 unpublished).

### Other potential sources of bias

#### Funding

Four studies reported the companies and institutions that provided funding for the study (Couzos 2003; Eason 1986; Indudharan 2005; Leach 2008). Five studies reported that a pharmaceutical provider supplied the interventions for the study (Browning 1988; Couzos 2003; Miro 2000; Panchasara 2015; Tong 1996). There were no details available for the four unpublished studies (Boesoirie 2000 unpublished; Gendeh 2001 unpublished; Helmi 2000 unpublished; Subramaniam 2001 unpublished). Five studies provided no information (Crowther 1991; Kaygusuz 2002; Lazo Saenz 2000; Picozzi 1983; Ramos 2003).

#### Declarations of interest

Only one study stated "none identified" (Couzos 2003). Miro 2000 did not provide information, but two investigators worked for Bayer, which funded the study. There were no details available for the four unpublished studies (Boesoirie 2000 unpublished;

Gendeh 2001 unpublished; Helmi 2000 unpublished; Subramaniam 2001 unpublished). The remaining 11 studies did not provide any information about conflicts of interest (Browning 1988; Crowther 1991; Eason 1986; Indudharan 2005; Kaygusuz 2002; Lazo Saenz 2000; Leach 2008; Panchasara 2015; Picozzi 1983; Ramos 2003; Tong 1996).

## Effects of interventions

See: **Summary of findings 1** Topical antibiotics with steroids compared to placebo/no treatment for chronic suppurative otitis media; **Summary of findings 2** Topical antibiotics with steroids compared to topical antibiotics alone (same antibiotics) for chronic suppurative otitis media; **Summary of findings 3** Topical antibiotics with steroids compared to topical antibiotics alone for chronic suppurative otitis media

### Comparison 1: Topical antibiotics with steroids versus placebo or no treatment

Three studies (210 participants) were included in this comparison: Browning 1988 (123 participants) and Picozzi 1983 (37 participants), which compared topical gentamicin and hydrocortisone to placebo ear drops or placebo tablets; and Eason 1986 (50 'high-risk' children; 67 ears), which compared a topical framycetin-gramicidin-dexamethasone combination (Sofradex) to no treatment.

Eason 1986 presented results for this outcome by ear and there were insufficient data to allow the results to be presented by patient, so the results were not included in the analysis but are presented narratively.

See also [Summary of findings 1](#).

#### Resolution of ear discharge or 'dry ear'

##### Between one week and up to two weeks

None of the studies reported results for this outcome at this time point.

##### Two weeks to up to four weeks

##### Gentamicin plus hydrocortisone

Two studies (Browning 1988; Picozzi 1983; 160 participants) found that more people had resolution of ear discharge at between two and up to four weeks with gentamicin plus hydrocortisone than placebo treatment (risk ratio (RR) 2.10, 95% confidence interval (CI) 1.33 to 3.31, 2 studies; 154 participants;  $I^2 = 0\%$ ; [Analysis 1.1](#)).

##### Framycetin sulphate, dexamethasone and gramicidin (FDG): high-risk population

One study (Eason 1986; 50 'high-risk' children; 67 ears) reported this outcome by ear at three weeks and found that 39% of 41 ears improved with FDG compared with 34% of 26 ears with no topical antibiotic treatment.

##### After four weeks

##### Framycetin sulphate, dexamethasone and gramicidin (FDG): high-risk population

One study (Eason 1986; 50 children; 67 ears) reported this outcome by ear at six weeks and found that 58% of 41 ears were improved

with topical antibiotics with steroids compared with 50% of 26 ears with no topical treatment.

#### Health-related quality of life using a validated instrument

None of the studies reported this outcome.

#### Ear pain (otalgia) or discomfort or local irritation

Browning 1988 reported that "side effects occurred in 16 per cent of patients in both active and placebo management groups and were minor" (very low-certainty evidence).

#### Hearing

Browning 1988 reported hearing outcomes but for the participants in this specific trial it was unclear what the outcomes were, as the results of participants from previous trials were also included.

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

Browning 1988 reported that no side effects occurred in any participants, which would include the defined serious complications. Eason 1986 reported one case of mastoiditis and one case of meningitis with focal encephalitis. It is not clear which group these patients were from (the study was a five-arm trial), or whether the complications occurred pre- or post-treatment. Picozzi 1983 did not report that any participant died or had any intracranial or extracranial complications.

#### Suspected ototoxicity

Browning 1988 stated that "in the majority there was no change in [bone conduction] thresholds and if a change did occur it was as likely to reflect an improvement as a deterioration...". Browning 1988 also reported "no increased incidence of otological symptoms, in particular of tinnitus or vertigo, was detected in patients complying to antibiotic-steroid ear drops compared with the pre-management incidence or against that in patients after placebo management" (very low-certainty evidence).

#### Subgroup analysis

The main results are presented by class of antibiotic.

#### High-risk population

Eason 1986 was the only study that included participants considered to be at 'high risk' as they included Indigenous populations (Solomon Islands). This study only presented results by ear.

### Comparison 2: Topical antibiotics with steroids versus topical antibiotics alone (same antibiotics)

Four studies (475 participants) were included in this comparison:

- Panchasara 2015 (110 participants) compared ofloxacin and dexamethasone to ofloxacin only.
- Ramos 2003 (150 participants) compared ciprofloxacin and fluocinolone to ciprofloxacin alone.
- Indudharan 2005 (135 participants; 152 ears) compared gentamicin with betamethasone to gentamicin alone. This study presented results for this outcome by ear and there were insufficient data to allow the results to be presented by patient,



so the results were not included in the analysis but are presented narratively.

- [Kaygusuz 2002](#) (80 participants) included two comparisons, topical ciprofloxacin and dexamethasone compared with topical ciprofloxacin alone, and topical tobramycin and dexamethasone compared with topical tobramycin only.

See also [Summary of findings 2](#).

## Resolution of ear discharge or 'dry ear'

### Between one week and up to two weeks

#### Overall

Three studies (four comparisons) ([Kaygusuz 2002](#); [Panchasara 2015](#); [Ramos 2003](#); 340 participants) found that topical antibiotics with steroids may result in little to no difference in resolution of ear discharge at one to two weeks compared with the same topical antibiotic alone (RR 1.08, 95% CI 0.96 to 1.21; 3 studies; 335 participants;  $I^2 = 0\%$ , low-certainty evidence; [Analysis 2.1](#)).

#### Quinolones

Three studies ([Kaygusuz 2002](#); [Panchasara 2015](#); [Ramos 2003](#); 300 participants) examined quinolones and found little to no difference in resolution of ear discharge at between one to two weeks between topical quinolones with steroids and topical quinolones alone (RR 1.05, 95% CI 0.93 to 1.17; 3 studies; 295 participants;  $I^2 = 0\%$ ; [Analysis 2.1](#)).

#### Aminoglycosides

One study ([Kaygusuz 2002](#); 40 participants) examined aminoglycosides and found that aminoglycosides with steroids may result in little or no difference compared with topical aminoglycosides alone (RR 1.36, 95% CI 0.85 to 2.18; 1 study; 40 participants; [Analysis 2.1](#)).

### Two weeks to up to four weeks

#### Overall

Three studies (340 participants) reported this outcome ([Kaygusuz 2002](#); [Indudharan 2005](#); [Panchasara 2015](#)), although [Indudharan 2005](#) (135 participants; 152 ears) only recorded results by ear and so the data were not included in the analysis. The remaining two studies (205 participants) found that topical antibiotics with steroids may result in little or no difference in resolution of ear discharge at between two and up to four weeks, compared with topical antibiotics alone (RR 1.05, 95% CI 0.88 to 1.26; 2 studies; 185 participants;  $I^2 = 0\%$ ; [Analysis 2.2](#)).

#### Quinolones

Two studies ([Kaygusuz 2002](#); [Panchasara 2015](#); 150 participants) found that topical quinolones with steroids may result in little or no difference in resolution of ear discharge at between two and up to four weeks, compared with topical quinolones alone (RR 1.05, 95% CI 0.85 to 1.28; 2 studies; 145 participants;  $I^2 = 0\%$ ; [Analysis 2.2](#)).

#### Aminoglycosides

One study ([Kaygusuz 2002](#); 40 participants) found that aminoglycosides with steroids may result in little or no difference in resolution of ear discharge at between two and up to four weeks, compared with topical aminoglycosides alone (RR 1.07, 95% CI 0.73 to 1.57; 40 participants; [Analysis 2.2](#)). [Indudharan 2005](#)

(135 participants; 152 ears) reported that 45 of 52 ears (86.5%) in the aminoglycoside with betamethasone group and 49 of 57 ears (86.0%) in the aminoglycoside alone group had resolution of ear discharge at four weeks.

#### After four weeks

None of the studies reported results for this outcome at this time point.

## Health-related quality of life using a validated instrument

None of the studies reported this outcome.

## Ear pain (otalgia) or discomfort or local irritation

[Panchasara 2015](#) (110 participants) reported one case of local itchiness in each group (RR 0.98, 95% CI 0.06 to 15.28; 1 study; 105 participants, very low-certainty evidence; [Analysis 2.3](#)).

## Hearing

[Indudharan 2005](#) (135 participants; 152 ears) reported that only 95 had pre- and post-treatment pure-tone audiograms, but it was not clear if this was by person or by ear. Of these, "28.85% (15/52) treated with gentamicin and 30.23% (13/43) with gentamicin with betamethasone had a bone conduction threshold shift of 5 dB or more, respectively. The deterioration in bone conduction was not statistically significant ( $p > 0.05$ ) whether gentamicin or gentamicin with betamethasone was used" and the "average bone conduction threshold was decreased by 7.70 dB with gentamicin and 8.75 dB with gentamicin with betamethasone ( $p > 0.05$ ) in our study, but it is impossible to distinguish whether this is due to bacterial toxins or the aminoglycoside or if it is due to the subjective nature of the test" (very low-certainty evidence).

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

None of the studies reported that any participant died or had any intracranial or extracranial complications.

## Suspected ototoxicity

One study ([Panchasara 2015](#); 110 participants) stated that one participant in both the intervention and control group reported vertigo, whereas another ([Ramos 2003](#); 150 participants) reported that no participants from either group had dizziness. [Indudharan 2005](#) (135 participants; 152 ears) reported that only 95 had pre- and post-treatment pure-tone audiograms, but it was not clear if this was by person or by ear. Of these, 13/43 in the intervention group and 15/52 in the control group showed deterioration in bone conduction thresholds of 5 dB or more across the three frequencies tested (500 Hz, 1000 Hz and 2000 Hz). No participants complained of tinnitus following treatment. One participant in the intervention group and no participants in the control group complained of vertigo following treatment (very low-certainty evidence).

## Subgroup analysis

The main results are presented by type of antibiotic.

## Diagnosis

One study included patients with a diagnosis of 'ear discharge' ([Ramos 2003](#); 150 participants), but given that there

was no heterogeneity between the studies, we did not carry out a subgroup analysis for this factor.

### Comparison 3: Topical antibiotic (non-quinolone) with steroids versus topical antibiotic (quinolones) alone

Nine studies (981 participants plus 40 ears) were included in this comparison:

- Six studies (754 participants plus 40 ears) compared neomycin with polymixin B and steroids to topical quinolones alone: [Boesoire 2000 unpublished](#) (92 participants); [Helmi 2000 unpublished](#) (138 participants); [Lazo Saenz 2000](#) (40 ears); [Miro 2000](#) (322 participants); [Ramos 2003](#) (150 participants); [Tong 1996](#) (52 participants).
- Three studies (227 participants) compared framycetin-gramicidin-dexamethasone to topical quinolones alone: [Gendeh 2001 unpublished](#) (70 participants); [Leach 2008](#) (97 participants); [Subramaniam 2001 unpublished](#) (60 participants).

Of these, two studies reported resolution of ear discharge by ear, rather than by person ([Lazo Saenz 2000](#); [Tong 1996](#)). It was not possible to adjust the results to 'per person' and so they are presented narratively.

See also [Summary of findings 3](#).

#### Resolution of ear discharge or 'dry ear'

##### Between one week and up to two weeks

##### Overall

Seven studies ([Boesoire 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Leach 2008](#); [Miro 2000](#); [Ramos 2003](#); [Subramaniam 2001 unpublished](#); 929 participants) found that quinolone topical antibiotics alone may increase the number of people with resolution of ear discharge at between one to two weeks compared with non-quinolone topical antibiotics with steroids (RR 0.77, 95% CI 0.71 to 0.84; 7 studies; 903 participants; low-certainty evidence; [Analysis 3.1](#)). There was low heterogeneity between the studies overall ( $I^2 = 32\%$ ).

In addition, two studies presented results by ear:

- [Lazo Saenz 2000](#) reported that at 10 days, 16 of 20 ears (80%) resolved with non-quinolone topical antibiotics with steroids compared with 17 of 20 ears (85%) with quinolone steroids alone.
- [Tong 1996](#) reported that at 14 days, 11 of 24 ears (46%) resolved with non-quinolone topical antibiotics with steroids compared with 20 of 28 ears (71%) with quinolone steroids alone.

##### Neomycin-polymixin B-steroids

Four studies ([Boesoire 2000 unpublished](#); [Helmi 2000 unpublished](#); [Miro 2000](#); [Ramos 2003](#); 702 participants) compared topical neomycin-polymixin B to topical quinolones and found that topical quinolone antibiotics may result in more people with resolution of ear discharge at between one to two weeks than in those given a neomycin-polymixin B-steroid combination (RR 0.78, 95% CI 0.72 to 0.86; 4 studies; 684 participants;  $I^2 = 56\%$ ; [Analysis 3.1](#)).

#### Framycetin-gramicidin-dexamethasone

Three studies ([Gendeh 2001 unpublished](#), [Leach 2008](#), [Subramaniam 2001 unpublished](#); 227 participants) compared topical framycetin-gramicidin-dexamethasone to topical quinolones and found that topical quinolone antibiotics alone may result in more people with resolution of ear discharge at between one to two weeks than those given framycetin-gramicidin-dexamethasone (RR 0.72, 95% CI 0.58 to 0.89; 3 studies; 219 participants;  $I^2 = 0\%$ ; [Analysis 3.1](#)).

#### Sensitivity analysis for unpublished studies

Four studies (360 participants) were not found in peer-reviewed journals ([Boesoire 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Subramaniam 2001 unpublished](#)); the data came from the [Abes 2003](#) systematic review. Three studies (569 participants) were published in peer-reviewed journals ([Leach 2008](#); [Miro 2000](#); [Ramos 2003](#)).

When we separated out the unpublished studies in a subgroup analysis, the unpublished studies were more favourable towards topical quinolones alone (RR 0.71, 95% CI 0.62 to 0.81; 342 participants; 4 studies;  $I^2 = 0\%$ ) than the published studies (RR 0.81, 95% CI 0.73 to 0.90; 561 participants; 3 studies;  $I^2 = 58\%$ ). However, the test for subgroup differences indicated no evidence of a difference ([Analysis 3.4](#)).

#### Two weeks to up to four weeks

None of the studies reported results for this outcome at this time point.

#### After four weeks

None of the studies reported results for this outcome at this time point.

#### Health-related quality of life using a validated instrument

None of the studies reported this outcome.

#### Ear pain (otalgia) or discomfort or local irritation

[Tong 1996](#) (52 participants) reported one case of localised irritation in each group. Therefore, the evidence is very uncertain about the effect of non-quinolone topical antibiotics with steroids on ear pain or discomfort at 14 weeks compared with quinolone topical antibiotics alone (RR 1.08, 95% CI 0.07 to 16.36; 52 participants; very low-certainty evidence; [Analysis 3.5](#)).

Two of the unpublished studies with data from the [Abes 2003](#) systematic review reported results for the resolution of otalgia from two studies ([Gendeh 2001 unpublished](#); [Subramaniam 2001 unpublished](#); 130 participants), although the time point that this was reported is not clear. The results presented show that in [Gendeh 2001 unpublished](#), 21/34 participants had resolution of otalgia in the group receiving topical antibiotics with steroids and 32/36 had resolution of otalgia in the group receiving quinolone topical antibiotics alone. This indicates that 13/34 (38%) had unresolved otalgia in the topical antibiotics with steroids arm and 4/36 (11%) in the topical antibiotics alone arm.

Similarly for [Subramaniam 2001 unpublished](#), it is reported that 32/40 and 34/39 had resolution of otalgia in the topical antibiotics with steroids and topical quinolone antibiotics alone

arms, respectively. In other words, 8/40 (20%) had unresolved otalgia in the arm receiving topical antibiotics and steroids and 5/39 (13%) had unresolved otalgia in the topical antibiotics alone arm.

**Miro 2000** (322 participants) stated that 9/165 in the polymyxin B, neomycin and hydrocortisone group and 7/153 in the ciprofloxacin group experienced this outcome, but as it was not clear whether the results were reported by event or by person there was a risk of double counting and the results were not included in the analysis.

### Hearing

**Leach 2008** (97 participants) reported that "... of 73 children who had hearing loss assessed, the mean hearing threshold was 38 dB for 41 children in the ciprofloxacin group and 35 dB for 32 children in the framycetin-gramicidin-dexamethasone group mean difference 3 dB; (95% confidence interval (CI): 1 to 6). The proportion of children with a hearing threshold greater than 25 dB was 93% overall and was similar for both treatment groups RD 10%; (95% CI: 2 to 22)."

**Miro 2000** (322 participants) reported one case of sensorineural hearing loss in the group receiving non-quinolone topical antibiotics plus steroids which "... evolved from a normal audiogram at visit 1 to hearing loss at all frequencies at visit 3." We determined this to be very low-certainty evidence.

**Lazo Saenz 2000** (40 ears) reported that the pre-treatment mean hearing level was 19.1 dB and the post-treatment mean hearing level was 19.5 dB; however, they did not provide the results by treatment group and so were not included in the analysis.

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

Two studies (**Leach 2008**; **Tong 1996**; 149 participants) reported enough information to determine that no serious complications occurred in any participants during the study (very low-certainty evidence).

### Suspected ototoxicity

The evidence is very uncertain about the effect of non-quinolone topical antibiotics with steroids on suspected ototoxicity.

### Dizziness/vertigo/balance

**Tong 1996** (52 participants) reported one case of dizziness/vertigo/balance problems in the group receiving antibiotics at 14 weeks and two cases in the group receiving topical quinolone antibiotics alone (RR 0.46, 95% CI 0.04 to 4.80; 52 participants; very low-certainty evidence; **Analysis 3.6**).

### Sensorineural hearing loss

**Miro 2000** (322 participants) reported one case of sensorineural hearing loss in the non-quinolone antibiotics with steroids group; no cases were reported in the topical quinolone antibiotics alone group. **Tong 1996** (52 participants) reported that none of the participants in their study had deterioration in hearing assessed audiometrically nor delayed side effects at three months post-treatment.

**Ramos 2003** (150 participants) reported a lack of symptoms suggesting vestibular problems, but did not provide details of how this was measured or defined.

### Tinnitus

No studies reported tinnitus as an outcome.

### Subgroup analysis

#### High-risk population

**Leach 2008** (97 participants) was the only study that included participants considered to be at 'high risk' as they included only Indigenous populations (Australian Aboriginal and Torres Strait islanders). This population also had recalcitrant CSOM, which had not resolved despite treatment with framycetin sulfate, gramicidin and dexamethasone. For resolution of ear discharge there was no heterogeneity between the risk ratio results for **Leach 2008** and the other included studies, although the absolute resolution rates were lower in both of the treatment arms.

#### Age

**Leach 2008** (97 participants) stratified randomisation by age of participant (up to age six years, and six years and older). Subgroup analysis was conducted. The results for children aged less than six years indicated that there was a difference between the two age groups with those under six years old having more resolution of discharge at one to two weeks with quinolones compared to topical antibiotics with steroids (RR 0.34, 95% CI 0.16 to 0.73; 35 participants) than those aged six years and older (RR 0.83, 95% CI 0.39 to 1.77; 62 participants), although the low numbers should be noted. The test for differences between subgroups indicated no evidence of a difference ( $P = 0.11$ ; **Analysis 3.2**).

#### Diagnosis

One study (**Ramos 2003**; 150 participants) included people with a diagnosis of 'ear discharge', while six studies included CSOM specifically (**Boesoire 2000 unpublished**; **Gendeh 2001 unpublished**; **Helmi 2000 unpublished**; **Leach 2008**; **Miro 2000**; **Subramaniam 2001 unpublished**; 779 participants).

For the resolution of ear discharge at one to two weeks of those with 'ear discharge' treated with quinolones compared to topical antibiotics with steroids the RR was 0.65 (95% CI 0.50 to 0.84; 1 study; 150 participants) compared to RR 0.79 (95% CI 0.73 to 0.86; 6 studies; 753 participants) for those with CSOM. The test for differences between subgroups indicated no evidence of a difference ( $P = 0.16$ ; **Analysis 3.3**).

### Comparison 4: Topical antibiotic (non-quinolone) with steroids versus topical antibiotic (quinolone) on top of antiseptics (povidone-iodine)

One study (**Couzos 2003**; 147 participants) compared a non-quinolone topical antibiotic plus steroids (framycetin-gramicidin-dexamethasone) versus a quinolone topical antibiotic (ciprofloxacin). Both treatment arms were also given daily treatment with topical antiseptics (povidone-iodine). This study was conducted in a population identified as 'high-risk' Indigenous (Australian Aboriginal and Torres Strait Islanders).

#### Resolution of ear discharge or 'dry ear'

##### Between one week and up to two weeks

**Couzos 2003** (147 participants) found that more people given a quinolone topical antibiotic on top of topical antiseptics had resolution of ear discharge at between one and up to two weeks

compared to those receiving non-quinolone topical antibiotics and steroids on top of antibiotics (RR 0.67, 95% CI 0.50 to 0.90; 1 study; 112 participants; [Analysis 4.1](#)).

#### Two weeks to up to four weeks

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

#### After four weeks

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

#### Health-related quality of life using a validated instrument

The study did not report this outcome.

#### Ear pain (otalgia) or discomfort or local irritation

[Couzou 2003](#) (147 participants) reported two events of 'minor adverse reactions' in the non-quinolone topical antibiotics with steroids group and three events in the quinolone topical antibiotics group, but the evidence is too uncertain to determine if there is a difference between the groups (RR 0.65, 95% CI 0.11 to 3.77; 1 study; 111 participants; [Analysis 4.2](#)).

#### Hearing

[Couzou 2003](#) (147 participants) measured average hearing thresholds before and approximately 14 days after treatment using pure-tone audiometry (air conduction) hearing thresholds. There were improvements reported in median air-conduction hearing thresholds for both the quinolone topical antibiotic group (1.9 dB) and the non-quinolone topical antibiotic and steroids group (1.3 dB). The difference between groups was not reported as significant ( $P = 0.59$ ).

#### 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

[Couzou 2003](#) (147 participants) reported "transient dizziness" in 2/55 in the ciprofloxacin group and 1/56 in the Sofradex group.

#### Subgroup analysis

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

#### Comparison 5: Topical antibiotics with steroids versus steroids only

One study ([Crowther 1991](#); 64 participants) compared topical gentamicin with hydrocortisone to betamethasone ear drops alone.

#### Resolution of ear discharge or 'dry ear'

##### Between one week and up to two weeks

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

##### Two weeks to up to four weeks

[Crowther 1991](#) (64 participants) found that more people receiving topical antibiotics and steroids had resolution of ear discharge at between two weeks and up to four weeks compared to those

receiving topical steroids alone (RR 2.74, 95% CI 1.43 to 5.25; 1 study; 54 participants; [Analysis 5.1](#)).

#### After four weeks

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

#### Health-related quality of life using a validated instrument

The study did not report this outcome.

#### Ear pain (otalgia) or discomfort or local irritation

[Crowther 1991](#) (64 participants) reported one event of 'burning sensation' in the group receiving topical antibiotics and steroids. No events were reported in the group receiving topical steroids alone (RR 2.42, 95% CI 0.10 to 56.85; 1 study; 54 participants; [Analysis 5.2](#)).

#### Hearing

The study did not report this outcome.

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

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

#### Suspected ototoxicity

The study did not report this outcome.

#### Subgroup analysis

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

#### Comparison 6: Topical antibiotics with steroids versus antiseptic

One study ([Eason 1986](#); 55 'high-risk' children; 73 ears) compared topical antibiotics with steroids (framycetin sulphate-gramicidin-dexamethasone (FDG)) to topical antiseptic (boric acid).

[Eason 1986](#) presented results for this outcome by ear and there were insufficient data to allow the results to be presented by patient, so the results were not included in the analysis but are presented narratively.

#### Resolution of ear discharge or 'dry ear'

##### Between one week and up to two weeks

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

##### Two weeks to up to four weeks

[Eason 1986](#) (55 'high-risk' children; 73 ears) reported that at three weeks, 48% of 32 ears improved with boric acid antiseptic compared with 39% of 41 ears with FDG.

#### After four weeks

[Eason 1986](#) (55 'high-risk' children; 73 ears) reported that at six weeks, 64% of 32 ears improved with boric acid antiseptic compared with 58% of 41 ears with FDG.

#### Health-related quality of life using a validated instrument

The study did not report this outcome.



### ***Ear pain (otalgia) or discomfort or local irritation***

The study did not report this outcome.

### ***Hearing***

The study did not report this outcome.

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

Eason 1986 reports one case of mastoiditis and one case of meningitis with focal encephalitis. It is not clear which group these patients were from (the study was a five-arm trial), or whether the complications occurred pre- or post-treatment.

### ***Suspected ototoxicity***

The study did not report this outcome.

### ***Subgroup analysis***

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

### **Comparison 7: Topical antibiotics with steroids versus oral antibiotics (same quinolone antibiotics)**

One study (Ramos 2003; 100 participants) compared topical ciprofloxacin and fluocinolone against oral ciprofloxacin. The study included patients with a diagnosis of chronic ear discharge.

### ***Resolution of ear discharge or 'dry ear'***

#### ***Between one week and up to two weeks***

One study (Ramos 2003; 100 participants) found that more people given topical antibiotics (quinolone) with steroids had resolution of ear discharge at between one week and up to two weeks compared with those receiving oral antibiotics (quinolone) alone (RR 1.50, 95% CI 1.17 to 1.92; 100 participants; Analysis 7.1).

#### ***Two weeks to up to four weeks***

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

#### ***After four weeks***

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

### ***Health-related quality of life using a validated instrument***

The study did not report this outcome.

### ***Ear pain (otalgia) or discomfort or local irritation***

The study did not report this outcome.

### ***Hearing***

The study did not report 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***

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

### ***Subgroup analysis***

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

### **Comparison 8: Topical antibiotics (non-quinolone) with steroids versus oral antibiotics (quinolone)**

One study (Ramos 2003; 100 participants) compared topical neomycin-polymyxin-hydrocortisone versus oral ciprofloxacin. The study included patients with a diagnosis of chronic ear discharge.

### ***Resolution of ear discharge or 'dry ear'***

#### ***Between one week and up to two weeks***

In Ramos 2003 (100 participants) the evidence for resolution of ear discharge at between one week and up to two weeks was uncertain in the comparison between people given non-quinolone topical antibiotics with steroids versus oral quinolones antibiotics (RR 0.93, 95% CI 0.67 to 1.30; 100 participants; Analysis 8.1).

#### ***Two weeks to up to four weeks***

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

#### ***After four weeks***

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

### ***Health-related quality of life using a validated instrument***

The study did not report this outcome.

### ***Ear pain (otalgia) or discomfort or local irritation***

The study did not report this outcome.

### ***Hearing***

The study did not report 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***

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

### ***Subgroup analysis***

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

### **Comparison 9: Topical antibiotics with steroids versus topical plus oral antibiotics (same quinolone antibiotics)**

One study (Ramos 2003; 100 participants) compared topical ciprofloxacin and fluocinolone against a combination of topical and oral ciprofloxacin. The study included patients with a diagnosis of chronic ear discharge.

## Resolution of ear discharge or 'dry ear'

### Between one week and up to two weeks

Ramos 2003 (100 participants) found no difference in the resolution of ear discharge at between one week and up to two weeks between people given topical quinolone antibiotics with steroids compared with oral and topical quinolones (RR 1.02, 95% CI 0.89 to 1.17; 100 participants; [Analysis 9.1](#)).

### Two weeks to up to four weeks

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

### After four weeks

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

## Health-related quality of life using a validated instrument

The study did not report this outcome.

## Ear pain (otalgia) or discomfort or local irritation

The study did not report this outcome.

## Hearing

The study did not report 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

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

## Subgroup analysis

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

## Comparison 10: Topical antibiotics (non-quinolone) with steroids versus topical plus oral antibiotics (quinolone)

One study (Ramos 2003; 100 participants) compared topical neomycin-polymyxin-hydrocortisone against a combination of topical and oral ciprofloxacin. The study included patients with a diagnosis of chronic ear discharge.

## Resolution of ear discharge or 'dry ear'

### Between one week and up to two weeks

Ramos 2003 (100 participants) found that more people had resolution of ear discharge at between one week and up to two weeks with oral and topical quinolones compared with topical non-quinolone antibiotics with steroids (RR 0.64, 95% CI 0.49 to 0.83; 100 participants; [Analysis 10.1](#)).

### Two weeks to up to four weeks

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

### After four weeks

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

## Health-related quality of life using a validated instrument

The study did not report this outcome.

## Ear pain (otalgia) or discomfort or local irritation

The study did not report this outcome.

## Hearing

The study did not report 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

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

## Subgroup analysis

With only one study, subgroup analysis was not possible.

## Comparison 11: Topical quinolone antibiotics with steroids versus topical non-quinolone antibiotics with steroids

One study (Ramos 2003; 100 participants) compared topical quinolone antibiotics and steroids (ciprofloxacin and fluocinolone) with topical non-quinolone antibiotics and steroids (neomycin-polymyxin-hydrocortisone). The study included patients with a diagnosis of chronic ear discharge.

## Resolution of ear discharge or 'dry ear'

### Between one week and up to two weeks

Ramos 2003 (100 participants) found that more people given topical quinolone antibiotics with steroids had resolution of ear discharge at one week and up to two weeks compared to those receiving topical non-quinolone antibiotics and steroids (RR 1.61, 95% CI 1.24 to 2.09; 100 participants; [Analysis 11.1](#)).

### Two weeks to up to four weeks

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

### After four weeks

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

## Health-related quality of life using a validated instrument

The study did not report this outcome.

## Ear pain (otalgia) or discomfort or local irritation

The study did not report this outcome.

## Hearing

The study did not report 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

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

## Subgroup analysis

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

## DISCUSSION

### Summary of main results

We found 17 studies reporting on 11 different comparisons (Boesoirie 2000 unpublished; Browning 1988; Couzos 2003; Crowther 1991; Eason 1986; Gendeh 2001 unpublished; Helmi 2000 unpublished; Indudharan 2005; Kaygusuz 2002; Lazo Saenz 2000; Leach 2008; Miro 2000; Panchasara 2015; Picozzi 1983; Ramos 2003; Subramaniam 2001 unpublished; Tong 1996). 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.

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

#### Topical antibiotics with steroids versus placebo or no treatment (Comparison 1)

See [Summary of findings 1](#).

We included three studies (210 participants) in the review examining topical antibiotics with steroids versus placebo or no treatment. Two studies compared aminoglycosides with steroids to placebo treatment (Browning 1988; Picozzi 1983; 160 participants). One compared a framycetin-gramicidin-dexamethasone combination (Sofradex) to no treatment (Eason 1986; 50 'high-risk' participants) but presented results by ear and it was not possible to adjust these to 'per person' results. Two studies reported that the resolution of discharge was otoscopically confirmed (Browning 1988; Eason 1986); the diagnostic method was not reported in the other study (Picozzi 1983). No studies presented results for resolution of ear discharge at between one and up to two weeks. At between two to four weeks there may be an increase in resolution of ear discharge for topical antibiotics (aminoglycosides) with steroids compared to no treatment (risk ratio (RR) 2.10, 95% confidence intervals (CI) 1.33 to 3.31; 2 studies; 154 participants). An additional study (Eason 1986; 50 participants) compared at this time point and after four weeks, but the results were presented by ear and we are unclear about the results as we assessed the evidence to be of very low certainty. However, these results are presented narratively in the [Effects of interventions](#) section.

The adverse effects of ear pain, discomfort or local irritation were not well reported, although Browning 1988 (123 participants) reported that minor side effects occurred in 16% of people in both the intervention and placebo groups (very low-certainty evidence). With regards to suspected ototoxicity, one study (Browning 1988; 123 participants; very low-certainty evidence) reported that "... in the majority there was no change in [bone conduction] thresholds and if a change did occur it was as likely to reflect an improvement as a deterioration...". The study also reported "... no increased incidence of otological symptoms, in particular of tinnitus or vertigo, was detected in patients complying to antibiotic-steroid

ear drops compared with the pre-management incidence or against that in patients after placebo management."

Browning 1988 (123 participants) reported that no side effects occurred in any participants, which would include the defined serious complications. Eason 1986 reported one case of mastoiditis and one case of meningitis with focal encephalitis. It is not clear which group these patients were from, or whether the complications occurred pre- or post-treatment.

Health-related quality of life and hearing were either not measured or not reported in any of the studies.

#### Topical antibiotics with steroids versus topical antibiotics alone (same antibiotics in both arms) (Comparison 2)

See [Summary of findings 2](#).

Four studies (five comparison arms; 475 participants) were included in this comparison, which used the same topical antibiotics in both arms (Indudharan 2005; Kaygusuz 2002; Panchasara 2015; Ramos 2003). Three studies used quinolones (Kaygusuz 2002; Panchasara 2015; Ramos 2003; 300 participants) and two used aminoglycosides (Indudharan 2005; Kaygusuz 2002; 175 participants). Three studies reported that the resolution of discharge was otoscopically confirmed (Kaygusuz 2002; Panchasara 2015; Ramos 2003); one study did not provide a method for identifying resolution of discharge (Indudharan 2005). When we combined the data at one to up to two weeks (Kaygusuz 2002; Panchasara 2015; Ramos 2003; 340 participants), the results indicated that topical antibiotics with steroids may result in little to no difference in resolution of ear discharge compared with the same topical antibiotic alone (RR 1.08, 95% CI 0.96 to 1.21;  $I^2 = 0\%$ , 3 studies, 335 participants; low-certainty evidence). The results for resolution of ear discharge at two to four weeks (Kaygusuz 2002; Panchasara 2015; 205 participants) were similar (RR 1.05, 95% CI 0.88 to 1.26; 185 participants; 2 studies). An additional study compared at this time point (Indudharan 2005; 135 participants), but presented results by ear and it was not possible to adjust these to 'per person' results, although the results are presented narratively in the [Effects of interventions](#) section. There were no results reported for resolution of ear discharge after four weeks.

In terms of hearing, Indudharan 2005 presented the following results but it is unclear if the results are presented per person or per ear: "28.85% (15/52) treated with gentamicin and 30.23% (13/43) with gentamicin with betamethasone had a bone conduction threshold shift of 5 dB or more, respectively. The deterioration in bone conduction was not statistically significant ( $p > 0.05$ ) whether gentamicin or gentamicin with betamethasone was used" and the "average bone conduction threshold was decreased by 7.70 dB with gentamicin and 8.75 dB with gentamicin with betamethasone ( $p > 0.05$ ) in our study, but it is impossible to distinguish whether this is due to bacterial toxins or the aminoglycoside or if it is due to the subjective nature of the test" (Indudharan 2005; very low certainty).

With regards to suspected ototoxicity, Panchasara 2015 (110 participants) stated that one participant in both the intervention and control group reported vertigo, where as another (Ramos 2003; 150 participants) reported that no people from either group experienced dizziness. Another study (Indudharan 2005; 135 participants; 152 ears) reported that only 95 had pre- and post-treatment pure-tone audiograms, but it was not clear if it was by

person or by ear. Of these, 13/43 in the intervention group and 15/52 in the control group showed deterioration in bone conduction thresholds of 5 dB or more across the three frequencies tested (at 500 Hz, 1000 Hz and 2000 Hz). No participants complained of tinnitus following treatment. One participant in the intervention group and no participants in the control group complained of vertigo following treatment (very low-certainty evidence).

[Panchasara 2015](#) (110 participants) reported one case of local itchiness in each group (very low-certainty evidence).

No results were reported for health-related quality of life or serious complications.

### Topical antibiotics with steroids versus different topical antibiotics (Comparison 3)

See [Summary of findings 3](#).

We included nine studies (981 participants plus 40 ears) that compared topical antibiotics with steroids versus a different type of topical antibiotic alone ([Boesoire 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Lazo Saenz 2000](#) (ears only); [Leach 2008](#); [Miro 2000](#); [Ramos 2003](#); [Subramaniam 2001 unpublished](#); [Tong 1996](#)). All studies used non-quinolone topical antibiotics with steroids compared with topical antibiotics alone, with six studies (754 participants plus 40 ears) looking at neomycin-polymyxin B with steroids and three studies (227 participants) using framycetin-gramicidin-dexamethasone with steroids. Three studies reported that the resolution of discharge was otoscopically confirmed ([Leach 2008](#); [Miro 2000](#); [Ramos 2003](#)), two studies either did not provide a method or the method was unclear ([Lazo Saenz 2000](#); [Tong 1996](#)), and for four studies there were no details ([Boesoire 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Subramaniam 2001 unpublished](#)). All of the studies used a quinolone topical antibiotic alone in the comparison arm. Two studies only reported results by ear (rather than by person) and were not included in the analysis, although the results are presented narratively in the [Effects of interventions](#) section ([Lazo Saenz 2000](#); [Tong 1996](#)).

For resolution of ear discharge at one to two weeks topical antibiotics alone may increase the number of people with resolution of ear discharge compared with non-quinolone topical antibiotics with steroids (RR 0.77, 95% CI 0.71 to 0.84; 903 participants; 7 studies;  $I^2 = 32\%$ ; [Analysis 3.1](#)). However, we assessed this result as being of low certainty using the GRADE assessment criteria because six of seven studies had an unclear risk of randomisation bias, all studies were at unclear or high risk of allocation concealment bias and four of seven studies were at high risk of bias for blinding. There was also a concern regarding publication bias as the results from four studies were unpublished, although there was no evidence of a difference between subgroups in a sensitivity analysis ([Analysis 3.4](#)). No resolution of ear discharge results beyond two weeks were reported.

Ear pain, discomfort or local irritation were reported in one study ([Tong 1996](#)), but the evidence is very uncertain due to the small numbers included (RR 1.08, 95% CI 0.07 to 16.36; 52 participants; very low-certainty evidence). [Miro 2000](#) (322 participants) also reported this outcome in 9/165 in the polymyxin B, neomycin and hydrocortisone group and 7/153 in the ciprofloxacin group, but it was not clear whether this was reported by event or by person and

so the results were not included in the analysis due to a risk of double counting.

Two studies reported hearing outcomes (419 participants). [Leach 2008](#) (97 participants) reported that "... of 73 children who had hearing loss assessed, the mean hearing threshold was 38 dB for 41 children in the ciprofloxacin group and 35 dB for 32 children in the framycetin-gramicidin-dexamethasone group, mean difference 3 dB; (95% CI 1 to 6). The proportion of children with a hearing threshold greater than 25 dB was 93% overall and was similar for both treatment groups RD 10%; (95% CI: 2 to 22; 97 participants)." [Miro 2000](#) (322 participants) reported one case of sensorineural hearing loss in the group receiving non-quinolone topical antibiotics and steroids (very low-certainty evidence).

There was limited reporting of serious complications in two studies ([Leach 2008](#); [Tong 1996](#); very low-certainty evidence), which stated that there were no serious complications or withdrawals due to increased severity of disease.

For suspected ototoxicity, one case of balance problems/vertigo/dizziness was reported (RR 0.46, 95% CI 0.04 to 4.80; 1 study; 52 participants; very low certainty; [Analysis 3.6](#); [Tong 1996](#)). [Miro 2000](#) (322 participants) reported one case of sensorineural hearing loss in the non-quinolone antibiotics plus steroids group (very low-certainty evidence).

No results for health-related quality of life were reported.

### Subgroup analysis

[Leach 2008](#) (97 children) presented results for resolution of ear discharge based on age: less than six years and six years and older. The subgroup contained low numbers and for the comparison of quinolones alone with topical antibiotics with steroids, there was no difference between the subgroups of those under six years old for resolution of discharge at one to two weeks (RR 0.34, 95% CI 0.16 to 0.73; 35 participants) and those aged six years and older (RR 0.83, 95% CI 0.39 to 1.77; 62 participants; [Analysis 3.2](#)). No differences between subgroups were identified for 'high-risk' populations as they included only Indigenous populations (Australian Aboriginals and Torres Strait Islanders). There was no heterogeneity between the results of this study and the other studies, although the resolution rates were lower. Of the studies reporting data quantitatively, one study ([Ramos 2003](#); 150 participants) included people with a diagnosis of 'ear discharge' rather than CSOM specifically and six studies (753 participants) specifically included CSOM as a diagnosis ([Boesoire 2000 unpublished](#); [Gendeh 2001 unpublished](#); [Helmi 2000 unpublished](#); [Leach 2008](#); [Miro 2000](#); [Subramaniam 2001 unpublished](#)). When we separated [Ramos 2003](#) from the rest as a subgroup there did not appear to be a difference between those with 'ear discharge' and those with a diagnosis of CSOM ([Analysis 3.3](#)).

### Topical antibiotics with steroids versus different topical antibiotics - with a background of topical antiseptics (Comparison 4)

One study ([Couzos 2003](#); 147 children) was included, which compared non-quinolone topical antibiotics with steroids against quinolone antibiotics. All patients also had twice daily irrigation with a topical antiseptic (povidone iodine). This was a 'high-risk' population of Australian Aboriginals and Torres Strait Islanders. The



study found that more people given quinolone topical antibiotics on top of topical antiseptics had resolution of discharge at between one and up to two weeks compared to those receiving non-quinolone topical antibiotics and steroids on top of antibiotics (RR 0.67, 95% CI 0.50 to 0.90; 112 participants; [Analysis 4.1](#)). No results for time points beyond two weeks were reported. The resolution of ear discharge was otoscopically confirmed.

For the adverse effect of ear pain, discomfort or local irritation, the evidence was uncertain and we could not determine whether there was a difference between the two treatment arms (RR 0.65, 95% CI 0.11 to 3.77; 111 participants; [Analysis 4.2](#)). For hearing, the difference between the groups was reported in the study as non-significant ( $P = 0.59$ ).

[Couzou 2003](#) reported "transient dizziness" in 2/55 in the ciprofloxacin group and 1/56 in the Sofradex group.

There was no information for health-related quality of life or serious complications.

### Topical antibiotics with steroids versus steroids only (Comparison 5)

One study examined topical antibiotics with steroids (aminoglycoside) versus steroids only ([Crowther 1991](#); 64 participants). For the primary outcome the treatment favoured topical antibiotics and steroids with more people having resolution of discharge at two to four weeks (RR 2.74, 95% CI 1.43 to 5.25; 54 participants; [Analysis 5.1](#)). Results were not reported at the one to two weeks or after four weeks time points. The resolution of discharge was otoscopically confirmed.

Ear pain was reported as a 'burning sensation' but it was uncertain whether there was a difference between the groups due to the low number of events (RR 2.42, 95% CI 0.1 to 56.85; 54 participants; [Analysis 5.2](#)). The study did not report health-related quality of life, hearing, serious complications or suspected ototoxicity.

### Topical antibiotics with steroids versus antiseptics (Comparison 6)

One study examined topical antibiotics with steroids (framycetin sulphate, dexamethasone and gramicidin) versus antiseptics alone (boric acid) ([Eason 1986](#); 55 'high-risk' children; 73 ears). Results for ear discharge were only presented by ear and so the results were not included in the analysis. No results for between one and up to two weeks were reported. The resolution of discharge was otoscopically confirmed.

The study did not report health-related quality of life, hearing, adverse effects (ear pain, discomfort or local irritation) or suspected ototoxicity. [Eason 1986](#) reported one case of mastoiditis and one case of meningitis with focal encephalitis. It is not clear which group these patients were from (the study was a five-arm trial), or whether the complications occurred pre- or post-treatment.

### Other comparisons of topical antibiotics with steroids (Comparisons 7 to 11)

[Ramos 2003](#) was a six-arm study that provided a small amount of data (100 participants) for other comparisons within this review for the outcome of resolution of ear discharge at between one and up to two weeks. The resolution of discharge was otoscopically confirmed.

- Topical antibiotics with steroids versus oral antibiotics (same quinolone antibiotics): favoured topical (quinolone) antibiotics with steroids (RR 1.50, 95% CI 1.17 to 1.92; 100 participants; comparison 7; [Analysis 7.1](#)).
- Topical antibiotics (non-quinolone) with steroids versus oral antibiotics (quinolone): uncertain evidence (RR 0.93, 95% CI 0.67 to 1.30; 100 participants; comparison 8; [Analysis 8.1](#)).
- Topical antibiotics with steroids versus topical plus oral antibiotics (same quinolone antibiotics): uncertain evidence (RR 1.02, 95% CI 0.89 to 1.17; 100 participants; comparison 9; [Analysis 9.1](#)).
- Topical antibiotics (non-quinolone) with steroids versus topical plus oral antibiotics (quinolone): favoured topical and oral quinolone antibiotics (RR 0.64, 95% CI 0.49 to 0.83; 100 participants; comparison 10; [Analysis 10.1](#)).
- Topical quinolone antibiotics with steroids versus topical non-quinolone antibiotics with steroids: favoured topical quinolone antibiotics with steroids (RR 1.61, 95% CI 1.24 to 2.09; 100 participants; comparison 11; [Analysis 11.1](#)).

The study did not report the resolution of ear discharge at any time point after two weeks, or any of the other primary or secondary outcomes.

### Overall completeness and applicability of evidence

The doses used in the included studies were in keeping with manufacturers' recommendations and are applicable to the population being studied. The population of patients with chronic suppurative otitis media (CSOM) is likely to receive treatment in both primary and secondary care settings.

Whilst the inclusion criterion 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 and this leaves us with no information on this important patient group. Three studies included participants classed as 'high-risk' in our protocol, as they recruited Indigenous participants ([Couzou 2003](#); [Eason 1986](#); [Leach 2008](#)). The risk ratio for resolution of ear discharge was consistent with the studies that did not include 'high-risk' 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. This 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

Where assessed, the certainty of the evidence for all outcomes in these comparisons was low or very low (GRADE assessment). The evidence was mainly downgraded due to study limitations (risk of bias) with many of the studies having poor reporting, especially around blinding of participants and outcome assessors. In addition, four of the studies we found were unpublished and identified through a systematic review. As it was not possible to locate the original studies we extracted the results only from the systematic review. It is possible that other unpublished studies have not been identified in this review. Lastly, the studies were generally small and so where adverse events were reported, the low numbers resulted in large confidence intervals. Accuracy of the diagnosis was also a potential issue throughout the studies included in this review. Of the 17 included studies, only nine 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.

One study reported employees with financial involvement in a pharmaceutical company and four studies reported support from a pharmaceutical provider in supplying medications for their study. A number of studies did not report any specific funding to support the study, but may have been sponsored by pharmaceutical companies, which could have introduced a potential source of bias.

## 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. Results 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 conclusions about the lack of difference between groups.

## Agreements and disagreements with other studies or reviews

This review is one of a series of reviews on CSOM (Bhutta 2018; Brennan-Jones 2020; Brennan-Jones 2018; Chong 2018a; Chong 2018b; Head 2020a; Head 2020b). A companion review looks at the effectiveness of topical antibiotics without steroids for the treatment of CSOM (CSOM-1; Brennan-Jones 2020). The results from our review are also consistent with CSOM-1 (topical antibiotics without steroids), which found that topical antibiotics may be more effective than placebo, or when used in addition to a systemic antibiotic (Brennan-Jones 2020).

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 Otolaryngology in 2000 came to a similar conclusion (Hannley 2000).

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

Although we planned to conduct subgroup analyses for different participant characteristics (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

There is a lot of uncertainty as to whether or not topical antibiotics with steroids improve the resolution of ear discharge in patients with chronic suppurative otitis media (CSOM). However, there is low-certainty evidence that some topical antibiotics (without steroids) may be better than topical antibiotics/steroid combinations in improving resolution of discharge. 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 March 2020, provide very low-certainty evidence that, for people with CSOM, treatment with topical antibiotics may be more beneficial in improving the short-term resolution of ear discharge when compared to combined topical antibiotic and steroid combinations. The low certainty of evidence for CSOM treatments in this review is common throughout this suite of seven reviews of CSOM treatments.

There is insufficient evidence to address the implications of topical antibiotics with 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 was also unclear.

Prior to commencing these reviews, we conducted a [scoping review](#) that identified two key questions that clinicians, researchers and consumers would like to see answered:

- Is a combination of topical antibiotics plus topical corticosteroids effective when added to other interventions (e.g. systemic antibiotics)?
- Is a combination of topical antibiotics plus topical corticosteroids effective compared to other interventions, when both groups also receive another intervention (e.g. aural toileting)?

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 with steroids 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 for CSOM. Topical steroids may also have an additive benefit for people with CSOM and granulation tissue receiving treatment with topical antibiotics, where steroids may impact both resolution of inflammation and penetration of topical antibiotics. This review did not consider people with CSOM and granulation tissue as a specific subgroup, but this may be a subgroup worth consideration in future clinical studies.

### 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 in to be included and analysed must be made *a priori*, and the method or criteria for the decision must be 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 the dosage form and/or regimen are different. Where it is not possible to blind participants and/or clinicians to the treatment received, efforts to blind the outcome assessment and analysis personnel should be made.

#### Population

- Diagnosis of CSOM should be according to the WHO criteria, be otoscopically confirmed and include an assessment of hearing level.

- Potentially important patient characteristics (such as existence of ear grommets) should be recorded and presented in the report.
- If patients from 'high-risk' groups are included, these characteristics should be accounted for and explored in the design of the study.

#### Interventions

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

#### Outcomes

- There is currently no core outcome set for CSOM, or a widely agreed set of priority outcomes and definitions for CSOM trials. The development of core outcome sets, using established methods ([Kirkham 2017](#)), for CSOM would be beneficial for future trials. This would help to ensure that trials are consistent, high-quality and examine appropriate outcomes. The standardisation of outcomes allows for analysis and comparison of data across trials (and treatments) using network meta-analysis or individual participant data meta-analysis.
- The assessment for adverse effects should be defined in the protocol and these should be systematically sought during the trial using explicit methods.
- All outcomes (including hearing and balance) 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]

**Boesoirie 2000 unpublished**
**Study characteristics**

Methods	Two-arm, double-blinded, clinical RCT, with 7 to 14 days duration of treatment; no details of follow-up
Participants	<p><b>Location:</b> no details</p> <p><b>Setting of recruitment and treatment:</b> no details</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> no details</li> <li><b>Number completed:</b> 92</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: &gt; 15 years</li> <li>Gender (F/M): no details</li> <li>Main diagnosis: CSOM</li> <li>High-risk population: <ul style="list-style-type: none"> <li>Cleft palate (or other craniofacial malformation): no details</li> <li>Down syndrome: no details</li> <li>Indigenous groups (Australian Aborigines/Greenland natives): no details</li> <li>Immunocompromised: no details</li> </ul> </li> <li>Diagnosis method: <ul style="list-style-type: none"> <li>Confirmation of perforated tympanic membrane: no details</li> <li>Presence of mucopurulent discharge: no details</li> <li>Duration of symptoms (discharge): &gt; 3 weeks</li> </ul> </li> </ul>

**Boesoirie 2000 unpublished** (Continued)

- Other important effect modifiers:
  - \* Alternative diagnosis of ear discharge: no details
  - \* Number who have previously had grommets inserted: no details
  - \* Number who have had previous ear surgery: no details
  - \* Number who have had previous antibiotic treatment for CSOM: no details

**Inclusion criteria:** no details

**Exclusion criteria:** no details

Interventions	<p><b>Intervention (n = unknown):</b> ofloxacin 0.3% otic solution, 6 drops twice a day for 7 to 14 days</p> <p><b>Comparator group (n = unknown):</b> neomycin-polymixin-hydrocortisone otic solution, 6 drops to affected ear twice daily for 7 to 14 days</p> <p><b>Concurrent treatment:</b> no details</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Resolution of ear discharge or 'dry ear' (unclear whether otoscopically confirmed or not)</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Not reported</li> </ul>
Funding sources	No details
Declarations of interest	No details
Notes	<p><b>Unit of randomisation:</b> unclear</p> <p><b>Methods for reporting outcomes of patients with bilateral disease:</b> unclear</p> <p>Data from <a href="#">Abes 2003</a>. No access to publication or data.</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomized controlled clinical trial" by <a href="#">Abes 2003</a>
Allocation concealment (selection bias)	Unclear risk	Described as "concealed allocation, double blind" by <a href="#">Abes 2003</a> ; not a published paper
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details

## Boesoirie 2000 unpublished (Continued)

Selective reporting (re-reporting bias)	Unclear risk	No details
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## Browning 1988

### Study characteristics

Methods	Two-arm, single-blinded, parallel-group RCT, with 4 to 6 weeks duration of treatment and follow-up
Participants	<p><b>Location:</b> Scotland, UK, 1 site</p> <p><b>Setting of recruitment and treatment:</b> Royal Infirmary Outpatient Department, published in 1988</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li>• <b>Number randomised:</b> not given</li> <li>• <b>Number completed:</b> 64 in gentamicin + hydrocortisone group, 59 in placebo group</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>• Age: gentamicin + hydrocortisone group: mean 51 years (range 20 to 79); placebo group: 47 years (range 21 to 68)</li> <li>• Gender (F/M): 54%/46%</li> <li>• Main diagnosis: adults with active mucosal chronic otitis media</li> <li>• High-risk population: No <ul style="list-style-type: none"> <li>* Cleft palate (or other craniofacial malformation): not reported</li> <li>* Down syndrome: not reported</li> <li>* Indigenous groups (Australian Aborigines/Greenland natives): not reported</li> <li>* Immunocompromised: not reported</li> </ul> </li> <li>• Diagnosis method: <ul style="list-style-type: none"> <li>* Confirmation of perforated tympanic membrane: yes (otoscopic evaluation)</li> <li>* Presence of mucopurulent discharge: yes (inclusion criteria)</li> <li>* Duration of symptoms (discharge): mean 46 weeks</li> </ul> </li> <li>• Other important effect modifiers: <ul style="list-style-type: none"> <li>* Alternative diagnosis of ear discharge: not reported</li> <li>* Number who have previously had grommets inserted: not reported</li> <li>* Number who have had previous ear surgery: not reported</li> <li>* Number who had previous antibiotic treatment for CSOM: not reported</li> </ul> </li> </ul> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Individuals over the age of 16 years with active mucosal chronic otitis media but without any evidence of a cholesteatoma or aural polyps</li> <li>• Active mucosal chronic otitis media considered present if there was permanent defect of the pars tensa and the middle ear mucosa was inflamed and oedematous with the production of mucopurulent discharge, which was often foul-smelling</li> <li>• Still active after 1 week of aural toilet and no medical treatment for the ear during the previous 4 weeks</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• None listed</li> </ul>
Interventions	<p><b>Intervention (n = 64):</b> gentamicin/hydrocortisone, ear drops, no dose given except to say "highest recommended daily dose" (4 drops/6 hours), duration of treatment = 4 to 6 weeks depending on success</p>

## Browning 1988 (Continued)

**Comparator group (n = 59):** initially placebo ear drops were used (0.9% sterile saline, 1 drop/8 hours) but this was changed in the second stage of the study to placebo tablets. It was not clear how many patients were in both groups. Duration of treatment = 4 to 6 weeks depending on success.

The patients on placebo therapy also performed regular aural toilet with cotton buds.

**Concurrent treatment:** not reported

Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>Resolution of ear discharge or "dry ear" measured at between 2 to 4 weeks. Otoscopically confirmed.</li> <li>Ear pain (otalgia) or discomfort or local irritation</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>Hearing measured as the pure-tone average of air conduction thresholds across 4 frequencies tested (at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz) of the affected ear. If this was not available, the pure-tone average of the thresholds measured was reported</li> <li>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</li> <li>Adverse effects from treatment (this will be dependent on the type of treatment reviewed)</li> </ul>
Funding sources	Quote: "The ear drops and placebo tablets were supplied by Nicholas Laboratories"
Declarations of interest	No information provided
Notes	<p><b>Unit of randomisation:</b> person</p> <p><b>Methods for reporting outcomes of patients with bilateral disease:</b> one ear chosen as study ear.</p> <p>Individuals with an open mastoid cavity were not excluded but were treated as a separate group for randomisation purposes.</p>

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "...randomly allocated by the pharmacist..."</p> <p>Comment: no information about method of randomisation</p>
Allocation concealment (selection bias)	Unclear risk	<p>Quote: "...randomly allocated by the pharmacist..."</p> <p>Comment: randomisation completed by someone not involved in the day to day care of the patient</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: although placebo was used, this was initially an ear drop but which was given on a different treatment regimen compared to the active intervention. In the second part of the study this was a placebo tablet. It is unclear whether the patients and healthcare professionals would remain blind to treatment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "...followed up at weekly intervals by an otologist who was unaware of the therapy prescribed", "hearing thresholds were assessed... using standard techniques and masking"

## Browning 1988 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: low dropout rate. 24/187 (12.8%) of participants were lost to follow-up but no information is provided about the reasons or to which group they were allocated
Selective reporting (reporting bias)	Unclear risk	Comment: hearing reported but was not reported per treatment group – other ears were included

## Couzos 2003

### Study characteristics

Methods	Two-arm, double-blind, multicentre, parallel-group RCT, with 9 days duration of treatment and 10 to 21 days duration of follow-up
Participants	<p><b>Location:</b> Australia, northern West Australia and Queensland</p> <p><b>Setting of recruitment and treatment:</b> 8 Aboriginal community clinics, April 2001 to June 2002</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> 72 in framycetin, gramicidin and dexamethasone (FGD) group, 75 in ciprofloxacin group</li> <li><b>Number completed:</b> 56 in FGD group, 55 in ciprofloxacin group</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: 1 to 14 years</li> <li>Gender (F/M): not reported (authors report not significant difference)</li> <li>Main diagnosis: children (&lt; 15 years) with perforation and ear discharge</li> <li>High-risk population: yes <ul style="list-style-type: none"> <li>Cleft palate (or other craniofacial malformation): not reported</li> <li>Down syndrome: not reported</li> <li>Indigenous groups (Australian Aboriginals): 100%</li> <li>Immunocompromised: not reported</li> </ul> </li> <li>Diagnosis method: <ul style="list-style-type: none"> <li>Confirmation of perforated tympanic membrane: yes (otoscopy)</li> <li>Presence of mucopurulent discharge: yes</li> <li>Duration of symptoms (discharge): &gt; 2 weeks</li> </ul> </li> <li>Other important effect modifiers: <ul style="list-style-type: none"> <li>Alternative diagnosis of ear discharge: not reported</li> <li>Number who have previously had grommets inserted: unknown. Patients with grommets in situ were excluded.</li> <li>Number who have had previous ear surgery: not reported (children who had ear surgery in the preceding 12 months were excluded)</li> <li>Number who had previous antibiotic treatment for CSOM: not reported. Patients using antibiotics in previous 2 weeks were excluded.</li> </ul> </li> </ul> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>Children aged less than 15 years with at least 2 weeks of otorrhoea and tympanic membrane perforation</li> </ul> <p><b>Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>Current febrile illness</li> <li>Current antibiotic use or use in the preceding 2 weeks</li> </ul>



**Couzos 2003** (Continued)

- Allergy to ototopical medication and specific allergy to fluoroquinolones
- Need for renal dialysis
- Recent ear surgery or an in situ grommet or tympanostomy tube, mastoid surgery in the preceding 12 months
- Congenital ear or hearing problems obstructed middle ear (e.g. polyp)
- Pregnancy
- Unlikely to be resident in the study region over the follow-up period

**Interventions**

**Intervention (n = 72):** framycetin (0.5%), gramicidin and dexamethasone (Sofradex) eardrops, 5 drops/12 hours. Treatment duration = 9 days.

**Comparator group (n = 75):** ciprofloxacin 0.3% eardrops, 5 drops/12 hours. Treatment duration = 9 days.

**Concurrent treatment:**

- During the treatment period, each child was assessed daily, with half of the ototopical treatments applied by health workers and the other half by parents/guardians
- Guardians were instructed in applying eardrops (supine into external meatus), including the use of tragal pressure (pressing several times on the flap of skin in front of the ear canal) which aids middle-ear penetration
- Ears were cleaned twice each day before the eardrops were administered. Cleaning comprised gentle syringing of the discharge in the external ear canal with 0.5% povidone-iodine solution until the tympanic membrane perforation was clear of purulent material

**Outcomes**

**Outcomes of interest in the review:**

**Primary outcomes:**

- Complete resolution of ear discharge, measured at between 1 week to 2 weeks
- 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 was not available, the pure-tone average of the thresholds measured was reported.

**Funding sources**

Quote: "The study was supported by: National Health and Medical Research Council, the Commonwealth Department for Education, Training and Youth Affairs, and RioTinto Aboriginal Foundation. Alcon Laboratories Australia Pty Ltd [manufacturer of Ciloxan] provided the pharmaceuticals"

**Declarations of interest**

Paper states "none identified"

**Notes**

**Unit of randomisation:** person

**Methods for reporting outcomes of patients with bilateral disease:**

- Random selection of one ear as the 'study ear'
- "Children with bilateral CSOM received treatment for both ears, although only one ear (randomly chosen) was monitored for the study"

**Risk of bias**

**Bias**

**Authors' judgement**

**Support for judgement**

Random sequence generation (selection bias)

Low risk

Quote: "A statistical program was used to produce balanced random sequences for each site to assign the two ototopical medications to a list of client identification numbers."

## Couzos 2003 (Continued)

Comment: adequate sequence generation

Allocation concealment (selection bias)	Unclear risk	<p>Quote: "Participants were then assigned a client number according to the sequence, which was concealed from them and from investigators for the duration of the trial and analysis"</p> <p>Comment: there was no information about how patients were recruited versus enrolled. Since the blinding may not be fully adequate for the healthcare workers, unclear if this may affect allocation concealment</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "None of the investigators, health team nor the children knew which agents had been allocated (double-blind)"</p> <p>From Couzos 2005: "Blinding was achieved by sterile transfer of ototopicals into identical glass droppers, so that it was not possible for health workers or clients to discern between randomly assigned treatments. Parents and guardians were aware that if their children took part in the trial they would receive either current ototopical treatment (as they would without trial participation) or the new ototopical and that both agents were effective treatments."</p> <p>Comment: although a different odour can often affect the blinding, the paper (Couzos 2005) also mentioned that this group of patients are unlikely to seek and obtain treatment if not part of a trial. Therefore, they are unlikely to have a prior perception of effectiveness of the agents or able to distinguish them. Workers and patients were told both agents were effective.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Quote: "During the treatment period, each child was assessed daily"</p> <p>Comment: it is uncertain if blinding was maintained over the course of trial; with 147 patients spread over 8 centres with a risk ratio of 1.5 for resolution favouring ciprofloxacin</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Quote: "36 children randomly allocated to the treatment arms did not complete the follow-up schedule"</p> <p>Comment: 26/147 (17.7%) participants were not analysed in the trial</p>
Selective reporting (reporting bias)	Unclear risk	<p>Comment: no protocol found in the WHO clinical trials database or <a href="http://www.anzctr.org.au">http://www.anzctr.org.au</a>. All outcomes presented in methods section were fully reported. Study unclear about how adverse events were elicited.</p>

## Crowther 1991

### Study characteristics

Methods	Two-arm, double-blind, parallel-group RCT, with 2 to 4 weeks duration of treatment and 4 weeks duration of follow-up
Participants	<p><b>Location:</b> Glasgow, Scotland</p> <p><b>Setting of recruitment and treatment:</b> general hospital, 1989</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> 64 in total, not reported by treatment group</li> <li><b>Number completed:</b> 30 in gentamycin plus hydrocortisone drops group, 24 in betamethasone drops group</li> </ul> <p><b>Participant (baseline) characteristics:</b></p>

**Crowther 1991** (Continued)

- Age: "average age of 48 years"
- Gender (F/M): 20 (37%)/34 (63%)
- Main diagnosis: "active non-cholesteatomatous chronic otitis media"
- High-risk population: no
  - \* Cleft palate (or other craniofacial malformation): not reported
  - \* Down syndrome: not reported
  - \* Indigenous groups (Australian Aborigines/Greenland natives): not reported
  - \* Immunocompromised: not reported
- Diagnosis method:
  - \* Confirmation of perforated tympanic membrane: yes (otoscopy)
  - \* Presence of mucopurulent discharge: not reported
  - \* Duration of symptoms (discharge): not reported
- Other important effect modifiers:
  - \* Alternative diagnosis of ear discharge: 18/54 completed had open mastoid cavity
  - \* Number who have previously had grommets inserted: not reported
  - \* Number who have had previous ear surgery: not reported
  - \* Number who had previous antibiotic treatment for CSOM: not reported

**Inclusion criteria:**

- Active non-cholesteatomatous chronic otitis media
- Including patients with simple perforations and open mastoid cavity

**Exclusion criteria:**

- Received treatments within the previous 3 weeks
- Aural polyps

Interventions	<p><b>Intervention (n = 30):</b> gentamicin with hydrocortisone drops, concentration not reported, 4 drops 4 times daily. Treatment duration = up to 4 weeks (if CSOM determined "inactive" at 2-week follow-up, treatment stopped)</p> <p><b>Steroid only (n = 24):</b> betamethasone drops, concentration not reported, 4 drops 4 times daily. Treatment duration = up to 4 weeks (if CSOM determined "inactive" at 2-week follow-up, treatment stopped)</p> <p><b>Concurrent treatment:</b> both groups underwent aural toileting with suction under an operating microscope, prior to treatment</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Resolution of ear discharge or "dry ear" measured at between 2 to 4 weeks. Otoscopically confirmed.</li> <li>• Ear pain (otalgia) or discomfort or local irritation</li> </ul>
Funding sources	No information provided
Declarations of interest	No information provided
Notes	<p><b>Unit of randomisation:</b> person</p> <p><b>Methods for reporting outcomes of patients with bilateral disease:</b></p> <ul style="list-style-type: none"> <li>• Did not report whether there were any bilateral patients, or how bilateral cases would be assessed</li> </ul>
<b>Risk of bias</b>	
<b>Bias</b>	<b>Authors' judgement      Support for judgement</b>

**Crowther 1991** (Continued)

Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were then randomly allocated..."  Comment: no details of method
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were then randomly allocated..."  Comment: no details of method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "... in a double-blind format... Hydrocortisone ear-drops are not commercially available and so betamethasone drops were chosen"  Comment: one group had gentamicin plus hydrocortisone, a commercial preparation, whereas the other had betamethasone drops. Unclear whether these would be in identical packaging and appearance when given to participants.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "their ear was assessed otoscopically by an independent examiner"  Comment: as above, unclear whether the blinding was adequate. No mention of outcome assessor blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "of the 64 patients entered into the study 54 returned for follow-up at the requested times having completed their course of treatment (used more than 75% of the prescribed drops)"  Comment: only participants who took at least 75% of the ear drops and completed the assessment were included the analysis. 10/64 randomised were excluded/dropped out, and the breakdown and reasons are not given. The number that dropped out per treatment arm is unknown.  If numbers were balanced at the start, dropout/exclusions would not have been balanced across groups - 2/32(6%) in gentamicin, 8/32 (25%) in betamethasone only.
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol was found. It was not possible to assess risk of reporting bias.

**Eason 1986**
**Study characteristics**

Methods	Five-arm, non-blinded, parallel-group RCT with 3 to 6 weeks duration of treatment and 6 weeks duration of follow-up
Participants	<p><b>Location:</b> Solomon Islands, 15 villages around Munda</p> <p><b>Setting of recruitment and treatment:</b> Helena Goldie Hospital, Munda; patients identified through community screening February 1985 to March 1986. Treatment was conducted in villages.</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> 134 children (184 ears)</li> <li><b>Number completed:</b> as above (no loss to follow-up mentioned)</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: mean (across whole trial): 5.4 ± 3.1 years (group 1 5.2, group 2 6.3, group 3 5.3, group 4 5.0, group 5 5.1)</li> <li>Gender (F/M): 49 (36.6%)/85 (63.4%)</li> </ul>

**Eason 1986** (Continued)

- Main diagnosis: chronic suppurative otitis media with presence of otorrhoea for more than 3 months and tympanic membrane perforation
- High-risk population: yes
  - \* Cleft palate (or other craniofacial malformation): not reported
  - \* Down syndrome: not reported
  - \* Indigenous groups (Australian Aboriginals/Greenland natives): yes – Solomon Islands - study noted prevalence is 3.8% for under 15-year olds
  - \* Immunocompromised: not reported
- Diagnosis method:
  - \* Confirmation of perforated tympanic membrane: yes (confirmed by otoscopic examination)
    - ☐ Central and tubotympanic perforations: 176 (130 were large (> ¼ ear drum); 46 were small)
    - ☐ Marginal tympanic perforations: 4
  - \* Presence of mucopurulent discharge: not reported
  - \* Duration of symptoms (discharge): mean age at CSOM onset: 1.5 ± 1.0 years; discharge for more than 3 months (inclusion criteria)
- 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 under 15 years old with CSOM (defined as presence of otorrhoea for more than 3 months and tympanic membrane perforation) living in Munda or principal villages

**Exclusion criteria:**

- None listed

**Interventions**

**Group 1 (n = 31, 40 ears):** 'Sofradex' eardrops (0.5% w/v of framycetin sulphate, 0.050% w/v of dexamethasone and 0.005% w/v of gramicidin) (no details of volume or frequency of administration), PLUS oral clindamycin (15 mg/kg/day) into 3 divided oral daily doses, PLUS aural toilet 4 times per day using cotton wool wisps twisted onto orange sticks. Treatment duration = 6 weeks.

**Group 2 (n = 31, 41 ears):** Sofradex eardrops (0.5% w/v of framycetin sulphate, 0.050% w/v of dexamethasone and 0.005% w/v of gramicidin) (no details of volume or frequency of administration), PLUS aural toilet 4 times per day using cotton wool wisps twisted on to orange sticks. Treatment duration = 6 weeks.

**Group 3 (n = 24, 32 ears):** 2% boric acid in 20% alcohol (3 drops after cleaning using intermittent tragal depression to assist middle ear permeation) given 4 times per day, PLUS aural toilet using cotton wool wisps twisted on to orange sticks. Treatment duration = 6 weeks.

**Group 4 (n = 19, 26 ears):** aural toilet 4 times per day using cotton wool wisps twisted on to orange sticks. Treatment duration = 6 weeks.

**Group 5 (n = 29, 41 ears):** no treatment.

All treatments administered by parents.

**Concurrent treatment:** parents were instructed to encourage nose blowing, forbid swimming and insert cotton wool/Vaseline ear plugs before washing.

For each child in groups 2 to 5, one of the authors stayed in the village for the first 3 days of treatment to provide parental tuition and supervision. This was continued by a nurse aid who remained until the medical team returned after 3 weeks. If the ear was then dry, the clinical response was judged good, ototopical solutions continued 1 further week only and aural toilet and clindamycin stopped. If the ear was still discharging, all treatment modalities were continued until the second assessment after 6 weeks.



**Eason 1986** (Continued)

## Outcomes

**Outcomes of interest in the review:**
**Primary outcomes:**

- Complete resolution of ear discharge, measured at 2 to 4 weeks and after 4 weeks. Unclear if otoscopically confirmed.

**Secondary outcomes:**

- Not reported

## Funding sources

Quote: "This study was made possible by a research grant from the Medical Research Council of New Zealand"

## Declarations of interest

No information provided

## Notes

**Unit of randomisation:** person

**Methods for including patients bilateral disease:** counting bilateral ears separately.

RCT was part of a larger epidemiological study. Hearing loss was measured for the epidemiological study but not specifically for the RCT. Results are not presented by those who have CSOM and those who do not.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	<p>Quote: "children from 15 villages with 184 diseased ears were randomly allocated into five treatment groups."</p> <p>Comment: insufficient information about sequence generation method.</p> <p>The largest group had 1.6 times (31 patients/41 ears) the number of participants compared to the number in the smallest group (19 patients/26 ears), with the larger number of patients (31 each) in the more effective treatment groups.</p> <p>Unit of randomisation unclear although it is likely to be by person. Results reported by percentage of affected ears.</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: no details about allocation concealment are provided in the paper</p>
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Comment: blinding is not specifically stated. The treatment arms involved different dosage forms (oral versus ear drops) – blinding of these interventions impossible without use of placebo.</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p>Comment: no clear information about who had assessed that the ears were "dry" versus "still discharging", whether these assessments were by patients or the medical team. No report of otoscopic examination for outcome. Therefore, in the absence of blinding, this is likely a high risk.</p>
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>Comment: no dropouts or missing data reported; no statements about missing data</p>
Selective reporting (reporting bias)	Unclear risk	<p>Comment: no protocol was available on clinicaltrials.gov. The level of reporting is extremely low. Outcome was reported as two categories: "improved" versus "no change" as opposed to "dry ear" versus others. The definition was</p>

## Eason 1986 (Continued)

not provided and it was unclear whether "improved" means "dry ear" or a reduction of discharge. Insufficient information to permit judgement of 'low risk' or 'high risk'.

## Gendeh 2001 unpublished

### Study characteristics

Methods	Two-arm, double-blinded, clinical RCT, with 2 weeks duration of treatment; no details of follow-up
Participants	<p><b>Location:</b> no details</p> <p><b>Setting of recruitment and treatment:</b> no details</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> no details</li> <li><b>Number completed:</b> 70</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: no details</li> <li>Gender (F/M): no details</li> <li>Main diagnosis: patients with otitis externa and CSOM (only data for CSOM was used for this meta-analysis)</li> <li>High-risk population: <ul style="list-style-type: none"> <li>* Cleft palate (or other craniofacial malformation): no details</li> <li>* Down syndrome: no details</li> <li>* Indigenous groups (Australian Aboriginals/Greenland natives): no details</li> <li>* Immunocompromised: no details</li> </ul> </li> <li>Diagnosis method: <ul style="list-style-type: none"> <li>* Confirmation of perforated tympanic membrane: no details</li> <li>* Presence of mucopurulent discharge: no details</li> <li>* Duration of symptoms (discharge): no details</li> </ul> </li> <li>Other important effect modifiers: <ul style="list-style-type: none"> <li>* Alternative diagnosis of ear discharge: no details</li> <li>* Number who have previously had grommets inserted: no details</li> <li>* Number who have had previous ear surgery: no details</li> <li>* Number who have had previous antibiotic treatment for CSOM: no details</li> </ul> </li> </ul> <p><b>Inclusion criteria:</b> no details</p> <p><b>Exclusion criteria:</b> no details</p>
Interventions	<p><b>Intervention (n = unknown):</b> ofloxacin 0.3% otic solution, 6 drops twice daily for 2 weeks</p> <p><b>Comparator group (n = unknown):</b> framycetin-dexamethasone-gramicidin otic solution, 6 drops twice daily for 2 weeks</p> <p><b>Concurrent treatment:</b> no details</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>Resolution of ear discharge or 'dry ear' (unsure whether otoscopically confirmed or not) and between 1 to 2 weeks</li> </ul>

## Gendeh 2001 unpublished (Continued)

- Ear pain (otalgia) or discomfort or local irritation - reported as resolution of otalgia

### Secondary outcomes:

- Not reported

Funding sources	No details
Declarations of interest	No details
Notes	<p><b>Unit of randomisation:</b> unclear</p> <p><b>Methods for reporting outcomes of patients with bilateral disease:</b> unclear</p> <p>Data from <a href="#">Abes 2003</a>. No access to publication or data.</p>

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomized controlled clinical trial" by <a href="#">Abes 2003</a>
Allocation concealment (selection bias)	Unclear risk	Described as "concealed allocation, double blind" by <a href="#">Abes 2003</a> . Not a published paper.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details
Selective reporting (reporting bias)	Unclear risk	No details

## Helmi 2000 unpublished

### Study characteristics

Methods	Two-arm, open-label, clinical RCT, with 14 days for duration of treatment; no details of follow-up
Participants	<p><b>Location:</b> no details</p> <p><b>Setting of recruitment and treatment:</b> no details</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li>• <b>Number randomised:</b> no details</li> <li>• <b>Number completed:</b> 138</li> </ul> <p><b>Participant (baseline) characteristics:</b></p>

## Topical antibiotics with steroids for chronic suppurative otitis media (Review)

## Helmi 2000 unpublished (Continued)

- Age: > 7 years old
- Gender (F/M): no details
- Main diagnosis: CSOM
- High-risk population:
  - \* Cleft palate (or other craniofacial malformation): no details
  - \* Down syndrome: no details
  - \* Indigenous groups (Australian Aboriginals/Greenland natives): no details
  - \* Immunocompromised: no details
- Diagnosis method:
  - \* Confirmation of perforated tympanic membrane: no details
  - \* Presence of mucopurulent discharge: no details
  - \* Duration of symptoms (discharge): no details
- Other important effect modifiers:
  - \* Alternative diagnosis of ear discharge: no details
  - \* Number who have previously had grommets inserted: no details
  - \* Number who have had previous ear surgery: no details
  - \* Number who have had previous antibiotic treatment for CSOM: no details

**Inclusion criteria:** no details

**Exclusion criteria:** no details

Interventions	<p><b>Intervention (n = unknown):</b> ofloxacin 0.3% otic solution, 6 to 10 drops twice daily for 14 days</p> <p><b>Comparator group (n = unknown):</b> neomycin-polymixin-hydrocortisone otic solution, 3 to 5 drops 3 times daily for 14 days</p> <p><b>Concurrent treatment:</b> no details</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Resolution of ear discharge or 'dry ear' (unsure whether otoscopically confirmed or not)</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Not reported</li> </ul>
Funding sources	No details
Declarations of interest	No details
Notes	<p><b>Unit of randomisation:</b> unclear</p> <p><b>Methods for reporting outcomes of patients with bilateral disease:</b> unclear</p> <p>Data from <a href="#">Abes 2003</a>. No access to publication or data.</p>

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomized controlled clinical trial" by <a href="#">Abes 2003</a>
Allocation concealment (selection bias)	Unclear risk	Described as "concealment of allocation not clear, open label" by <a href="#">Abes 2003</a> . Not a published paper.

## Helmi 2000 unpublished (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	"Open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	"Open label"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details
Selective reporting (reporting bias)	Unclear risk	No details

## Indudharan 2005

### Study characteristics

Methods	Two-arm, non-blinded, multicentre, quasi-randomised trial, with 3 weeks duration of treatment and 4 weeks duration of follow-up
Participants	<p><b>Location:</b> Malaysia, Kota Bahru, Kelantan</p> <p><b>Setting of recruitment and treatment:</b> University Hospital and General Hospital, the two referral centres in Kelantan, from July 1995 until December 1996 (reviewers' note – patient catchment likely to be areas that are considered rural)</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> 135 participants; 152 ears (75 ears into gentamicin with steroids drops group, 77 ears in gentamicin drops group)</li> <li><b>Number completed:</b> 109 ears (52 ears in gentamicin with steroid drops group, 57 ears in gentamicin drops group)</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: 2 to 84 years</li> <li>Gender (F/M): 69 (51%)/66 (49%)</li> <li>Main diagnosis: CSOM with central perforation without cholesteatoma</li> <li>High-risk population: no <ul style="list-style-type: none"> <li>* Cleft palate (or other craniofacial malformation): not reported</li> <li>* Down syndrome: not reported</li> <li>* Indigenous groups (Australian Aborigines/Greenland natives): none</li> <li>* Immunocompromised: not reported</li> </ul> </li> <li>Diagnosis method: <ul style="list-style-type: none"> <li>* Confirmation of perforated tympanic membrane: yes, method unclear. All cases were seen by a consultant.</li> <li>* Presence of mucopurulent discharge: not reported</li> <li>* Duration of symptoms (discharge): 1 month to 40 years (means 7.21 years, SD 9.72 years)</li> </ul> </li> </ul>



**Indudharan 2005** (Continued)

- Other important effect modifiers:
  - \* Alternative diagnosis of ear discharge: none
  - \* 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 with central perforation without cholesteatoma
- No antibiotic therapy for a minimum period of 1 month prior to the study

**Exclusion criteria:**

- Systemic diseases
- Complications of the disease

Interventions	<p><b>Intervention (n = 75 ears, patient number unknown):</b> gentamicin 0.3% with betamethasone 0.1% ear drops, 3 drops 3 times daily for 3 weeks using displacement method</p> <p><b>Comparator group (n = 77 ears, patient number unknown):</b> gentamicin 0.3% ear drops, 3 drops 3 times daily for 3 weeks using displacement method</p> <p><b>Additional intervention common for both arms:</b> at entry of study, "the external ear canals of these patients were cleaned with cotton swabs soaked in 70% ethyl alcohol and then with povidone-iodine followed by dry sterile swabs to mop the remaining antiseptic solution ...Then the middle ear was cleaned of the discharge by suction."</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Resolution of ear discharge or "dry ear" (whether otoscopically confirmed or not) measured at between 2 to 4 weeks. Unclear if otoscopically confirmed.</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Hearing measured as the pure-tone average of air conduction thresholds across 4 frequencies tested (at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz) of the affected ear. If this was not available, the pure-tone average of the thresholds measured was reported.</li> <li>• Ototoxicity 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:           <ul style="list-style-type: none"> <li>* Sensorineural hearing loss; if pure-tone audiogram measured deterioration in bone conduction threshold of 5 dB or more across 3 frequencies tested (at 500 Hz, 1000 Hz and 2000 Hz). Measured at 4 weeks.</li> <li>* Tinnitus measured at 4 weeks</li> <li>* Vertigo measured at 4 weeks</li> </ul> </li> </ul>
Funding sources	Research grant provided by University Sains Malaysia
Declarations of interest	No information provided
Notes	<p><b>Unit of randomisation:</b> person</p> <p><b>Methods for reporting outcomes of patients with bilateral disease:</b></p> <ul style="list-style-type: none"> <li>• Reported outcomes from both ears separately. The study did not specify how many participants in each arm.</li> </ul>
<b>Risk of bias</b>	

**Indudharan 2005** (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Every alternate patient was given..."  Comment: quasi-randomised trial
Allocation concealment (selection bias)	High risk	Quote: "Every alternate patient was given..."  Comment: since an alternation allocation was used, it was possible to predict which intervention the patient would receive before enrolment. The study was not blinded.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: this is not a blinded study. Allocation was by alternation. No mention of masking of treatment option.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The ear becoming dry was considered clinical improvement"  Comment: no description of blinding. The main outcome of interest was described as "ear becoming dry", which is a subjective outcome.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Of the 77 ears that received GM, and 75 that received GM-S, only 57 (74.03%) and 52 (69.33%) could be followed-up. The rest either defaulted or did not comply strictly with medication as instructed by us and hence were not analysed for treatment response. 95/152 ears had pre and post treatment pure tone audiometry"  Comment: a large proportion of participants were either excluded or lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Comment: outcomes described in methods reported. No access to protocol.

**Kaygusuz 2002**
**Study characteristics**

Methods	Four-arm, non-blinded, single-centre, parallel-group RCT, with 3 weeks duration of treatment and follow-up
Participants	<p><b>Location:</b> Turkey, 1 site</p> <p><b>Setting of recruitment and treatment:</b> university ENT clinic; no dates (published in 2002)</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> 20 in each intervention group</li> <li><b>Number completed:</b> 20 in each intervention group</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: 18 to 60, mean 31 ± 11.5 years</li> <li>Gender (F/M): 31 (39%)/49 (61%)</li> <li>Main diagnosis: chronic suppurative otitis media (CSOM) with ear discharge without cholesteatoma. Perforation in ear membrane and ear discharge longer than 3 months.</li> </ul>

## 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: yes, 100%
  - \* Duration of symptoms (discharge): longer than 3 months (inclusion criteria)
- 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% (exclusion criteria)
  - \* 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	<p><b>Topical ciprofloxacin (n = 20):</b> 0.3% ciprofloxacin hydrochloride ear drop, 2 drops, 3 times a day, treatment duration = 21 days</p> <p><b>Topical tobramycin (n = 20):</b> 0.3% tobramycin ear drop, 2 drops, 3 times a day, treatment duration = 21 days</p> <p><b>Topical ciprofloxacin + dexamethasone (n = 20):</b> 0.3% ciprofloxacin hydrochloride PLUS 0.1% dexamethasone combination ear drops, 2 drops, 3 times a day, treatment duration = 21 days</p> <p><b>Topical tobramycin + dexamethasone (n = 20):</b> 0.3% tobramycin PLUS 0.1% dexamethasone combination ear drops, 2 drops, 3 times a day, treatment duration = 21 days</p> <p><b>Concurrent treatment:</b> daily aspiration during exam for 3 weeks</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Resolution of ear discharge, "dry ear", measured at between 2 to 4 weeks. Otoloscopically confirmed.</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Not reported</li> </ul>
Funding sources	No information provided
Declarations of interest	No information provided
Notes	<p><b>Unit of randomisation:</b> person</p> <p><b>Methods for including patients bilateral disease:</b> not reported</p>

## Kaygusuz 2002 (Continued)

Part of a four arm trial with the following treatment groups:

- Topical ciprofloxacin
- Topical tobramycin
- Topical ciprofloxacin + dexamethasone
- Topical tobramycin + dexamethasone

Only the last 2 arms are presented in this review

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no clear statement of "randomized". No description of randomisation method.
Allocation concealment (selection bias)	Unclear risk	Comment: no clear statement of "randomized". No description of randomisation method.
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 patients were lost to follow-up
Selective reporting (reporting bias)	Low risk	<p>Comment: there was no study protocol mentioned within the paper and no protocol was found on clinicaltrials.gov.</p> <p>All of the outcomes mentioned in the methods section are reported in the results.</p>

## Lazo Saenz 2000

### Study characteristics

Methods	Two-arm, double-blind, single-centre, parallel-group RCT, with 10 days duration of treatment and 10 days duration of follow-up
Participants	<p><b>Location:</b> single centre, Centro Medico de Torreón, Mexico</p> <p><b>Setting of recruitment and treatment:</b> specialist hospital, Centro Medico de Torreon, Coahuila, May 1994 to August 1995</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li>• <b>Number randomised:</b> 20 ears in group A, 20 ears in group B</li> <li>• <b>Number completed:</b> 20 ears in group A, 20 ears in group B</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>• Age: 15 to 71 years (SD mean 38 ± 18.5)</li> </ul>

**Lazo Saenz 2000** (Continued)

- Gender (F/M): 21 (53%)/19 (47%)
- Main diagnosis: chronic suppurative otitis media
- 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, otoscopy
  - \* 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:**

- Clinical diagnosis of chronic suppurative otitis media, no mention of diagnostic criteria

**Exclusion criteria:**

- Not reported

Interventions	<p><b>Group A (n = 20 ears):</b> ciprofloxacin ear drops 200 µg/ml, 3 drops, 3 times a day for 10 days</p> <p><b>Group B (n = 20 ears):</b> neomycin (0.35%)-polymyxin B (10,000 U/mL)-fludrocortisone (0.25%) with 20% lidocaine ear drops administered 3 drops, 3 times/day for 10 days</p> <p><b>Concurrent treatment:</b> not reported</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Complete resolution of ear discharge, measured at between 1 week to 2 weeks</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Hearing loss (as change in hearing threshold from baseline or at endpoint): baseline air-bone gap audiometry was performed in all participants, pre-treatment mean)</li> </ul>
Funding sources	No information provided
Declarations of interest	No information provided
Notes	<p><b>Unit of randomisation:</b> unclear</p> <p><b>Methods for including patients bilateral disease:</b> not reported</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "the random allocation was through assignment blocks for random allocation: a table with random numbers."</p> <p>Comment: a random number table was used</p>



**Lazo Saenz 2000** (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "Patients randomly pick up a number that was written on an opaque envelope."  Comment: if an opaque envelope was used, it should be well concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Comment: identical containers used but there was no mention of characteristics, i.e. whether solutions looked/smelled the same. Study reported as double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: no information was provided about who assessed outcomes or about blinding of assessors. Outcomes were assessed clinically, i.e. were subjective and knowledge of treatment group could be influenced by the results. Response to treatment was defined according to clinical characteristics as good (no discharge, normal mucosa), regular (no discharge with mucosal oedema) or bad (discharge and mucosal oedema). Blinding was adequate therefore is not probable that the knowledge of treatment group influenced the results.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear if loss to follow-up was reported
Selective reporting (reporting bias)	Unclear risk	Comment: unclear if hearing is reported

**Leach 2008**
**Study characteristics**

Methods	Two-arm, double-blind, multicentre, parallel-group RCT, with 6 to 8 weeks duration of treatment and 10 to 20 weeks of duration of follow-up
Participants	<p><b>Location:</b> Australia, 3 remote Aboriginal communities</p> <p><b>Setting of recruitment and treatment:</b> remote communities, 2001</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number screened:</b> 171, 110 had persistent CSOM despite treatment (framycetin-gramicidin-dexamethasone)</li> <li><b>Number randomised:</b> 47 in framycetin sulfate, gramicidin + dexamethasone (FGD) group, 50 in ciprofloxacin group</li> <li><b>Number completed:</b> 44 in FGD group, 45 in ciprofloxacin group</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age (mean <math>\pm</math> SD): FGD: <math>7.8 \pm 3.7</math>, ciprofloxacin: <math>7.7 \pm 3.2</math></li> <li>Gender (F/M): 60 (72%)/37 (38%)</li> <li>Main diagnosis: active CSOM despite treatment with 4 drops twice daily FGD for an unclear duration</li> <li>High-risk population: yes <ul style="list-style-type: none"> <li>Cleft palate (or other craniofacial malformation): none</li> <li>Down syndrome: none</li> <li>Indigenous groups (Australian Aboriginals): 97/97 (100%)</li> <li>Immunocompromised: none</li> </ul> </li> </ul>

**Leach 2008** (Continued)

- Diagnosis method:
  - \* Confirmation of perforated tympanic membrane: yes (by otoscopy). Mean perforation size at entry: FGD  $31\% \pm 23\%$ ; ciprofloxacin  $30\% \pm 20\%$ .
  - \* Presence of mucopurulent discharge: yes (evaluated through otoscopy and video-otoscopy). Bi-lateral discharge  $\geq$  scant (scant = present in middle ear) 30 (60%) ciprofloxacin, 23 (49%) FGD.
  - \* Duration of symptoms (discharge): not reported. Mean age (SD) in years at first perforation: FGD  $0.85 \pm 0.9$  years; ciprofloxacin  $0.83 \pm 0.6$  years.
- Other important effect modifiers:
  - \* Alternative diagnosis of ear discharge: none
  - \* Number who have previously had grommets inserted: none
  - \* Number who have had previous ear surgery: previous tympanoplasty excluded
  - \* Number who had previous antibiotic treatment for CSOM: all participants were treated with FGD immediately preceding

**Inclusion criteria:**

- Children 1 to 16 years old with chronic perforation, who had persistent disease despite treatment with FGD for an unknown period

**Exclusion criteria:**

- Allergic to ciprofloxacin or FGD, pregnant or breast-feeding, diagnosed with cholesteatoma, previously treated with tympanoplasty, suffering from any other medical condition that could interfere with participation in the study

Interventions	<p><b>Intervention (n = 47):</b> framycetin sulfate 0.5% + gramicidin 0.005% + dexamethasone 0.05% ear drops (Sofradex), 4 drops twice daily</p> <p><b>Comparator group (n = 50):</b> ciprofloxacin 0.3% ear drops, 4 drops twice daily</p> <p><b>Intervention applicable to both arms:</b></p> <ul style="list-style-type: none"> <li>• Treatment duration 6 to 8 weeks</li> <li>• Ears examined every week and treatment stopped if ear dried for 3 days or more. Treatment restarted if discharge recurred</li> <li>• Treatment occurred after ear cleaning by dry mopping; instillation of the ear drops occurred with head tilted and was followed by pumping the tragus against the ear canal at least 10 times</li> <li>• Morning dose usually supervised by ear health team operating out of the local school or clinic; evening treatment provided by the family</li> </ul> <p><b>Use of additional interventions (common to both treatment arms):</b> dry mopping by tissue spears (rolled toilet paper) before every instillation</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Complete resolution of ear discharge, after 4 weeks defined as "clinical failure" – "clinical failure was defined as otoscopic signs of otorrhoea in the canal or middle ear space, including otorrhoea in the canal despite healing of the tympanic membrane"</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Hearing loss (measured as pure-tone average hearing levels averaged across 4 frequencies (500 Hz, 1000 Hz, 2000 Hz and 4000 Hz) – 4.5 to 8 months after randomisation</li> <li>• Pain</li> </ul>
Funding sources	Supported by grant from the National Health and Medical Research Council of Australia and the Menzies School of Health Research

## Leach 2008 (Continued)

Declarations of interest      No information provided

Notes      **Unit of randomisation:** patients  
**Methods for reporting outcomes of patients with bilateral disease:** no mention of laterality in outcomes reporting/methods/results. The only mention of bilateral ear disease is in the baseline characteristics.

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A random sequence stratified by community and age group (6 years or 6 years of age) was generated using Stata Version 7.0."  Comment: computer-generated sequence
Allocation concealment (selection bias)	Unclear risk	Quote: "The allocation sequence was concealed throughout the study."  Comment: no information about how allocation concealment was done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "... were prescribed (or continued) topical FGD 4 drops twice daily"  Comment: there was no description of whether the drops appeared identical. All patients had been exposed to one of the treatments before randomisation. It is unclear whether they could recognise the treatment by the visual appearance or taste.  Participants randomised in this study are patients who had failed to improve despite treatment with FGD. The selection of this patient group potentially biases the effect to favour ciprofloxacin by the selection of a group of non-responders.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "All clinical and microbiologic data were collected by observers who were unaware of the treatment allocation... The audiologist .... laboratory staff were also blinded to the allocation status".  "Ear outcomes were also confirmed by a third assessor (blinded to the allocation group) using video recordings"  Comment: all outcomes assessors were well blinded and a third assessor was involved in assessment of subjective outcomes (presence of discharge)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "End of therapy clinical assessments were achieved in 89 children (45 in the CIP group and 44 in the FGC group) .... Subsequent follow-up assessments were made for 90 children (47 CIP and 43 FGD). For 85 children who also had assessments at the end of therapy..."  Comment: there were two descriptions of number of patients available at end of therapy, either a total of 8/97 (8%) or 12/97 (12%) were not available for assessment of clinical failure  Quote: "the mean hearing threshold ... 41 children in CIP, 32 in FGD group"  Comment: although percentage of patients not available for outcome measurement is low, this was sufficient to change the direction of effect for treatment failure. The number of patients who missed hearing outcome assessment was almost 1.5 times higher for the FGD group (32% loss) compared to the ciprofloxacin group (18%).

## Leach 2008 (Continued)

Selective reporting (reporting bias)

Low risk

Comment: all outcomes reported as expected

## Miro 2000

### Study characteristics

Methods	Two-arm, non-blinded, multicentre, parallel-group RCT, with 10 days duration of treatment and 4 weeks duration of follow-up
Participants	<p><b>Location:</b> Spain</p> <p><b>Setting of recruitment and treatment:</b> 16 centres across Spain from February 1996 to May 1997</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> 154 in polymyxin B sulfate, neomycin and hydrocortisone (PNH) group, 168 in ciprofloxacin group</li> <li><b>Number completed:</b> 113 in PNH group, 119 in ciprofloxacin group (per protocol)</li> </ul> <p><b>Participant (baseline) characteristics:</b> (information provided only for per protocol participants)</p> <ul style="list-style-type: none"> <li>Age: median 44 (range 14 to 71)</li> <li>Gender (F/M): 90 (39%)/142 (61%)</li> <li>Main diagnosis: CSOM with at least 6 weeks of discharge</li> <li>High-risk population: no <ul style="list-style-type: none"> <li>* Cleft palate (or other craniofacial malformation): not reported</li> <li>* Down syndrome: not reported</li> <li>* Indigenous groups (Australian Aborigines/Greenland natives): not reported</li> <li>* Immunocompromised: not reported</li> </ul> </li> <li>Diagnosis method: <ul style="list-style-type: none"> <li>* Confirmation of perforated tympanic membrane: yes, otoscopy</li> <li>* Presence of mucopurulent discharge: yes, 204/232 (88%)</li> <li>* Duration of symptoms (discharge): median 6 to 7 years since first CSOM, median 15 days (range 1 to 365) for current episode</li> </ul> </li> <li>Other important effect modifiers: <ul style="list-style-type: none"> <li>* Alternative diagnosis of ear discharge: exclusion criteria "acute otitis externa, fungal otitis, otorrhea associated with the presence of cholesteatoma". However, 2 patients were excluded from the per protocol analysis as they had cholesteatoma.</li> <li>* Number who have previously had grommets inserted: not reported</li> <li>* Number who have had previous ear surgery: 79/232 (34%)</li> <li>* Number who had previous antibiotic treatment for CSOM: 103/232 (44%) "treated during previous episode". However, "if patient received topical or systemic antibiotic therapy a 72-hour washout period was required before enrolment in study"</li> </ul> </li> </ul> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>14 to 71 years old</li> <li>CSOM defined as serous, mucous, mucopurulent or purulent otorrhea; a history of persistent tympanic perforation or the presence of a tympanostomy tube along with the current episode lasting for at least 6 weeks; and bacteriologic confirmation of ear infection</li> <li>Patients presenting with mucopurulent or purulent discharge were enrolled, irrespective of the culture results</li> <li>Subjects with persistent ear infection despite topical or systemic antibacterial therapy could be enrolled after a 72-hour washout period</li> </ul>

**Miro 2000** (Continued)

**Exclusion criteria:**

- Acute otitis externa, fungal otitis
- Otorrhoea associated with the presence of cholesteatoma
- Presence of severe otalgia or fever greater than 38°C
- Infection requiring systemic therapy
- Participation in another clinical trial in the previous 30 days

Interventions	<p><b>Intervention group (n = 168):</b> polymyxin B sulfate, neomycin and hydrocortisone suspension supplied in multiple-dose containers (Otosporin; Gayoso Wellcome, SA); 3 drops (0.15 mL) 4 times daily for 10 days (valid interval 6 to 12 days)</p> <p><b>Comparator (n = 154):</b> ciprofloxacin 0.2% solution, supplied in 0.5 mL single-dose containers (Laboratorios Vita, SA, and Química Farmacéutica Bayer, SA), 0.5 mL twice daily for 10 days (valid interval 6 to 12 days)</p> <p><b>Concurrent treatment:</b> at baseline, all patients received aural toilet by microscopic examination</p> <p>Patients advised to apply the medication in a supine position with the target ear facing the ceiling. The tragus was to be massaged repeatedly and the same position was maintained for 5 minutes.</p> <p>No other treatment for CSOM was permitted</p>	
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"><li>• Resolution of ear discharge or "dry ear" (whether otoscopically confirmed or not) 1 to 2 weeks and after 4 weeks. Unclear if otoscopically confirmed.</li><li>• Ear pain (otalgia) or discomfort or local irritation</li></ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"><li>• 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</li></ul>	
Funding sources	Sponsored by Laboratorios Vita, SA and Química Farmacéutica Bayer, SA, Barcelona, Spain	
Declarations of interest	No information provided for authors and most investigators, but 2 investigators worked for Bayer	
Notes	<p><b>Unit of randomisation:</b> person</p> <p><b>Methods for reporting outcomes of patients with bilateral disease:</b> not reported</p>	
<b>Risk of bias</b>		
<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to study treatments"  Comment: no details provided
Allocation concealment (selection bias)	Unclear risk	Comment: no details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Because of different dosing schedules (0.5ml twice daily vs 0.15 mL 4 times daily), packaging (singled dose vs multiple-dose containers), and galenic form (solution vs suspension), a double-blind design had to be discarded. The limited capacity of the external auditory canal precluded the use of the double-dummy technique."



**Miro 2000** (Continued)

Comment: no blinding		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The study coordinator (N.M.) blindly reviewed all pre-treatment and posttreatment audiograms to identify any ototoxicity evidence arising from the treatments."  Comment: no blinding of assessors mentioned except for ototoxicity evaluation (which was not reported)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: only 72% of patients randomised were included in the per protocol analyses – the main analyses. The 29 patients considered as "not evaluable" included 7 patients with fungal otitis and 12 where bacteriological analysis was not done. 17% (18% from ciprofloxacin and 16% from PNH) did not attend the follow-up visit, but it was unclear if these percentages represented the randomised participants or per protocol participants. The losses and exclusions could possibly affect the findings reported.
Selective reporting (reporting bias)	Unclear risk	Comment: study protocol not available. Outcomes such as ototoxicity were measured but not fully reported.

**Panchasara 2015**
**Study characteristics**

Methods	Two-arm, double-blind, single-centre, parallel-group RCT, with 10 days duration of treatment and 15 days follow-up
Participants	<p><b>Location:</b> Bhavnagar, Gujarat, India</p> <p><b>Setting of recruitment and treatment:</b> Government Medical College, outpatient ENT department</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> 55 in intervention group, 55 in comparison group</li> <li><b>Number completed:</b> 53 in intervention group, 52 in comparison group</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: &gt; 18 years old</li> <li>Gender (F/M): 60 (54.5%)/50 (45.5%)</li> <li>Main diagnosis: "ear discharge with tympanic membrane perforation. Patient with culture lacking sensitivity to ofloxacin were excluded"</li> <li>High-risk population: no <ul style="list-style-type: none"> <li>* Cleft palate (or other craniofacial malformation): not reported</li> <li>* Down syndrome: not reported</li> <li>* Indigenous groups (Australian Aboriginals/Greenland natives): none</li> <li>* Immunocompromised: none</li> </ul> </li> <li>Diagnosis method: <ul style="list-style-type: none"> <li>* Confirmation of perforated tympanic membrane: yes, all (otoscopic examination), 16.3% in intervention group and 7.2% in ofloxacin group had a small perforation</li> <li>* Presence of mucopurulent discharge: yes (100%)</li> <li>* Duration of symptoms (discharge): not reported, minimum duration of discharge not specified</li> </ul> </li> </ul>

## Panchasara 2015 (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: unclear – surgery within preceding 12 months excluded
  - \* Number who had previous antibiotic treatment for CSOM: unclear

### Inclusion criteria:

- > 18 years of age
- Having ear discharge with tympanic membrane perforation
- Willing to give written informed consent

### Exclusion criteria:

- A history of sensitivity to any of the trial drugs
- Tuberculosis, diabetes mellitus, immunosuppressive disease, fungal or viral diseases
- Any clinically significant systemic diseases, chronic nasal obstruction, persistent rhinorrhoea, cholesteatoma, active atticofurunculosis
- Patients with ear surgery in the preceding 12 months, congenital ear or hearing problems, middle ear obstruction (e.g. polyp)
- Patients who had taken systemic steroids, high dose of topical steroids and/or antibiotics in the previous one week
- Fever (> 38°C)

Interventions	<p><b>Intervention (n = 53):</b> ofloxacin (0.3% w/v) + dexamethasone (0.1% w/v) combination, 5 drops twice a day for 10 days</p> <p><b>Comparator group (n = 52):</b> ofloxacin (0.3% w/v) ear drops, 5 drops twice a day, for 10 days</p> <p><b>Concurrent treatment:</b> after cleaning the ear discharge, the patient was instructed to instil 5 drops in the affected ear in a supine position with that ear facing the ceiling. The same position was maintained for 10 minutes, tragus was massaged repeatedly and the whole procedure was repeated twice daily</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Clinical cure rate</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Subjective assessment of otorrhoea, change in size of perforation, isolated organisms, bacteriological examination improvement and safety analysis. Headache, vertigo, local itchiness and 'other'.</li> </ul>
Funding sources	FDC Pvt. Ltd. Mumbai provided the ear drops of ofloxacin and ofloxacin + dexamethasone used in the study. No other information provided
Declarations of interest	No information provided
Notes	<p>Protocol registration CTRI/2012/07/002784</p> <p><b>Unit of randomisation:</b> person</p> <p><b>Methods for including patients bilateral disease:</b> not specified; baseline characteristics only recorded one affected ear per person</p>
<b>Risk of bias</b>	
<b>Bias</b>	<b>Authors' judgement      Support for judgement</b>

## Panchasara 2015 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomised by Rando software at a 1:1 ratio to receive either ofloxacin or ofloxacin + dexamethasone ear drops for 10 days"  Comment: statistical software used
Allocation concealment (selection bias)	Low risk	Quote: "Containers of ofloxacin and ofloxacin + dexamethasone combination ear drops were identical in appearance. The label was covered and coded according to the randomisation sequence by a third person who was not involved in the study."  Comment: should be adequate
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Containers of ofloxacin and ofloxacin + dexamethasone combination ear drops were identical in appearance. The label was covered and coded according to the randomisation sequence by a third person who was not involved in the study. Neither the participants nor the investigators knew the sequence"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Neither the participants or the investigators know the sequence" (of randomisation or treatment)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2/55 versus 3/55 patients were lost to follow-up in each arm. Small percentage of loss to follow-up and balanced between arms.
Selective reporting (reporting bias)	High risk	Quote: "The primary outcome measures will be clinical cure on review and secondary outcome measure will be size of tympanic membrane perforation and pure tone audiometry" was recorded in the CTRI.  Comment: hearing was not reported in the paper

## Picozzi 1983

### Study characteristics

Methods	Two-arm, double-blind, parallel-group RCT, with 4-week duration of treatment and follow-up
Participants	<p><b>Location:</b> unclear – Scotland?</p> <p><b>Setting of recruitment and treatment:</b> unclear setting, published in 1983</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> 37, number randomised to each group not given</li> <li><b>Number completed:</b> 17 in gentamicin plus hydrocortisone group, 14 in placebo group</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: not reported</li> <li>Gender (F/M): not reported</li> <li>Main diagnosis: active chronic otitis media</li> <li>High-risk population: no <ul style="list-style-type: none"> <li>* Cleft palate (or other craniofacial malformation): not reported</li> <li>* Down syndrome: not reported</li> <li>* Indigenous groups (Australian Aborigines/Greenland natives): not reported</li> <li>* Immunocompromised: not reported</li> </ul> </li> </ul>

**Picozzi 1983** (Continued)

- 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: not reported

**Inclusion criteria:**

- Active chronic otitis media who had received no topical or systemic antibiotics in the preceding 4 weeks and with only potentially pathogenic aerobic organisms had been isolated

**Exclusion criteria:**

- None listed

Interventions	<p><b>Intervention (n = 17 completed):</b> gentamicin plus hydrocortisone ear drops, no information on dose, frequency of administration, treatment duration = 4 weeks</p> <p><b>Comparator group (n = 14 completed):</b> placebo (no further information given), ear drops, treatment duration = 4 weeks</p> <p><b>Concurrent treatment:</b> self-mopping with fine cotton buds prior to instilling the ear drops</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Resolution of ear discharge or "dry ear" (whether otoscopically confirmed or not) measured at between 2 to 4 weeks. Unclear if otoscopically confirmed.</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Not reported</li> </ul>
Funding sources	No information provided
Declarations of interest	No information provided
Notes	<p><b>Unit of randomisation:</b> person</p> <p><b>Methods for reporting outcomes of patients with bilateral disease:</b> not stated</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly allocated"  Comment: no description of method used. No information about number of people randomised to each group or baseline characteristics.
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: placebo was used, which implies that the trial was blinded but no further information is provided to qualify this point

**Picozzi 1983** (Continued)

## All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: placebo was used, which implies that the trial was blinded but no further information is provided to qualify this point
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: unclear how many people were randomised to each group. 6/37 (16%) participants were not included in the analysis. Analysis only included "compliers" but this is not described and details are not provided. It is not clear whether there was a difference between the groups.
Selective reporting (reporting bias)	Unclear risk	Comment: data only presented as an abstract. No protocol for the trial was available in the WHO ICTRP trials database.

**Ramos 2003**
**Study characteristics**

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	<p><b>Location:</b> Spain</p> <p><b>Setting of recruitment and treatment:</b> 3 ENT department of 3 tertiary hospitals</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> 50 in each group, total 300 participants</li> <li><b>Number completed:</b> 50 in each group</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: 5 to 73, n = 36 (12%) were children (&lt; 14 years)</li> <li>Gender (F/M): 134 (44.7%)/166 (55.3%)</li> <li>Main diagnosis: chronic ear discharge, which comprised the following groups: <ul style="list-style-type: none"> <li>* 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</li> <li>* Chronic otitis media with osteolysis (OMCO) (n = 57): included osteolytic lesions and alterations of the mucosa of medium type, type of pansclerosis, granulomatous lesions, atelectasis or marginal perforation, without signs of cholesteatoma</li> <li>* Chronic cholesteatoma (n = 42): signs of infection of middle cholesteatoma</li> <li>* Chronic otorrhoea in operated ears (n = 73): radical mastoidectomy (n = 40), tympanoplasty infection (n = 21), transtympanic grommets (n = 12)</li> </ul> </li> <li>High-risk population: <ul style="list-style-type: none"> <li>* Cleft palate (or other craniofacial malformation): not reported</li> <li>* Down syndrome: not reported</li> <li>* Indigenous groups (Australian Aborigines/Greenland natives): not reported</li> <li>* Immunocompromised: not reported</li> </ul> </li> <li>Diagnosis method: <ul style="list-style-type: none"> <li>* 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)</li> <li>* Presence of mucopurulent discharge: otoscopic examination</li> <li>* Duration of symptoms (discharge): for more than 6 weeks or sporadically with 3 or more episodes in the last year</li> </ul> </li> </ul>



## Ramos 2003 (Continued)

- 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 had 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	<p><b>Group A (n = 50):</b> oral ciprofloxacin 500 mg 12-hourly PLUS topical ciprofloxacin 0.2% 0.5 mL 8-hourly for 7 days</p> <p><b>Group B (n = 50):</b> topical ciprofloxacin 0.3% PLUS fluocinolone 0.5 mL 8-hourly for 7 days</p> <p><b>Group C (n = 50):</b> topical ciprofloxacin 0.5%, 0.5 mL 8-hourly for 7 days</p> <p><b>Group D (n = 50):</b> topical ciprofloxacin 0.2%, 0.5 mL 8-hourly for 7 days</p> <p><b>Group E (n = 50):</b> topical polymyxin 10,000 IU, neomycin 0.0035 g, hydrocortisone 0.00025 g, 8-hourly for 7 days</p> <p><b>Group F (n = 50):</b> oral ciprofloxacin 500 mg twice 12-hourly for 7 days</p> <p><b>Concurrent treatment:</b> not reported</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcome:</b></p> <ul style="list-style-type: none"> <li>• Resolution of ear discharge ('dry ear'), measured otoscopically confirmed at 1 to 2 weeks</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Hearing: hearing tests at time of diagnosis, at 8 days and at 15 days</li> <li>• Suspected ototoxicity           <ul style="list-style-type: none"> <li>* Suspected ototoxicity: diagnosed with audiogram (specific definition not stated, but study reports 0/125 patients had ototoxicity from treatment)</li> <li>* Balance problems/dizziness/vertigo: not reported</li> <li>* Tinnitus: not reported</li> </ul> </li> </ul>
Funding sources	No information provided
Declarations of interest	No information provided
Notes	<p><b>Unit of randomisation:</b> person</p> <p><b>Methods for including patients with bilateral disease:</b> not reported</p>

## Ramos 2003 (Continued)

### 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 also stated that children were not randomised to oral ciprofloxacin; 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 impossible without the use of 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) the knowledge of treatment group may influence the results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 2 participants on oral treatment were reported as withdrawn due to gastrointestinal adverse events. Unclear which group this was from and whether these participants were counted in the percentages reported. The percentage of withdrawals is small.
Selective reporting (reporting bias)	Unclear risk	Comment: audiogram was performed at baseline and end of treatment, but not reported

## Subramaniam 2001 unpublished

### Study characteristics

Methods	Two-arm, open-label, clinical RCT, with 14 days duration of treatment; no details of follow-up
Participants	<p><b>Location:</b> no details</p> <p><b>Setting of recruitment and treatment:</b> no details</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> no details</li> <li><b>Number completed:</b> 60</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: &gt; 12 years</li> <li>Gender (F/M): no details</li> <li>Main diagnosis: CSOM</li> </ul>

**Subramaniam 2001 unpublished** (Continued)

- High-risk population:
  - \* Cleft palate (or other craniofacial malformation): no details
  - \* Down syndrome: no details
  - \* Indigenous groups (Australian Aboriginals/Greenland natives): no details
  - \* Immunocompromised: no details
- Diagnosis method:
  - \* Confirmation of perforated tympanic membrane: no details
  - \* Presence of mucopurulent discharge: no details
  - \* Duration of symptoms (discharge): no details
- Other important effect modifiers:
  - \* Alternative diagnosis of ear discharge: no details
  - \* Number who have previously had grommets inserted: no details
  - \* Number who have had previous ear surgery: no details
  - \* Number who have had previous antibiotic treatment for CSOM: no details

**Inclusion criteria:** no details

**Exclusion criteria:** no details

Interventions	<p><b>Intervention (n = unknown):</b> ofloxacin 0.3% otic solution, 6 drops twice daily for 14 days</p> <p><b>Comparator group (n = unknown):</b> neomycin-polymixin-hydrocortisone otic solution, 3 drops 3 times daily for 14 days</p> <p><b>Concurrent treatment:</b> no details</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Resolution of ear discharge or 'dry ear' (unsure whether otoscopically confirmed or not) at 1 to 2 weeks</li> <li>• Ear pain (otalgia) or discomfort or local irritation - reported as resolution of otalgia</li> </ul> <p><b>Secondary outcomes:</b></p> <ul style="list-style-type: none"> <li>• Not reported</li> </ul>
Funding sources	No details
Declarations of interest	No details
Notes	<p><b>Unit of randomisation:</b> unclear</p> <p><b>Methods for reporting outcomes of patients with bilateral disease:</b> unclear</p> <p>Data from <a href="#">Abes 2003</a>. No access to publication or data.</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as a "randomized controlled clinical trial" by <a href="#">Abes 2003</a>
Allocation concealment (selection bias)	High risk	Described as "no concealment of allocation, open label" by <a href="#">Abes 2003</a> . Not a published paper.
Blinding of participants and personnel (performance bias)	High risk	"open label"

**Topical antibiotics with steroids for chronic suppurative otitis media (Review)**

## Subramaniam 2001 unpublished (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	High risk	"open label"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details
Selective reporting (reporting bias)	Unclear risk	No details

## Tong 1996

### Study characteristics

Methods	Two-arm, double-blind, parallel-group RCT, with 2 weeks duration of treatment and 14 weeks duration of follow-up
Participants	<p><b>Location:</b> Hong Kong, Prince of Wales Hospital, single site</p> <p><b>Setting of recruitment and treatment:</b> specialist outpatient clinic between October 1993 and December 1994</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> 52 in total, unclear how many in each arm</li> <li><b>Number completed:</b> 21 in intervention group (24 ears), 26 in comparison group (28 ears)</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age: not reported ("unselected for age, race, sex")</li> <li>Gender (F/M): not reported</li> <li>Main diagnosis: otorrhoea-associated recurrent otitis media with tympanic perforations</li> <li>High-risk population: no <ul style="list-style-type: none"> <li>* Cleft palate (or other craniofacial malformation): not reported</li> <li>* Down syndrome: not reported</li> <li>* Indigenous groups (Australian Aboriginals/Greenland natives): not reported</li> <li>* Immunocompromised: not reported</li> </ul> </li> <li>Diagnosis method: <ul style="list-style-type: none"> <li>* Confirmation of perforated tympanic membrane: yes, the authors present the numbers by size of perforation, but there is an error in the paper</li> <li>* Presence of mucopurulent discharge: not reported</li> <li>* Duration of symptoms (discharge): not reported</li> </ul> </li> <li>Other important effect modifiers: <ul style="list-style-type: none"> <li>* Alternative diagnosis of ear discharge: 0%</li> <li>* Number who have previously had grommets inserted: not reported</li> <li>* Number who have had previous ear surgery: not reported</li> <li>* Number who had previous antibiotic treatment for CSOM: unclear (not excluded)</li> </ul> </li> </ul> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li>Otorrhoea-associated recurrent otitis media with tympanic perforations</li> <li>Prior antibiotic use is acceptable, but a 2-week medication-free period was enforced before admitting the patient into the study</li> </ul>

**Tong 1996** (Continued)

**Exclusion criteria:**

- Patients with history of sensitivity to any of the trial drugs
- Pregnant or lactating women
- Patients with tuberculosis, fungal or viral diseases
- Patients with unsafe ears - active attico-antral disease
- Patients who were unable to continue for the proposed length of treatment or return for follow-up visits

**Interventions**

**Intervention (n = 21, 24 ears):** neomycin-polymyxin b-hydrocortisone ear drops, 6 drops twice daily for 2 weeks

**Comparator group (n = 26, 28 ears):** ofloxacin 0.3% ear drops, 6 drops twice daily for 2 weeks

**Concurrent treatment:** the participant was advised to apply the medication in a supine position with the target ear facing the ceiling. Ear drops were to be introduced into the external meatus at each application. The tragus was massaged repeatedly and the same position maintained for 10 minutes.

All patients received aural toilet by microscopic suction on each visit (D1-baseline, D7, D14)

**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. Unclear if otoscopically confirmed, method not stated.
- 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 was not available, the pure-tone average of the thresholds measured was reported.
- 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, except that Daiichi Pharmaceutical company supplied the ofloxacin drops

**Declarations of interest**

No information provided

**Notes**

**Unit of randomisation:** person

**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: "patients were assigned randomly to either of the treatment groups" and "allocation numbers on coded medications were used sequentially from 1 to 52, the dispensing of medication depended on the coded number without informing the patient the name of the drug"

Comment: no detailed information about the method of sequence generation provided. Few baseline characteristics reported and there was an error in the

**Tong 1996** (Continued)

		denominator for the neomycin-polymyxinB-hydrocortisone group; not able to determine whether the size of perforation was balanced between groups.
Allocation concealment (selection bias)	Low risk	<p>Quote: "allocation numbers on coded medications were used sequentially from 1 to 52, the dispensing of medication depended on the coded number without informing the patient the name of the drug"</p> <p>Comment: unclear whether the allocation concealment was effective. Probably low risk.</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "the dispensing of medication depended on the coded number without informing the patient the name of the drug"</p> <p>Comment: study described as double-blind. Unclear whether the interventions had identical smell and appearance. Probably low risk.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Quote: "assessment was based on symptomatology and observation by the attending investigator who was blind to the subject's medication"</p> <p>Comment: study described the assessors as blinded but did not provide a definition of how outcomes were determined. Unclear whether blinding was effective.</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>Quote: "... three patients were excluded because a fungus was isolated from the first culture. One subject in the ofloxacin group defaulted because of vertigo after applying the ear drops. Another patient in the neomycin-polymyxin B-hydrocortisone group was found not to comply with the required application of the eardrops. These five patients were excluded from analysis."</p> <p>Comment: it was unclear whether the 3 patients with fungal infection were excluded before or after randomisation, and if after randomisation which group they were randomised to. It is also unclear whether these were the patients reported in the overall "complications" - the study reported 3 adverse events of <i>Candida</i> overgrowth as a complication in the neomycin-polymyxin B-hydrocortisone arm. Exclusion of 4/25 (16%) patients from one treatment arm versus 1/27 (3.7%) could have affected the results.</p>
Selective reporting (reporting bias)	High risk	<p>Quote: "audiometric tests were performed initially and at Day 14 after cleaning the ears."</p> <p>Comment: no protocol or trial registry found. Study did not report any hearing data</p>

CSOM: chronic suppurative otitis media; F: female; M: male; RCT: randomised controlled trial; SD: standard deviation; WHO: World Health Organization

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

Study	Reason for exclusion
<a href="#">Abbott 2016</a>	POPULATION: not CSOM (acute otitis media without perforation)
<a href="#">Asmatullah 2014</a>	COMPARISON: variety of topical antibiotics (see CSOM-1)
<a href="#">Baba 1980</a>	INTERVENTION: comparison of antibiotics within same class and spectrum of activity (cefraxadine versus cephalixin). Cefraxadine a withdrawn drug; DURATION: only 6 days of follow-up
<a href="#">Baba 1982b</a>	POPULATION: acute suppurative otitis media, including acute otitis media

**Topical antibiotics with steroids for chronic suppurative otitis media (Review)**

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Study	Reason for exclusion
Baba 1983	POPULATION: acute suppurative otitis media
Baba 1983b	POPULATION: acute suppurative otitis media
Baba 1986	STUDY DESIGN: not a RCT (all patients received the same treatment, aztreonam)
Baba 1987	POPULATION: acute suppurative otitis media
Baba 2008	STUDY DESIGN: not RCT (all patients received the same intervention)
Berman 1990	POPULATION: middle ear effusion, not CSOM
Block 2000	POPULATION: not CSOM (acute otitis media without perforation of tympanic membrane)
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: acute otitis media; patients with CSOM were excluded
Browning 1983	INTERVENTION: standard antibiotics were not given, the choice was dependent on cultures
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
De Miguel 1999	COMPARISON: variety of topical antibiotics (see CSOM-1), systemic antibiotics versus none (see CSOM-2), topical versus systemic antibiotics (see CSOM-3)
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)
Esposito 1990	COMPARISON: systemic antibiotics versus none (see CSOM-2), topical antibiotics versus none (see CSOM-1), topical versus systemic antibiotic (see CSOM-3)
Esposito 1992	COMPARISON: topical versus systemic antibiotics (see CSOM-3)
Esposito 2000	STUDY DESIGN: not a RCT (all patients had the same intervention - ceftazidime)
Fombeur 1994	STUDY DESIGN: not a RCT (no mention of randomisation); INTERVENTION: high-dose versus low-dose ciprofloxacin
Fradis 1997	COMPARISON: variety of topical antibiotics (see CSOM-1) and topical antiseptic versus none (see CSOM-6)

Study	Reason for exclusion
<a href="#">Frayse 1988</a>	INTERVENTION: fenspiride (a bronchodilator/anti-inflammatory agent) is not an intervention under investigation
<a href="#">Garcia-Rodriguez 1993</a>	POPULATION: mixture of patients, less than half had CSOM; patients were not stratified by diagnosis
<a href="#">Gehanno 1997</a>	STUDY DESIGN: not a RCT (all patients had the same intervention)
<a href="#">Granath 2007</a>	POPULATION: not CSOM (patients with recurrent acute otitis media with discharge through tympanostomy tube)
<a href="#">Gupta 2015</a>	COMPARISON: antibiotic versus antiseptic (see CSOM-6)
<a href="#">Gyde 1978</a>	COMPARISON: variety of topical antibiotics (see CSOM-1)
<a href="#">Gyde 1981</a>	POPULATION: less than 50% (27/68) had CSOM
<a href="#">Gyde 1982</a>	POPULATION: less than 50% had CSOM
<a href="#">Hemlin 1997</a>	POPULATION: unilateral or bilateral secretory otitis media (COME); INTERVENTION: systemic corticosteroids
<a href="#">Hwang 2015</a>	STUDY DESIGN: not a RCT (case control study)
<a href="#">I-HEAR-BETA</a>	COMPARISON: systemic antibiotic versus none (see CSOM-2), topical antiseptic versus none (see CSOM-5), topical antiseptic versus topical antibiotic (see CSOM-6)
<a href="#">IRCT20130427013136N6</a>	POPULATION: patients had otitis externa
<a href="#">IRCT2016082313136N4</a>	POPULATION: patients had otomycosis
<a href="#">ISRCTN12149720</a>	INTERVENTION: antimicrobial peptide OP145
<a href="#">ISRCTN84220089</a>	INTERVENTION: antimicrobial peptide OP145
<a href="#">Jahn 1984</a>	STUDY DESIGN: not a RCT
<a href="#">Jamallulah 2016</a>	COMPARISON: variety of topical antibiotics (see CSOM-1)
<a href="#">Jang 2004</a>	STUDY DESIGN: not a RCT (mentioned use of a "control group", no mention of randomisation)
<a href="#">Jaya 2003</a>	COMPARISON: topical antibiotic versus topical antiseptic (see CSOM-6)
<a href="#">Jiang 2016</a>	INTERVENTION: comparison of two agents of the same class of antibiotics (erythromycin versus azithromycin) used in addition to a traditional Chinese medicine product
<a href="#">Kadar 2003</a>	STUDY DESIGN: not a randomised controlled trial
<a href="#">Kasemsuwan 1997</a>	COMPARISON: topical antibiotic versus none (see CSOM-1)
<a href="#">Kashiwamura 2004</a>	STUDY DESIGN: cohort (no comparison group); POPULATION: less than 50% with CSOM
<a href="#">Kenna 1986</a>	STUDY DESIGN: not a RCT - cohort study (no comparison group)
<a href="#">Khanna 2000</a>	INTERVENTION: culture sensitivity based prescribing

Study	Reason for exclusion
<a href="#">Khon 2012</a>	POPULATION: not CSOM - either diffuse otitis externa or acute otitis externa; STUDY DESIGN: no evidence of randomisation
<a href="#">Kothari 1969</a>	STUDY DESIGN: not a RCT (no comparison)
<a href="#">Kovacic 1999</a>	STUDY DESIGN: not a RCT (compared ofloxacin in patients who had previous ear surgery versus no previous ear surgery)
<a href="#">Kurilin 1976</a>	STUDY DESIGN: not a RCT (no mention of randomised controlled study design or control group included for comparison)
<a href="#">Lancaster 1999</a>	STUDY DESIGN: not a RCT (cross-sectional survey)
<a href="#">Lancaster 2003</a>	STUDY DESIGN: not an RCT (compared compliance)
<a href="#">Lang 1992</a>	STUDY DESIGN: not a RCT (case series)
<a href="#">Lautala 1983</a>	STUDY DESIGN: not a RCT (case series)
<a href="#">Liu 2003</a>	COMPARISON: variety of topical antibiotics (see CSOM-1)
<a href="#">Loock 2012</a>	COMPARISON: variety of topical antibiotics (see CSOM-1)
<a href="#">Lorente 1995</a>	COMPARISON: variety of topical antiseptics (see CSOM-5) and topical antibiotic versus topical antiseptic (see CSOM-6)
<a href="#">Lorentzen 1978</a>	POPULATION: acute otitis media with intact or spontaneously erupted tympanic membrane; INTERVENTION: surgery
<a href="#">Macfadyen 2005</a>	COMPARISON: topical antibiotic versus topical antiseptic (see CSOM-6)
<a href="#">Merifield 1993</a>	STUDY DESIGN: not a RCT (case series)
<a href="#">Measure 1973</a>	POPULATION: in clinical trial part of study (part 2) only one case of chronic otitis media
<a href="#">Mira 1993</a>	COMPARISON: adding topical antibiotic to systemic antibiotic (see CSOM-1)
<a href="#">Mora 2012</a>	INTERVENTION: polyvalent bacterial lysate (antigens)
<a href="#">Morgon 1976</a>	STUDY DESIGN: single-arm study
<a href="#">Nawasreh 2001</a>	COMPARISON: variety of topical antibiotics (see CSOM-1)
<a href="#">NCT02592096</a>	INTERVENTION: phase I dose finding trial - compared different concentrations of pazufloxacin
<a href="#">NCT02817347</a>	INTERVENTION: phase II trial - compared different concentrations of piperacillin against tazobactam plus dexamethasone
<a href="#">Poliakova 1991</a>	STUDY DESIGN: not a RCT
<a href="#">Povedano 1995</a>	COMPARISON: systemic versus topical antibiotics (see CSOM-3)
<a href="#">Principi 1995</a>	POPULATION: acute and recurrent otitis media

Study	Reason for exclusion
<a href="#">Quick 1973</a>	POPULATION: not CSOM (included acute tonsillitis, acute pharyngitis, acute sinusitis, acute otitis media, chronic sinusitis and peritonsillar abscess)
<a href="#">Quick 1975</a>	POPULATION: not CSOM (only 6/145 patients had otitis media)
<a href="#">Saez-Llorens 2005</a>	POPULATION: acute otitis media
<a href="#">Siddique 2016</a>	COMPARISON: variety topical antibiotics (see CSOM-1)
<a href="#">Singhal 1992</a>	STUDY DESIGN: not a RCT (no comparison group)
<a href="#">Stenstrom 1991</a>	POPULATION: acute otitis media; not CSOM
<a href="#">Sumitsawan 1995</a>	STUDY DESIGN: not a RCT - single intervention (ofloxacin drops) studied
<a href="#">Supiyaphun 1995</a>	STUDY DESIGN: not a RCT (cohort - all patients received same treatment)
<a href="#">Tachibana 1986</a>	STUDY DESIGN: not a RCT (all patients received the same treatment)
<a href="#">Thomsen 1976</a>	STUDY DESIGN: not a RCT; POPULATION: acute suppurative otitis media
<a href="#">Tutkun 1995</a>	COMPARISON: variety of topical antibiotics (see CSOM-1)
<a href="#">van Dongen 2014</a>	POPULATION: 1) inclusion of minimum 2 weeks (review defined exclusion of 6 weeks perioperatively); 2) max duration of otorrhoea was 1 week
<a href="#">van Hasselt 1997</a>	COMPARISON: variety of topical antibiotics (see CSOM-1) and topical antibiotics versus topical antiseptics (see CSOM-6)
<a href="#">van Hasselt 1998</a>	COMPARISON: variety of topical antibiotics (see CSOM-1)
<a href="#">Vishwakarma 2015</a>	COMPARISON: topical antiseptic versus topical antibiotic (see CSOM-6)
<a href="#">Wilde 1995</a>	INTERVENTION: different ways of administering the same ear drops (ribbon gauze versus drops)
<a href="#">Wintermeyer 1997</a>	STUDY DESIGN: not a RCT (cohort)
<a href="#">Xu 1999</a>	INTERVENTION: not a comparison of interest - antibiotics versus Chinese medicine
<a href="#">Yuen 1994</a>	COMPARISON: systemic versus topical antibiotics (see CSOM-3)

CSOM: chronic suppurative otitis media

RCT: randomised controlled trial

The titles, interventions and comparisons in Cochrane Reviews CSOM-1 to CSOM-7 are shown in [Table 1](#).

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

#### [Roy 2003](#)

Methods	Double-blind randomised controlled trial
Participants	Unknown
Interventions	Topical ciprofloxacin ear drops

### Topical antibiotics with steroids for chronic suppurative otitis media (Review)

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**Roy 2003** (Continued)

Outcomes	Unknown
Notes	Poor quality

**DATA AND ANALYSES**
**Comparison 1. Topical antibiotics with steroids versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Resolution of ear discharge 2 to 4 weeks	2	154	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [1.33, 3.31]
1.1.1 Neomycin-polymixin B-steroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.1.2 Aminoglycosides plus steroids	2	154	Risk Ratio (M-H, Fixed, 95% CI)	2.10 [1.33, 3.31]
1.1.3 Framycetin-gramicidin-dexamethasone	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

**Analysis 1.1. Comparison 1: Topical antibiotics with steroids versus placebo, Outcome 1: Resolution of ear discharge 2 to 4 weeks**

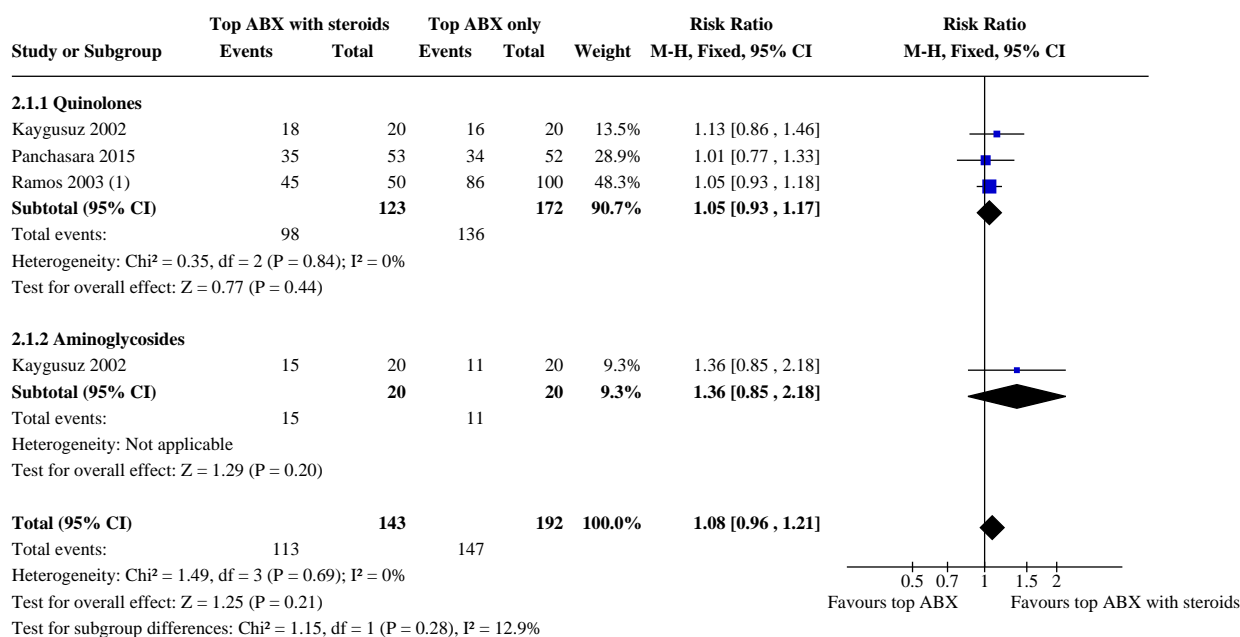
Study or Subgroup	Top ABX with steroids Events	Total	Placebo/no treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
<b>1.1.1 Neomycin-polymixin B-steroids</b>							
<b>Subtotal (95% CI)</b>		<b>0</b>		<b>0</b>		<b>Not estimable</b>	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
<b>1.1.2 Aminoglycosides plus steroids</b>							
Browning 1988	31	64	15	59	82.6%	1.91 [1.15, 3.16]	
Picozzi 1983	11	17	3	14	17.4%	3.02 [1.04, 8.74]	
<b>Subtotal (95% CI)</b>		<b>81</b>		<b>73</b>	<b>100.0%</b>	<b>2.10 [1.33, 3.31]</b>	
Total events:	42		18				
Heterogeneity: Chi <sup>2</sup> = 0.59, df = 1 (P = 0.44); I <sup>2</sup> = 0%							
Test for overall effect: Z = 3.19 (P = 0.001)							
<b>1.1.3 Framycetin-gramicidin-dexamethasone</b>							
<b>Subtotal (95% CI)</b>		<b>0</b>		<b>0</b>		<b>Not estimable</b>	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
<b>Total (95% CI)</b>		<b>81</b>		<b>73</b>	<b>100.0%</b>	<b>2.10 [1.33, 3.31]</b>	
Total events:	42		18				
Heterogeneity: Chi <sup>2</sup> = 0.59, df = 1 (P = 0.44); I <sup>2</sup> = 0%							
Test for overall effect: Z = 3.19 (P = 0.001)							
Test for subgroup differences: Not applicable							

0.1 0.2 0.5 1 2 5 10  
Favours placebo/NT Favours with steroids

## Comparison 2. Topical antibiotics with steroids versus topical antibiotics alone (same antibiotics)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">2.1 Resolution of ear discharge 1 to 2 weeks</a>	3	335	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.96, 1.21]
2.1.1 Quinolones	3	295	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.93, 1.17]
2.1.2 Aminoglycosides	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.85, 2.18]
<a href="#">2.2 Resolution of ear discharge 2 to 4 weeks</a>	2	185	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.88, 1.26]
2.2.1 Quinolones	2	145	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.85, 1.28]
2.2.2 Aminoglycosides	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.73, 1.57]
<a href="#">2.3 Ear pain or discomfort</a>	1	105	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.28]

### Analysis 2.1. Comparison 2: Topical antibiotics with steroids versus topical antibiotics alone (same antibiotics), Outcome 1: Resolution of ear discharge 1 to 2 weeks

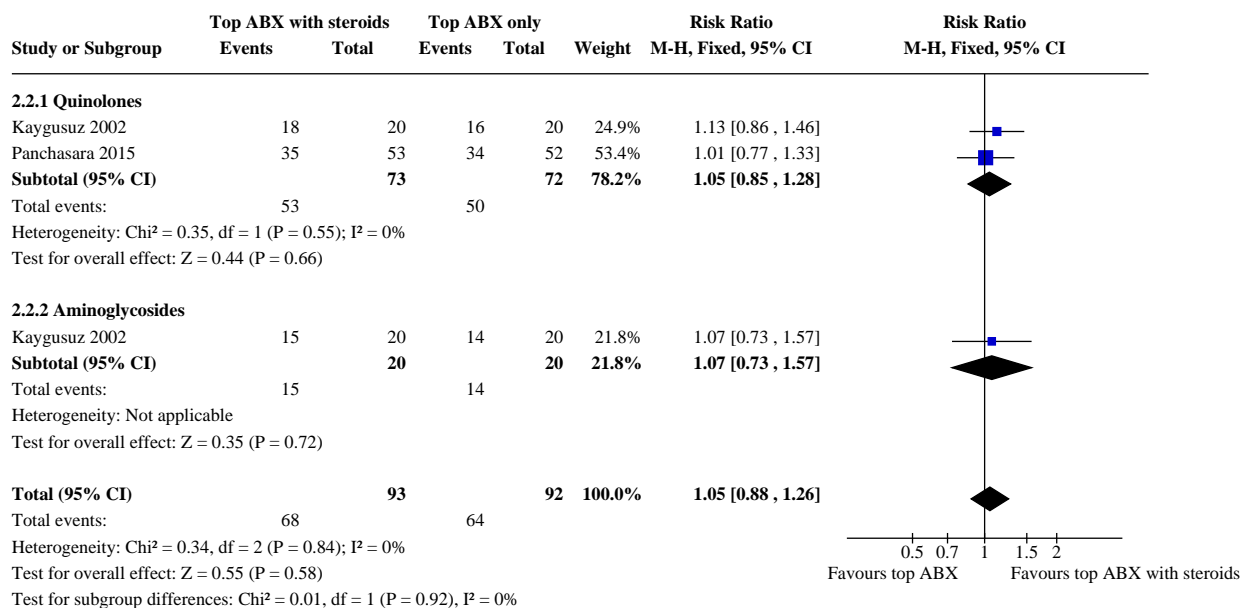


#### Footnotes

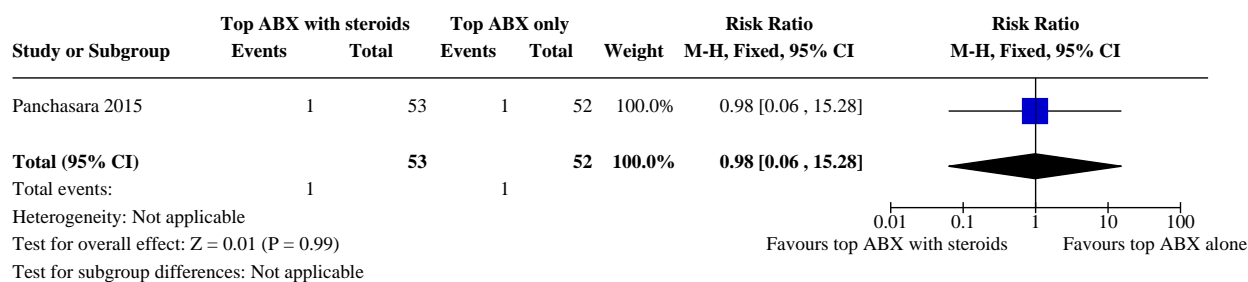
(1) Ciprofloxacin 0.3% with steroids vs 0.2% and 0.5% (two groups)



### Analysis 2.2. Comparison 2: Topical antibiotics with steroids versus topical antibiotics alone (same antibiotics), Outcome 2: Resolution of ear discharge 2 to 4 weeks



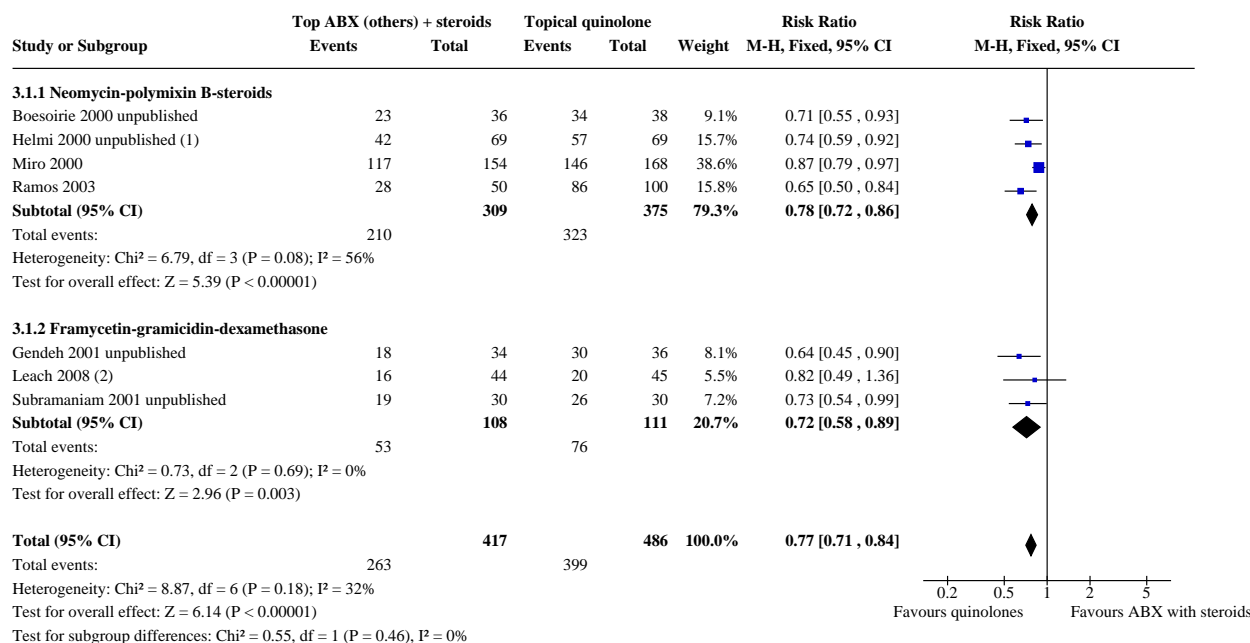
### Analysis 2.3. Comparison 2: Topical antibiotics with steroids versus topical antibiotics alone (same antibiotics), Outcome 3: Ear pain or discomfort



### Comparison 3. Topical antibiotic (non-quinolone) with steroids versus topical quinolones

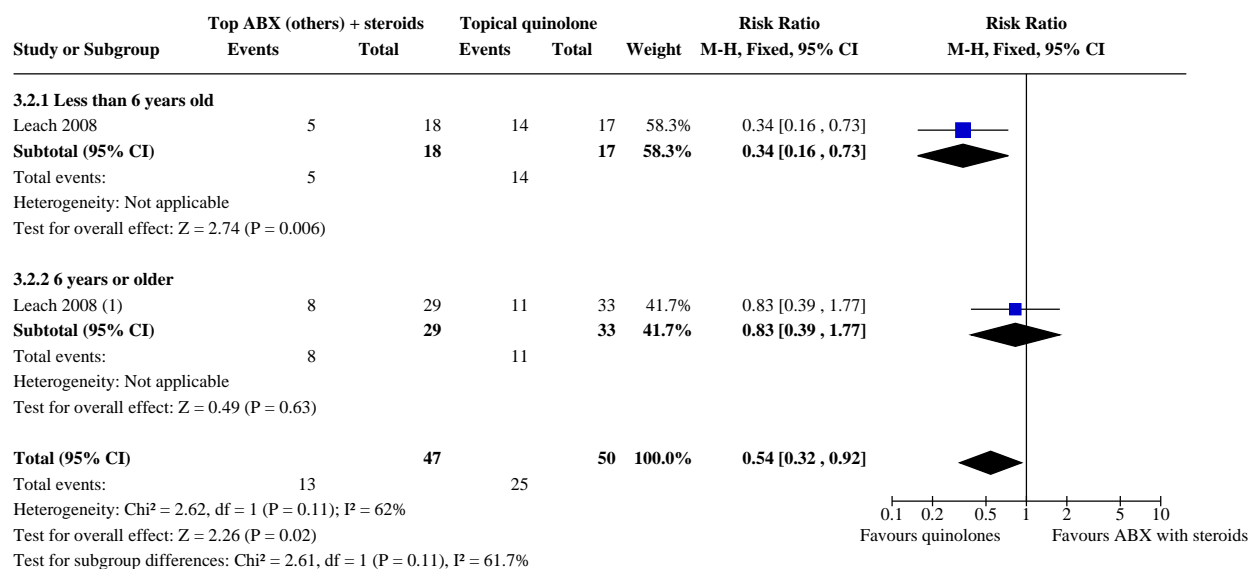
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">3.1 Resolution of ear discharge 1 to 2 weeks</a>	7	903	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.71, 0.84]
3.1.1 Neomycin-polymixin B-steroids	4	684	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.72, 0.86]
3.1.2 Framycetin-gramicidin-dexamethasone	3	219	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.58, 0.89]
<a href="#">3.2 Subgroup analysis: age - resolution of ear discharge 1 to 2 weeks</a>	1	97	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.32, 0.92]
3.2.1 Less than 6 years old	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.16, 0.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2.2 6 years or older	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.39, 1.77]
3.3 Subgroup analysis: diagnosis - resolution of ear discharge 1 to 2 weeks	7	903	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.71, 0.84]
3.3.1 CSOM	6	753	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.73, 0.86]
3.3.2 Ear discharge	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.50, 0.84]
3.4 Sensitivity analysis: unpublished - resolution of ear discharge 1 to 2 weeks	7	903	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.71, 0.84]
3.4.1 Published	3	561	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.73, 0.90]
3.4.2 Unpublished	4	342	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.62, 0.81]
3.5 Ear pain or discomfort	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.07, 16.36]
3.5.1 Neomycin-polymixin B-steroids	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.07, 16.36]
3.6 Dizziness/vertigo/balance	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 4.80]
3.6.1 Neomycin-polymixin B-steroids	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 4.80]

**Analysis 3.1. Comparison 3: Topical antibiotic (non-quinolone) with steroids versus topical quinolones, Outcome 1: Resolution of ear discharge 1 to 2 weeks****Footnotes**

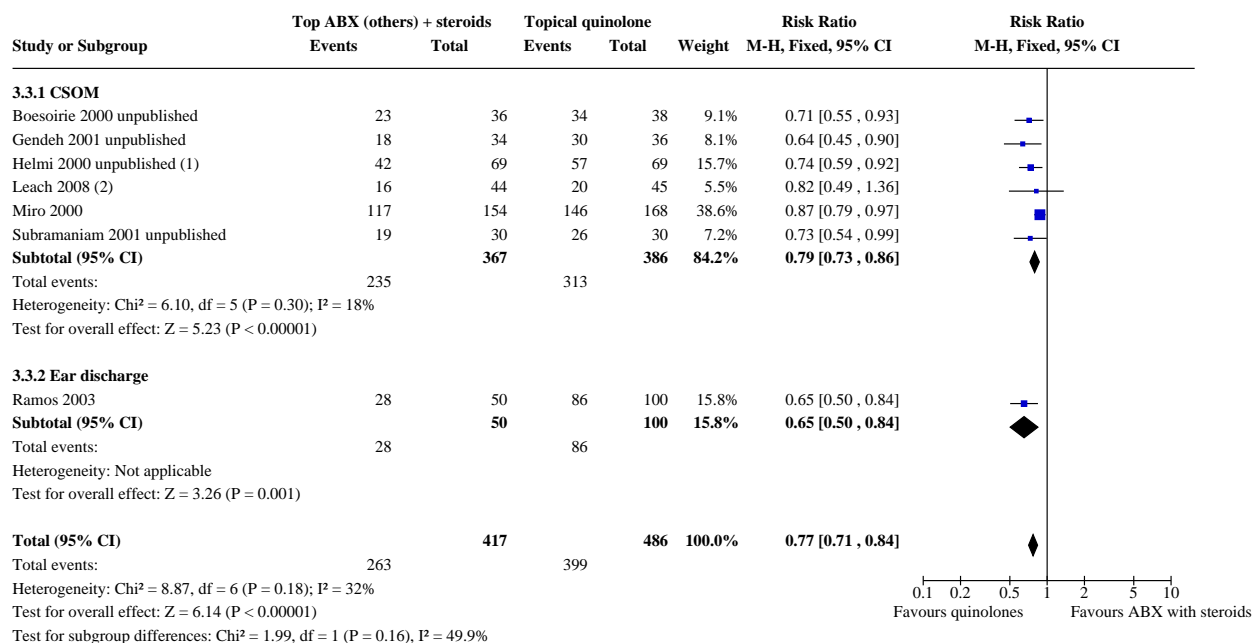
(1) Data from unpublished studies taken from Table 6 of Abes2003.

(2) Recruited only children who failed FGD. ACA data, rather than modified ITT used. Study had categorised children not seen as treatment failure in the ITT analysis

**Analysis 3.2. Comparison 3: Topical antibiotic (non-quinolone) with steroids versus topical quinolones, Outcome 2: Subgroup analysis: age - resolution of ear discharge 1 to 2 weeks****Footnotes**

(1) Only Modified ITT data reported by study available for subgroup. Children not seen (3 in FGD, 5 in ciprofloxacin) were considered as treatment failure

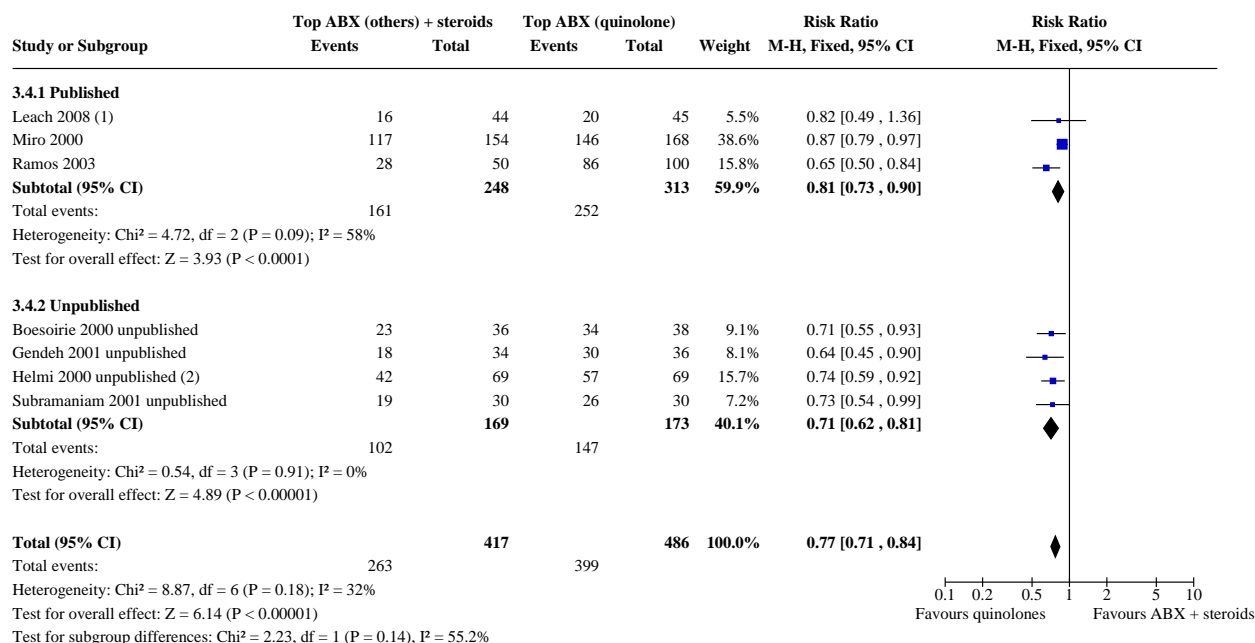
### Analysis 3.3. Comparison 3: Topical antibiotic (non-quinolone) with steroids versus topical quinolones, Outcome 3: Subgroup analysis: diagnosis - resolution of ear discharge 1 to 2 weeks



#### Footnotes

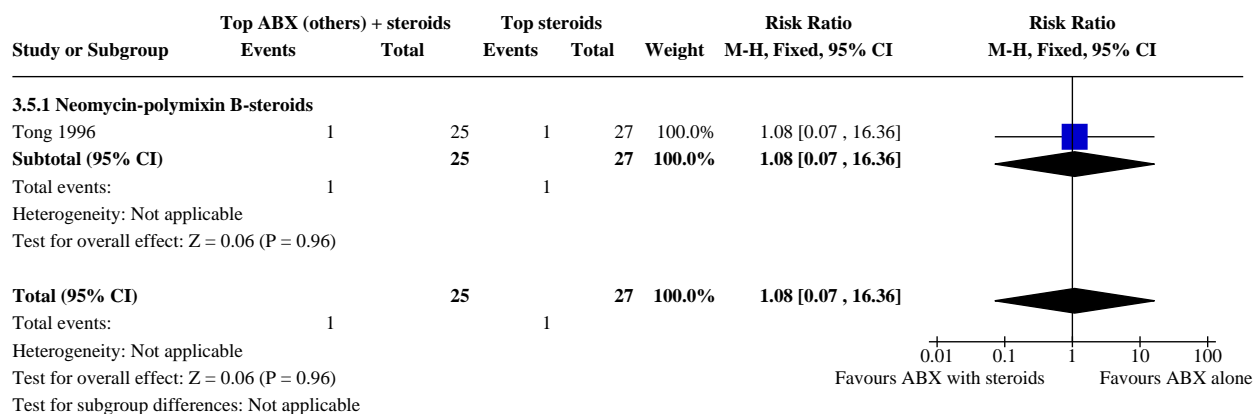
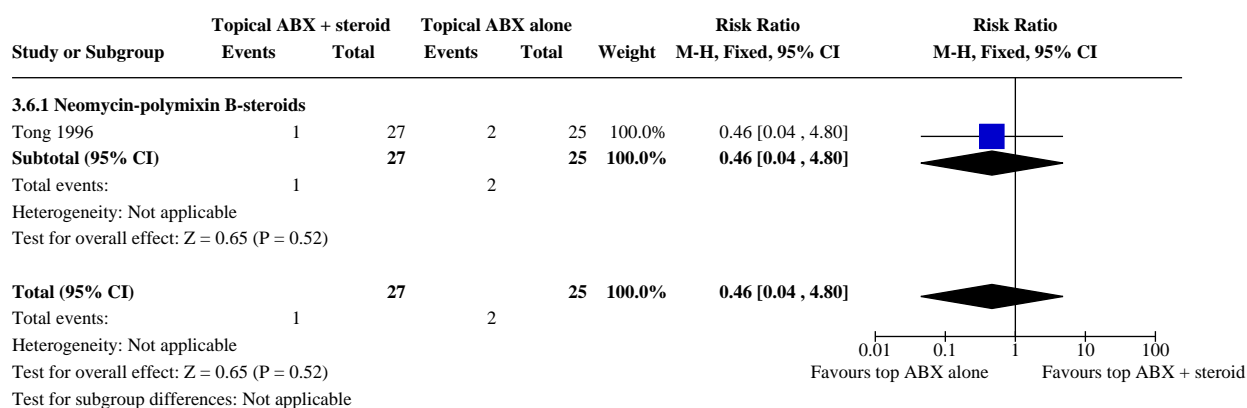
- (1) Data from unpublished studies taken from Table 6 of Abes2003.  
(2) Recruited only children who failed FGD. ACA data, rather than modified ITT used. Study had categorised children not seen as treatment failure in the ITT analysis

### Analysis 3.4. Comparison 3: Topical antibiotic (non-quinolone) with steroids versus topical quinolones, Outcome 4: Sensitivity analysis: unpublished - resolution of ear discharge 1 to 2 weeks



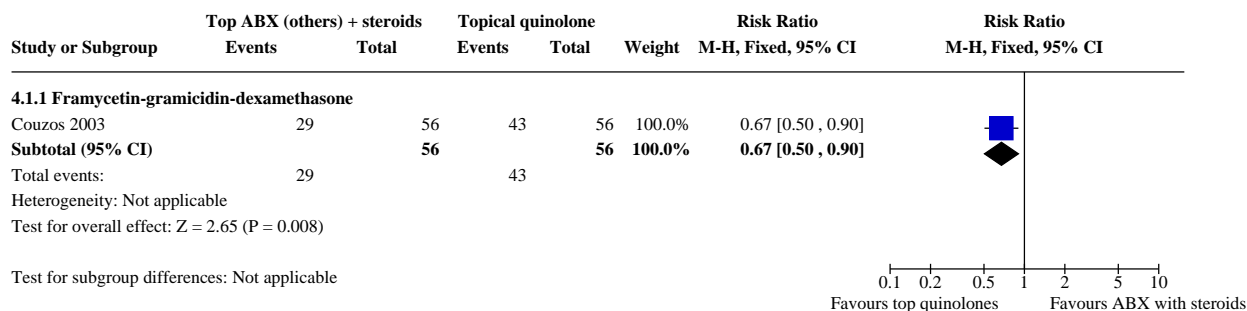
#### Footnotes

- (1) Recruited only children who failed FGD. ACA data, rather than modified ITT used. Study had categorised children not seen as treatment failure in the ITT analysis  
(2) Data from unpublished studies taken from Table 6 of Abes2003.

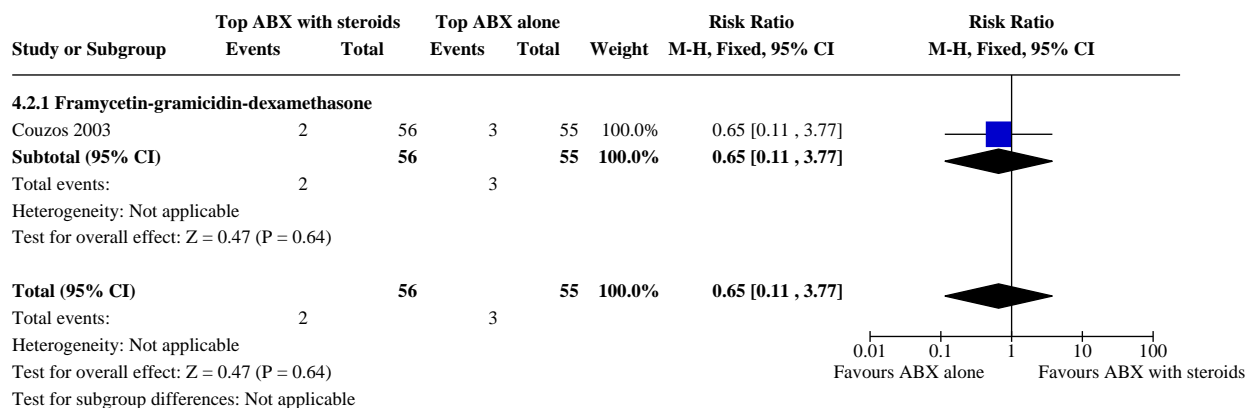
**Analysis 3.5. Comparison 3: Topical antibiotic (non-quinolone) with steroids versus topical quinolones, Outcome 5: Ear pain or discomfort****Analysis 3.6. Comparison 3: Topical antibiotic (non-quinolone) with steroids versus topical quinolones, Outcome 6: Dizziness/vertigo/balance****Comparison 4. Topical antibiotic (non-quinolone) with steroids versus topical quinolone on top of PVP-I**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Resolution of ear discharge 1 to 2 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1.1 Framycetin-gramicidin-dexamethasone	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.50, 0.90]
4.2 Ear pain or discomfort	1	111	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.11, 3.77]
4.2.1 Framycetin-gramicidin-dexamethasone	1	111	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.11, 3.77]

### Analysis 4.1. Comparison 4: Topical antibiotic (non-quinolone) with steroids versus topical quinolone on top of PVP-I, Outcome 1: Resolution of ear discharge 1 to 2 weeks



### Analysis 4.2. Comparison 4: Topical antibiotic (non-quinolone) with steroids versus topical quinolone on top of PVP-I, Outcome 2: Ear pain or discomfort

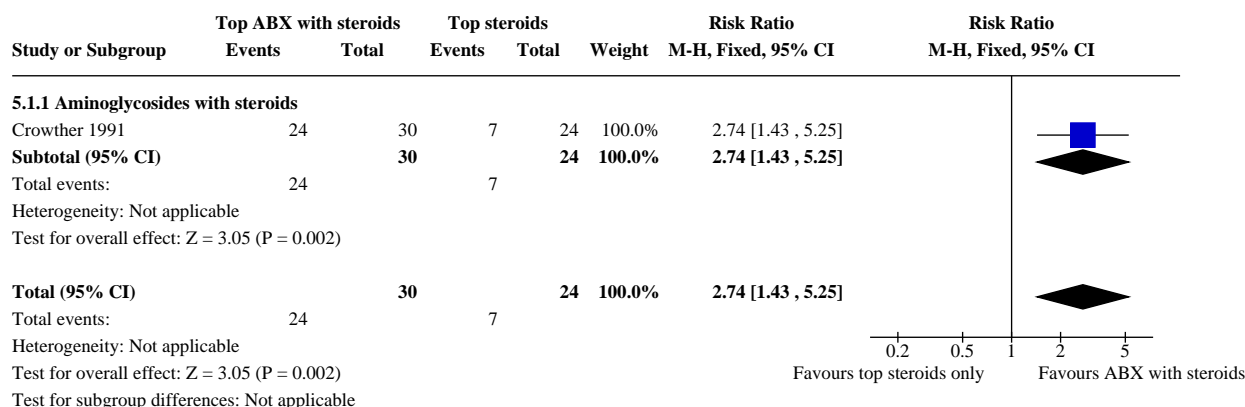


### Comparison 5. Topical antibiotics with steroids versus steroids only

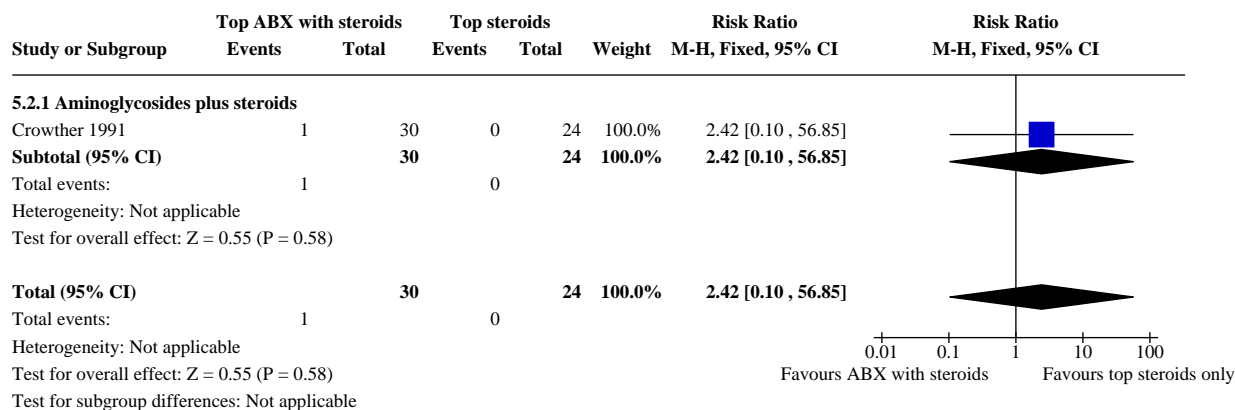
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">5.1 Resolution of ear discharge 2 to 4 weeks</a>	1	54	Risk Ratio (M-H, Fixed, 95% CI)	2.74 [1.43, 5.25]
5.1.1 Aminoglycosides with steroids	1	54	Risk Ratio (M-H, Fixed, 95% CI)	2.74 [1.43, 5.25]
<a href="#">5.2 Ear pain or discomfort at 4 weeks</a>	1	54	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [0.10, 56.85]
5.2.1 Aminoglycosides plus steroids	1	54	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [0.10, 56.85]



### Analysis 5.1. Comparison 5: Topical antibiotics with steroids versus steroids only, Outcome 1: Resolution of ear discharge 2 to 4 weeks



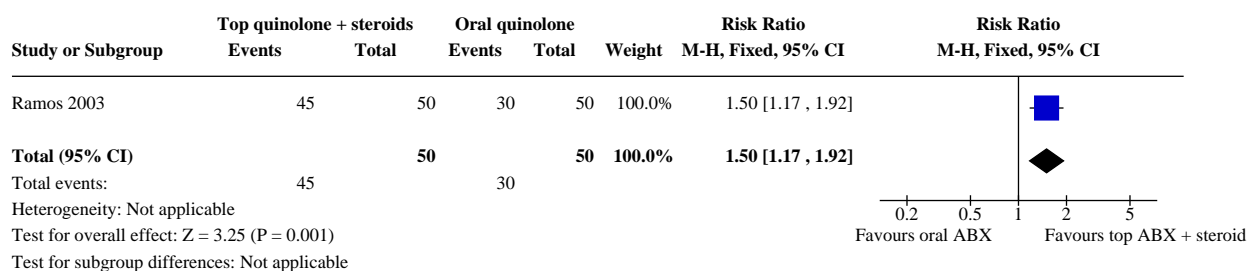
### Analysis 5.2. Comparison 5: Topical antibiotics with steroids versus steroids only, Outcome 2: Ear pain or discomfort at 4 weeks



### Comparison 7. Topical antibiotics (quinolone) with steroids versus oral antibiotics (quinolone)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Resolution of ear discharge 1 to 2 weeks	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.17, 1.92]

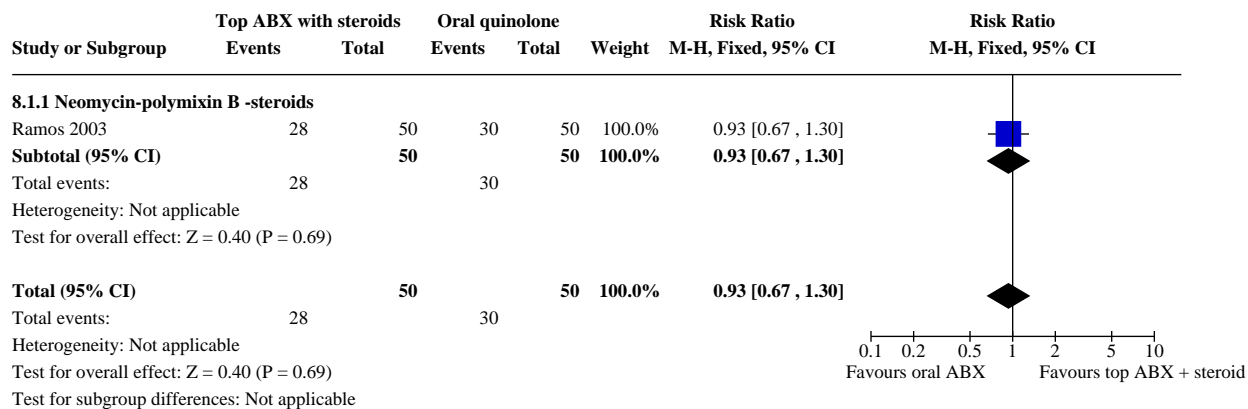
### Analysis 7.1. Comparison 7: Topical antibiotics (quinolone) with steroids versus oral antibiotics (quinolone), Outcome 1: Resolution of ear discharge 1 to 2 weeks



### Comparison 8. Topical antibiotics (non quinolone) with steroids versus oral antibiotics (quinolone)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Resolution of ear discharge 1 to 2 weeks	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.67, 1.30]
8.1.1 Neomycin-polymixin B -steroids	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.67, 1.30]

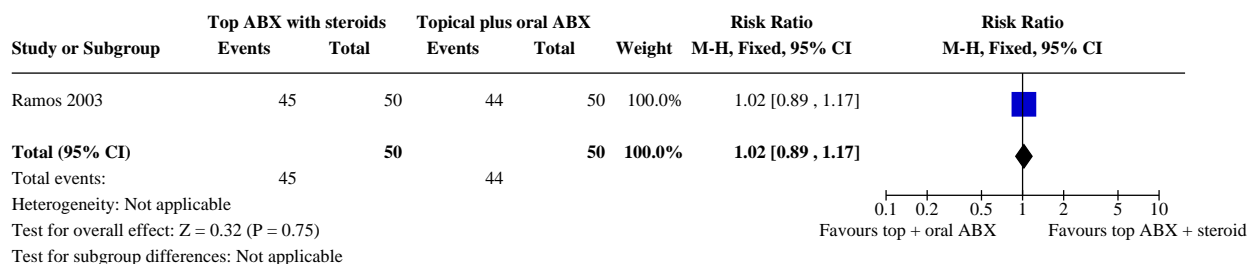
### Analysis 8.1. Comparison 8: Topical antibiotics (non quinolone) with steroids versus oral antibiotics (quinolone), Outcome 1: Resolution of ear discharge 1 to 2 weeks



### Comparison 9. Topical antibiotics (quinolone) with steroids versus topical plus oral antibiotics (quinolone)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Resolution of ear discharge 1 to 2 weeks	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.89, 1.17]

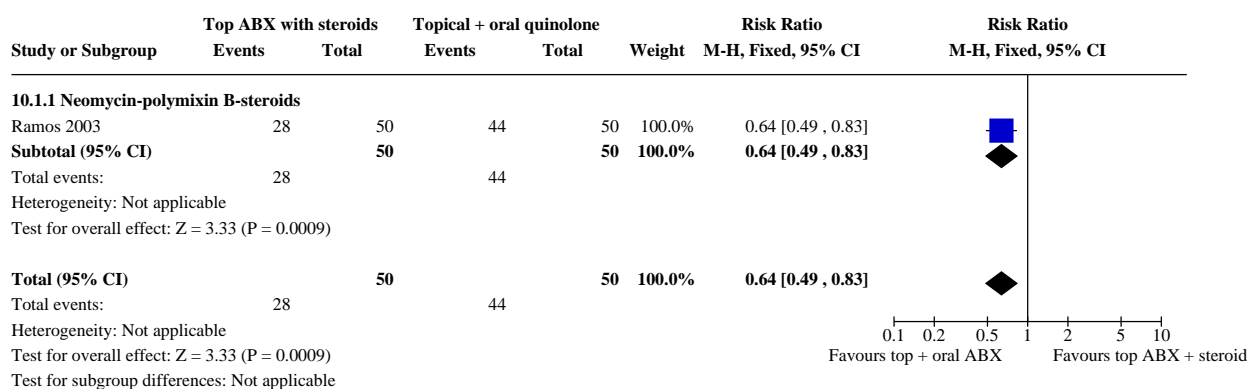
### Analysis 9.1. Comparison 9: Topical antibiotics (quinolone) with steroids versus topical plus oral antibiotics (quinolone), Outcome 1: Resolution of ear discharge 1 to 2 weeks



### Comparison 10. Topical antibiotics (non-quinolone) with steroids versus topical plus oral antibiotics (quinolone)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Resolution of ear discharge 1 to 2 weeks	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.49, 0.83]
10.1.1 Neomycin-polymixin B-steroids	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.49, 0.83]

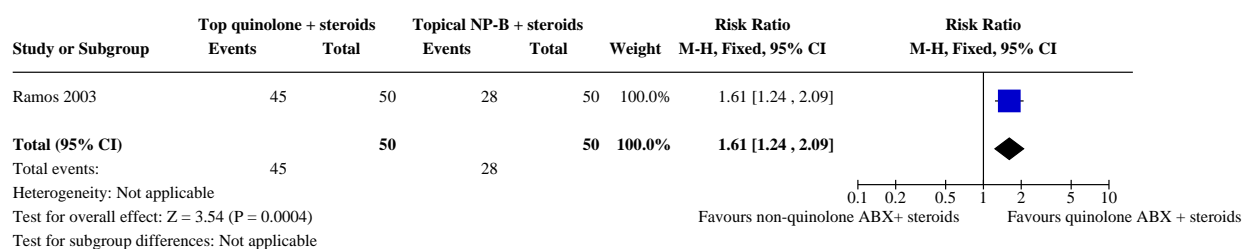
### Analysis 10.1. Comparison 10: Topical antibiotics (non-quinolone) with steroids versus topical plus oral antibiotics (quinolone), Outcome 1: Resolution of ear discharge 1 to 2 weeks



### Comparison 11. Topical antibiotics (quinolone) with steroids versus topical antibiotics (non-quinolone) with steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Resolution of ear discharge 1 to 2 weeks	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.24, 2.09]

### Analysis 11.1. Comparison 11: Topical antibiotics (quinolone) with steroids versus topical antibiotics (non-quinolone) with steroids, 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 2018a](#); [Brennan-Jones 2020](#)).

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 2018](#)).

CSOM-5: Topical antiseptics for chronic suppurative otitis media ([Head 2018a](#); [Head 2020a](#)).

CSOM-6: Antibiotics versus topical antiseptics for chronic suppurative otitis media ([Head 2018b](#); [Head 2020b](#)).

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

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

Penicillins	Ticarcillin plus clavulanic acid	Parenteral
Monobactams	Aztreonam	Parenteral

**Table 3. Inclusion criteria for comparison interventions**

Intervention	Inclusion criteria
Antibiotics (topical)	<p><b>Include:</b> all <i>topical antibiotics</i> applied directly into the ear canal. The most common formulations are ear drops but other formulations such as sprays will also be included.</p> <p><b>Exclude:</b> studies that conduct swabs and tests for antimicrobial sensitivity and then base the choice of antibiotics for each participant on the results of the laboratory test.</p> <p><b>Duration:</b> at least 5 days of treatment with antibiotics is required, except for antibiotics where a shorter duration is equivalent (e.g. azithromycin).</p> <p><b>Dose:</b> there is no limitation on the dose or frequency of application.</p>
Antibiotics (systemic)	<p><b>Include:</b> all <i>systemic antibiotics</i> administered orally or parenterally (intramuscular or intravenous).</p> <p><b>Exclude:</b> studies that conduct swabs and tests for antimicrobial sensitivity and then base the choice of antibiotics for each participant on the results of the laboratory test.</p> <p><b>Duration:</b> at least 5 days of treatment with antibiotics is required, except for antibiotics where a shorter duration is equivalent (e.g. azithromycin).</p> <p><b>Dose:</b> there is no limitation on the dose, concentration, volume or frequency of application.</p>
Antiseptics (topical)	<p><b>Include:</b> any single, or combination of, topical antiseptic agent(s) of any class. The topical antiseptics can be applied directly into the ear canal as ear drops, powders or irrigations, or as part of an aural toileting procedure.</p> <p><b>Dose/duration:</b> there is no limitation on the dose, concentration, duration or frequency of application.</p>
Aural toileting	<p><b>Include:</b> all aural toileting methods, frequencies and durations, including but not limited to the following:</p> <ul style="list-style-type: none"> <li>• Dry mopping ('wicking'): with cotton bud; Jobson-Horne or other ear probe wrapped in cotton wool; or tissue spears (rolled up tissue papers).</li> <li>• Irrigation of the external auditory canal using a syringe or similar device. Different solutions (antiseptics versus normal water/saline) and types of irrigation instrument (e.g. manual syringe versus automated Propulse) have been described. Irrigation may be followed by dry mopping or vice versa.</li> <li>• Microsuction of the external auditory canal to remove discharge.</li> </ul>
Corticosteroids (topical)	<p><b>Include:</b> any corticosteroid applied to the ear canal. The most common formulations are ear drops but other formulations such as sprays will also be included if the intervention arm was also using a similar administration method.</p> <p><b>Dose/duration:</b> there is no limitation on the dose, concentration, duration or frequency of application.</p>

**Table 4. Summary of study characteristics**

Study ID (no. participants)	Setting	Population	Intervention 1	Intervention 2	Treatment duration	Follow-up	Background treatment	Notes
<b>Topical antibiotics plus steroids versus placebo</b>								
<a href="#">Browning 1988</a> (123 people)	UK (ENT outpatient clinic)	Adults with active mucosal chronic otitis media  Mean age: 49 years	Gentamicin/hydrocortisone, ear drops. No details of dose or frequency	Placebo ear drops or placebo tablets	4 to 6 weeks (depending on outcome)	Up to 6 weeks	Aural toilet with daily dry mopping	—
<a href="#">Picozzi 1983</a> (37 people)	UK (unclear setting)	Active chronic otitis media  No age information	Gentamicin plus hydrocortisone ear drops. No details of dose or frequency	Placebo ear drops	4 weeks	4 weeks	Dry mopping before ear drop instillation	—
<a href="#">Eason 1986</a> (50 children, 67 ears)	Solomon Islands (community)	Children with CSOM for more than 3 months  Mean age 5.4 years	Framycetin sulphate (0.5% w/v), dexamethasone (0.05% w/v) and gramicidin (0.005% w/v). No details of volume or frequency of administration	No treatment	3 to 6 weeks	Up to 6 weeks	Aural toiletting with dry mopping 4 times daily	Part of a 5-arm trial
<b>Topical antibiotics plus steroids versus topical antiseptics</b>								
<a href="#">Eason 1986</a> (55 children, 73 ears)	Solomon Islands (community)	Children with CSOM for more than 3 months  Mean age 5.4 years	Framycetin sulphate (0.5% w/v), dexamethasone (0.05% w/v) and gramicidin (0.005% w/v). No details of volume or frequency of administration	2% boric acid in 20% alcohol (3 drops after cleaning using intermittent tragal Depression to assist middle ear permeation) given 4 times per day	3 to 6 weeks	Up to 6 weeks	Aural toiletting with dry mopping 4 times daily	Part of a 5-arm trial
<b>Topical antibiotics plus steroids versus steroids</b>								
<a href="#">Crowther 1991</a> (64 people)	UK (general hospital)	People with active non-cholesteatomatous chronic otitis media  Mean age: 48 years	Gentamicin with hydrocortisone drops, concentration not reported, 4 drops/6 hours	Betamethasone drops, concentration not reported, 4 drops/6 hours	4 weeks	4 weeks	No ongoing concurrent treatment	—



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

**Topical antibiotics plus steroids versus topical antibiotics**
**Same antibiotics**

<a href="#">Indudharan 2005</a> (135 people, 152 ears)	Malaysia (university and general hospital)	CSOM with central perforation without cholesteatoma  Age range: 2 to 84 years	Gentamicin 0.3% with betamethasone 0.1% ear drops, 3 drops/8 hours	Gentamicin 0.3% ear drops, 3 drops/12 hours	3 weeks	4 weeks	No ongoing concurrent treatment	—
<a href="#">Kaygusuz 2002</a> (40 people)	Turkey (university ENT clinic)	CSOM without cholesteatoma with ear discharge longer than 3 months  Mean age: 31 years	0.3% tobramycin PLUS 0.1% dexamethasone ear drops, 2 drops/8 hours	0.3% tobramycin ear drops, 2 drops/8 hours	3 weeks	3 weeks	Daily aspiration	Part of 4-arm trial
<a href="#">Kaygusuz 2002</a> (40 people)	Turkey (university ENT clinic)	CSOM without cholesteatoma with ear discharge longer than 3 months  Mean age: 31 years	0.3% ciprofloxacin hydrochloride PLUS 0.1% dexamethasone ear drops, 2 drops/8 hours	0.3% ciprofloxacin hydrochloride ear drops, 2 drops/8 hours	3 weeks	3 weeks	Daily aspiration	Part of 4-arm trial
<a href="#">Ramos 2003</a> (150 people)	Spain (ENT department of 3 centres)	Chronic ear discharge  Age range 5 to 73 years (12% less than 14 years)	Topical ciprofloxacin 0.3% PLUS fluocinolone 0.5 ml/8 hours	Topical ciprofloxacin 0.2%/0.5%, 0.5 ml/8 hours	7 days	10 days	Not reported	Part of 6-arm trial
<a href="#">Panchasara 2015</a> (110 people)	India (outpatient ENT clinic)	Adults with ear discharge with tympanic membrane perforation. Patients with culture lacking sensitivity to ofloxacin were excluded.  No age information	Ofloxacin (0.3%) PLUS dexamethasone (0.1%), 5 drops/12 hours	Ofloxacin (0.3% w/v) ear drops, 5 drops/12 hours	10 days	15 days	Daily ear cleaning before instillation	—

**Different antibiotics**

<a href="#">Boesoirie 2000 unpublished</a> (92 people)	Indonesia (unclear setting)	Patients more than 15 years old with CSOM (13 weeks)  No age information provided	Neomycin-polymixin-hydrocortisone 6 drops every 12 hours	Ofloxacin 0.3% otic solution, 6 drops every 12 hours	7 to 14 days	1 to 2 weeks	None reported	Unpublished data - included in <a href="#">Abes 2003</a>
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**Table 4. Summary of study characteristics** (Continued)

							systematic review	
<a href="#">Helmi 2000 unpublished</a> (138 people)	Indonesia (unclear setting)	Patients greater than 7 years old with CSOM  No age information provided	Neomycin-polymyxin-hydrocortisone otic solution, 3 to 5 drops/8 hours	Ofloxacin 0.3% otic solution, 6 to 10 drops/12 hours	14 days	14 days	None reported	Unpublished data - included in <a href="#">Abes 2003</a> systematic review
<a href="#">Subramaniam 2001 unpublished</a> (60 people)	Malaysia (unclear setting)	Patients > 12 years old with CSOM  No age information provided	Neomycin-polymyxin hydrocortisone otic solution, 3 to 5 drops/8 hours	Ofloxacin 0.3% otic solution, 6 to 10 drops/12 hours	14 days	14 days	None reported	Unpublished data - included in <a href="#">Abes 2003</a> systematic review
<a href="#">Tong 1996</a> (52 people)	Hong Kong (specialist outpatient clinic)	Otorrhea-associated recurrent otitis media with tympanic perforation  No age information provided	Neomycin-polymyxin b-hydrocortisone ear drops, 6 drops/12 hours	Ofloxacin 0.3% ear drops, 6 drops/12 hours	14 days	14 weeks	Microscopic suction at each clinic visit (D1-baseline, D7, D14)	—
<a href="#">Miro 2000</a> (322 people)	Spain (unclear setting - multi-centre study 16 centres)	CSOM with at least 6 weeks of discharge  Median age: 44 years	Neomycin, polymyxin B sulfate and hydrocortisone, 3 drops/6 hours	Ciprofloxacin 0.2% solution, 0.5 ml/12 hours	6 to 10 days	4 weeks	None reported	—
<a href="#">Ramos 2003</a> (150 people)	Spain (ENT department of 3 centres)	Chronic ear discharge  Age range 5 to 73 years (12% less than 14 years)	Neomycin 0.0035 g, polymyxin 10,000 IU, hydrocortisone 0.00025 g/8 hours	Topical ciprofloxacin 0.2%/0.5%, 0.5 ml/8 hours	7 days	10 days	None reported	Part of 6-arm trial
<a href="#">Lazo Saenz 2000</a> (40 ears)	Mexico (ENT hospital)	CSOM  Mean age: 38 years	Neomycin (0.35%)-polymyxin B (10,000U/mL)-fludrocortisone (0.25%) with 20% lidocaine ear drops administered 3 drops/8 hours	Ciprofloxacin ear drops 200 µg/mL 3 drops/8 hours	10 days	10 days	None reported	—

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

<a href="#">Couzos 2003</a> (147 people)	Australia (community clinics)	Children with CSOM (< 15 years) with perforation and ear discharge  Age range: 1 to 14 years	Sofradex: framycetin (0.5%), gramicidin and dexamethasone eardrops, 5 drops/12 hours	Ciprofloxacin 0.3% eardrops, 5 drops/12 hours	9 days	10 to 21 days	Aural toiletting plus topical antiseptics: syringing with 0.5% povidone-iodine	—
<a href="#">Gendeh 2001 unpublished</a> (70 people)	Malaysia (ENT department)	Patients with otitis externa and CSOM (only data for CSOM was used for this meta-analysis)  No age information	Framycetin sulphate (0.5% w/v), dexamethasone (0.05% w/v) and gramicidin (0.005% w/v), 6 drops/12 hours	Ofloxacin 0.3% otic solution, 6 drops/12 hours	14 days	14 days	None reported	Unpublished data - included in <a href="#">Abes 2003</a> systematic review
<a href="#">Leach 2008</a> (97 people)	Australia (community setting)	Children with active CSOM despite treatment with 4 drops/12 hours Sofradex for an unclear duration  Mean age: 7.7 years	Framycetin sulphate (0.5% w/v), dexamethasone (0.05% w/v) and gramicidin (0.005% w/v), 4 drops/12 hours	Ciprofloxacin 0.3% ear drops, 4 drops/12 hours	6 to 8 weeks	Up to 20 weeks	Dry mopping before ear drop instillation	—
<b>Comparing different topical antibiotics plus steroids</b>								
<a href="#">Ramos 2003</a> (100 people)	Spain (ENT department of 3 centres)	Chronic ear discharge  Age range 5 to 73 years (12% less than 14 years)	Neomycin 0.0035 g, polymyxin 10,000 IU, hydrocortisone 0.00025 g/8 hours	Topical ciprofloxacin 0.3% PLUS fluocinolone 0.5 ml/8 hours	7 days	10 days	None reported	Part of 6-arm trial
<b>Topical antibiotics plus steroids versus oral antibiotics</b>								
<a href="#">Ramos 2003</a> (100 people)	Spain (ENT department of 3 centres)	Chronic ear discharge  Age range 5 to 73 years (12% less than 14 years)	Topical ciprofloxacin 0.3% PLUS fluocinolone 0.5 ml/8 hours	Oral ciprofloxacin 500 mg twice 12-hourly	7 days	10 days	None reported	Part of 6-arm trial
<a href="#">Ramos 2003</a> (100 people)	Spain (ENT department of 3 centres)	Chronic ear discharge  Age range 5 to 73 years (12% less than 14 years)	Neomycin 0.0035 g, polymyxin 10,000 IU, hydrocortisone 0.00025 g/8 hours	Oral ciprofloxacin 500 mg twice 12-hourly	7 days	10 days	None reported	Part of 6-arm trial
<b>Topical antibiotics plus steroids versus oral antibiotics plus topical antibiotics</b>								

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

Ramos 2003 (100 people)	Spain (ENT department of 3 centres)	Chronic ear discharge  Age range 5 to 73 years (12% less than 14 years)	Topical ciprofloxacin 0.3% PLUS fluocinolone 0.5 ml/8 hours	Oral ciprofloxacin 500 mg 12-hourly PLUS topical ciprofloxacin 0.2%, 0.5 ml/8 hours	7 days	10 days	None re- ported	Part of 6- arm trial
Ramos 2003 (100 people)	Spain (ENT department of 3 centres)	Chronic ear discharge  Age range 5 to 73 years (12% less than 14 years)	Neomycin 0.0035 g, polymyxin 10,000 IU, hy- drocortisone 0.00025 g/8 hours	Oral ciprofloxacin 500 mg 12-hourly PLUS topical ciprofloxacin 0.2%, 0.5 ml/8 hours	7 days	10 days	None re- ported	Part of 6- arm trial

**Table 5. Resolution of ear discharge outcome**

Reference	Unit of randomisation	Reported	Definition	Otoscopically confirmed?	Time points	Notes
Boesoirie 2000 unpublished	No details	No details	No details	No details	No details	No access to publication or data
Browning 1988	Person	Person	Otoscopically inactive, without pooling of mucus or mucopus in the middle ear or external auditory canal and without inflammation of the middle ear mucosa	Yes	2 to 4 weeks (4 weeks)	One ear chosen as the study ear for bilateral disease
Couzos 2003	Person	Person	Absence of discharge in the middle ear and canal determined by otoscopy	Yes	1 to 2 weeks (day 10, day 14)	"Children with bilateral CSOM received treatment for both ears, although only one ear (randomly chosen) was monitored for the study"
Crowther 1991	Person	Person	Clearance of the presence of mucoid or mucopurulent secretions in the middle ear or mastoid	Yes	1 to 2 weeks (2 weeks) and 2 to 4 weeks (4 weeks)	—
Eason 1986	Person	Ear	Ear was "dry", "not discharging"	Yes	2 to 4 weeks (3 weeks) and after 4 weeks (6 weeks)	Counting bilateral ears separately
Gendeh 2001 unpublished	No details	No details	No details	No details	No details	No access to publication or data
Helmi 2000 unpublished	No details	No details	No details	No details	No details	No access to publication or data
Indudhara 2005	Person	Ear	"Ear becoming dry"	Unclear	2 to 4 weeks (4 weeks)	Reported outcomes from both ears separately
Kaygusuz 2002	Person	Person	Otoscopy evaluation assessed using a 3-point scale; 2 points = no damage	Yes	1 to 2 weeks (day 14) and 2 to 4 weeks (day 21)	—
Lazo Saenz 2000	Ear	Ear	"Good response" defined as no otorrhoea and normal mucosa	Yes	1 to 2 weeks (day 10)	—
Leach 2008	Person	Person	"Clinical failure was defined as otoscopic signs of otorrhoea in the canal or middle	Yes	After 4 weeks (10 to 20 weeks)	—

**Table 5. Resolution of ear discharge outcome** *(Continued)*

ear space, including otorrhoea in the canal despite healing of the tympanic membrane"

Miro 2000	Person	Person	"Cure, absence of otorrhoea or presence of serous/mucous otorrhoea with negative microbiological culture"	Unclear	Between 12 to 17 days	—
Panchasara 2015	Person	Person	"Clinical cure rate", conversion of wet ear to dry ear	Yes	1 to 2 weeks (day 10) and 2 to 4 weeks (day 15)	Baseline characteristics only recorded for one affected ear per person
Picozzi 1983	Person	Person	"Inactive"	Most likely	4 weeks	—
Ramos 2003	Person	Person	"Cured" according to "indices de curacion"	Unclear	1 to 2 weeks (day 10)	—
Subramaniam 2001 unpublished	No details	No details	No details	No details	No details	No access to publication or data
Tong 1996	Person	Ear	"Inactive"	Yes	1 to 2 weeks (day 7 and day 14)	Counting bilateral ears separately

## 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	1 exp Otitis Media/	1 exp otitis media/
2 ("otitis media" or OME):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET	2 ("otitis media" or OME).ab,ti.	2 ("otitis media" or OME).ab,ti.
3 MESH DESCRIPTOR Tympanic Membrane Perforation EXPLODE ALL AND CENTRAL:TARGET	3 exp Tympanic Membrane Perforation/	3 exp eardrum perforation/
4 MESH DESCRIPTOR Tympanic Membrane EXPLODE ALL AND CENTRAL:TARGET	4 exp Tympanic Membrane/	4 exp eardrum/
5 ("ear drum*" or eardrum* or tympanic):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET	5 ("ear drum*" or eardrum* or tympanic).ab,ti.	5 ("ear drum*" or eardrum* or tympanic).ab,ti.
6 #4 OR #5 AND CENTRAL:TARGET	6 4 or 5	6 4 or 5
7 (perforat* or hole or ruptur*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET	7 (perforat* or hole or ruptur*).ab,ti.	7 (perforat* or hole or ruptur*).ab,ti.
8 #6 AND #7 AND CENTRAL:TARGET	8 6 and 7	8 6 and 7
9 #1 OR #2 OR #3 OR #8 AND CENTRAL:TARGET	9 1 or 2 or 3 or 8	9 1 or 2 or 3 or 8
10 MESH DESCRIPTOR Suppuration EXPLODE ALL AND CENTRAL:TARGET	10 exp suppuration/	10 exp suppuration/
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 discom-		

(Continued)

fort or earach* or mucopurulen*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET	9 1 or 2 or 3 or 4 or 8	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 (pain):AB,TI,TO AND CENTRAL:TARGET	10 exp Suppuration/ n	12 10 or 11
13 #10 or #11 or #12 AND CENTRAL:TARGET	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.	13 exp chronic disease/
14 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND CENTRAL:TARGET	12 10 or 11	14 exp recurrent disease/
15 MESH DESCRIPTOR Recurrence EXPLODE ALL AND CENTRAL:TARGET	13 exp Chronic Disease/	15 (chronic* or persist* or recurr* or repeat*).ab,ti.
16 (chronic* or persist* or recurr* or repeat*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET	14 exp Recurrence/	16 13 or 14 or 15
17 #14 OR #15 OR #16 AND CENTRAL:TARGET	15 (chronic* or persist* or recurr* or repeat*).ab,ti.	17 9 and 12 and 16
18 #9 AND #17 AND #13 AND CENTRAL:TARGET	16 13 or 14 or 15	18 exp suppurative otitis media/
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	17 9 and 12 and 16	19 CSOM.ab,ti.
20 ((earach* near (chronic or persist* or recurr* or repeat*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET	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.	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)).ab,ti.
21 MESH DESCRIPTOR Otitis Media, Suppurative EXPLODE ALL AND CENTRAL:TARGET	19 CSOM.ab,ti.	21 (earach* adj3 (chronic or persist* or recurr* or repeat*)).ab,ti.
22 (CSOM):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET	20 exp Otitis Media, Suppurative/	22 17 or 18 or 19 or 20 or 21
23 #20 OR #21 OR #22 OR #18 OR #19 AND CENTRAL:TARGET	21 (earach* adj6 (chronic or persist* or recurr* or repeat*)).ab,ti.	
	22 17 or 18 or 19 or 20 or 21	

Web of Science (Web of Knowledge)	CINAHL (EBSCO)	Cochrane ENT Register (the Cochrane Register of Studies)
#1 TOPIC: ("otitis media" or OME)  Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years	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))	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
#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		4 #2 AND #3 AND INREGISTER



(Continued)

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

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")

S3 (MH "Tympanic Membrane Perforation")

S2 TX "otitis media" or OME

S1 (MH "Otitis Media+")

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,M-C,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,M-C,MH,TI,TO AND INREGISTER

10 #5 AND #8 AND #9 AND INREGISTER

11 (csom):AB,EH,KW,KY,M-C,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,M-C,MH,TI,TO AND INREGISTER

13 ((earach\* and (chronic or persist\* or recurr\* or repeat\*)):AB,EH,KW,KY,M-C,MH,TI,TO AND INREGISTER

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

## ClinicalTrials.gov

### 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

## ICTRP (WHO Portal)

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

## Other

### 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)

(Continued)

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

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

OR eardrum AND hole OR eardrum AND perforation

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)

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 <i>(name the intervention)</i>	Comparison <i>(name the intervention)</i>
No. of people screened		
No. of participants randomised - all		
No. randomised to each group		
No. receiving treatment as allocated		
No. not receiving treatment as allocated		
- Reason 1		
- Reason 2		
No. that dropped out <sup>1</sup> (no follow-up data for any outcome available)		
No. excluded from analysis <sup>2</sup> (for all outcomes)		
- Reason 1		
- Reason 2		

<sup>1</sup>This includes patients who withdrew and provided no data, or did not turn up for follow-up.

<sup>2</sup>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	<p><b>Location:</b> [country, rural?, no. of sites etc.]</p> <p><b>Setting of recruitment and treatment:</b> [specialist hospital? general practice? school? state YEAR]</p> <p><b>Sample size:</b></p> <ul style="list-style-type: none"> <li><b>Number randomised:</b> x in intervention, y in comparison</li> <li><b>Number completed:</b> x in intervention, y in comparison</li> </ul> <p><b>Participant (baseline) characteristics:</b></p> <ul style="list-style-type: none"> <li>Age:</li> <li>Gender (F/M): number of females (%) / number of males (%)</li> <li>Main diagnosis: <i>[as stated in paper – state the diagnostic criteria used]</i></li> <li>High-risk population: Yes/No <ul style="list-style-type: none"> <li>* Cleft palate (or other craniofacial malformation): y/N (%)</li> <li>* Down syndrome: n/N (%)</li> <li>* Indigenous groups (Australian Aboriginals/Greenland natives): n/N (%)</li> <li>* Immunocompromised: n/N (%)</li> </ul> </li> <li>Diagnosis method <i>[if reported]</i>: <ul style="list-style-type: none"> <li>* Confirmation of perforated tympanic membrane: Yes/No/NR or unclear <i>[Method]</i></li> <li>* Presence of mucopurulent discharge: Yes/No/NR or unclear – if 'yes', record n/N (%)</li> <li>* Duration of symptoms (discharge): x weeks</li> </ul> </li> <li>Other important effect modifiers, if data available: <ul style="list-style-type: none"> <li>* Alternative diagnosis of ear discharge (where known): n/N (%)</li> <li>* Number who have previously had grommets inserted (and, where known, number where grommets are still in place): n/N (%)</li> <li>* Number who have had previous ear surgery: n/N (%)</li> <li>* Number who have had previous antibiotic treatment for CSOM: n/N (%)</li> </ul> </li> </ul> <p><b>Inclusion criteria:</b></p> <ul style="list-style-type: none"> <li><i>[State diagnostic criteria used for CSOM, if available]</i></li> </ul> <p><b>Exclusion criteria:</b></p>
Interventions	<p><b>Intervention (n = x):</b> drug name, method of administration, dose per day/frequency of administration, duration of treatment</p> <p><u>For aural toileting:</u> who does it, methods or tools used, frequency, duration</p> <p><b>Comparator group (n = y):</b></p> <p><b>Concurrent treatment:</b></p> <p>Use of additional interventions (common to both treatment arms):</p>
Outcomes	<p><b>Outcomes of interest in the review:</b></p> <p><b>Primary outcomes:</b></p>

(Continued)

- Resolution of ear discharge or 'dry ear' (whether otoscopically confirmed or not), measured at between 1 week to 2 weeks, 2 to 4 weeks and after 4 weeks
- 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	<p><b>Clinical trial registry no:</b> (if available)</p> <p><b>Unit of randomisation:</b> person/ears/other (e.g. cluster-randomised by hospital/school)</p> <p><i>[In the case of randomisation by person]:</i></p> <p><b>Methods for including patients with bilateral disease, for example:</b></p> <ul style="list-style-type: none"> <li>• Random selection of one ear as the 'study ear'</li> <li>• Selecting worse/least affected ear as the 'study ear'</li> <li>• Counting bilateral ears separately</li> <li>• Reporting 2 sets of results (please specify)</li> <li>• Other (please state)</li> <li>• Not stated</li> </ul>

#### 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:

(Continued)

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



Other  
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Results (continuous data table)						
Outcome	Intervention (name the intervention)			Comparison (name the intervention)		
	Mean	SD	N	Mean	SD	N
<b>Disease-specific health-related quality of life</b>						
(COMQ-12, COMOT-15, CES) <sup>1</sup>						
Time point: (state)						
<b>Hearing:</b>						
[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: <a href="http://arohatgi.info/WebPlotDigitizer/app/">http://arohatgi.info/WebPlotDigitizer/app/</a> , and save a copy of your charts in a folder]						



<sup>1</sup>State the measurement method: this will be instrument name/range for patient-reported outcomes.

## DICHOTOMOUS OUTCOMES

Results (dichotomous data table)						
Outcome	Ap- plica- ble re- view/  Inter- ven- tion <sup>1</sup>	Group A - inter- vention arm		Group B – con- trol		Other sum- mary statis- tics/Notes
		No. of peo- ple with events	No. of peo- ple analysed	No. of peo- ple with events	No. of peo- ple analysed	P val- ues, RR (95% CI), OR (95% CI)
<b>Resolution of ear discharge or 'dry ear' at 1 to 2 weeks</b>						
[Measurement method or definition used: not/unclear if/otoscopically confirmed] <sup>1</sup>						
Time point: [State actual time point]						
<b>Resolution of ear discharge or 'dry ear' at 2 to 4 weeks</b>						
[Measurement method or definition used: not/unclear if/otoscopically confirmed]						
Time point: [xx]						
<b>Resolution of ear discharge or 'dry ear' after 4 weeks</b>						
[Measurement method or definition used: not/unclear if/otoscopically confirmed]						
Time point: [xx]						
<b>Ear pain/discomfort/local irritation</b>						
[Measurement method or definition used e.g. patient-reported]						
Time point: [xx]						
<b>Suspected ototoxicity</b>						
[Measurement method or definition used]						
Time point: [xx]						
<b>Sensorineural hearing loss</b>						
[Measurement method or definition used]						
Time point: [xx]						
<b>Tinnitus</b>						

(Continued)

[Measurement method or definition used]

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

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**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**

---

(Continued)

[How was this diagnosed?]

---

Comment/additional notes:

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

---

<sup>1</sup>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).

## HISTORY

Protocol first published: Issue 6, 2018

Review first published: Issue 8, 2020

## CONTRIBUTIONS OF AUTHORS

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

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

Karen Head: scoped review, designed and wrote protocol. Screened search results and selected studies, carried out data extraction and '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 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 analyses and reviewed and edited the text of the review.

Mahmood F Bhutta: helped to scope, design and write the protocol; reviewed 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.

Lee Yee Chong: none known.

Karen Head: 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 was until March 2020 the 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).

## SOURCES OF SUPPORT

### Internal sources

- No sources of support supplied

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**Topical antibiotics with steroids for chronic suppurative otitis media (Review)**

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## External sources

- National Institute for Health Research, UK  
Infrastructure funding for Cochrane ENT
- NHMRC Centre of Research Excellence in Ear and Hearing Health of Aboriginal and Torres Strait Islander Children, Australia

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

One comparison, topical antibiotics plus steroid versus topical antibiotics plus oral antibiotics, was not included in the list of possible comparisons at the protocol stage ([Brennan-Jones 2018](#)). Evidence was found for this comparison and, as it meets the overall aim of the review, we subsequently amended the inclusion criteria.

We had originally planned two 'Summary of findings' tables: one for 'Topical antibiotics with steroids compared to placebo for chronic suppurative otitis media' and the second for 'Topical antibiotics with steroids compared to topical antibiotics alone for chronic suppurative otitis media'. For the second comparison we identified some studies that used the same topical antibiotic in each comparison arm (thus testing the effect of adding steroids), and others where different topical antibiotics were used in different arms. The author team felt that it was appropriate to separate these into two comparisons with separate 'Summary of findings' tables.

We completed an unplanned sensitivity analysis for unpublished studies to evaluate the impact of unpublished data on the overall results.