Cochrane Library

Cochrane Database of Systematic Reviews

Topical versus systemic antibiotics for chronic suppurative otitis media (Review)

Chong LY, Head K, Webster KE, Daw J, Richmond P, Snelling T, Bhutta MF, Schilder AGM, Burton MJ, Brennan-Jones CG

Chong L-Y, Head K, Webster KE, Daw J, Richmond P, Snelling T, Bhutta MF, Schilder AGM, Burton MJ, Brennan-Jones CG.
Topical versus systemic antibiotics for chronic suppurative otitis media.
Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD013053.
DOI: 10.1002/14651858.CD013053.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Topical versus systemic antibiotics for chronic suppurative otitis media

Lee-Yee Chong[1], Karen Head[2], Katie E Webster[2], Jessica Daw[3], Peter Richmond[4], Tom Snelling[5], Mahmood F Bhutta[6], Anne GM Schilder[7], Martin J Burton[8], Christopher G Brennan-Jones[9]

[1]Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK. [2]Cochrane ENT, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK. [3]Telethon Kids Institute, The University of Western Australia, Perth, Australia. [4]Division of Paediatrics, The University of Western Australia, Perth, Australia. [5]Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Perth, Australia. [6]Department of Otolaryngology, Brighton and Sussex University Hospitals NHS Trust, Brighton, UK. [7]evidENT, Ear Institute, University College London, London, UK. [8]Cochrane UK, Oxford, UK. [9]Telethon Kids Institute, The University of Western Australia, Perth, Australia

Contact address: Christopher G Brennan-Jones, chris.brennan-jones@telethonkids.org.au, c.brennan.jones@gmail.com.

Editorial group: Cochrane ENT Group.
Publication status and date: New, published in Issue 2, 2021.

Citation: Chong L-Y, Head K, Webster KE, Daw J, Richmond P, Snelling T, Bhutta MF, Schilder AGM, Burton MJ, Brennan-Jones CG. Topical versus systemic antibiotics for chronic suppurative otitis media. *Cochrane Database of Systematic Reviews* 2021, Issue 2. Art. No.: CD013053. DOI: 10.1002/14651858.CD013053.pub2.

ABSTRACT

Background

Chronic suppurative otitis media (CSOM), sometimes referred to as chronic otitis media (COM), is a chronic inflammation and often polymicrobial infection (involving more than one micro-organism) of the middle ear and mastoid cavity, characterised by ear discharge (otorrhoea) through a perforated tympanic membrane. The predominant symptoms of CSOM are ear discharge and hearing loss. Antibiotics are the most common treatment for CSOM, which act to kill or inhibit the growth of micro-organisms that may be responsible for the infection. Antibiotics can be administered both topically and systemically, and can be used alone or in addition to other treatments for CSOM such as ear cleaning (aural toileting).

Objectives

To assess the effects of topical versus systemic antibiotics for people with CSOM.

Search methods

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

Selection criteria

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

The studies compared topical antibiotics against systemic (oral, injection) antibiotics. We separated studies according to whether they compared the same type of antibiotic in both treatment groups, or different types of antibiotics. For each comparison we considered whether there was background treatment for both treatment groups, for example aural toileting (ear cleaning).

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 up to four weeks, and after four weeks), health-related quality of life using a validated instrument, ear pain (otalgia) or discomfort or local irritation. Secondary outcomes included hearing, serious complications and ototoxicity measured in several ways.

Main results

Six studies (445 participants), all with high risk of bias, were included. All but two studies included patients with confirmed CSOM, where perforation of the ear drum was clearly documented. None of the studies reported results for resolution of ear discharge after four weeks or health-related quality of life.

1. Topical versus systemic administration of the same type of antibiotics (quinolones)

Four studies (325 participants) compared topical versus systemic (oral) administration of ciprofloxacin. Three studies reported resolution of ear discharge at one to two weeks and found that the topical administration may slightly increase resolution (risk ratio (RR) 1.48, 95% confidence interval (CI) 1.24 to 1.76; 285 participants; 3 studies; $I^2 = 0\%$; low-certainty evidence). In these studies, aural toileting was either not mentioned, or limited to the first visit.

Three studies (265 participants) reported that they did not suspect ototoxicity in any participants, but it is unclear how this was measured (very low-certainty evidence). No studies reported the outcomes of ear pain or serious complications. No studies reported results for hearing, despite it being measured in three studies.

2. Topical versus systemic administration of different types of antibiotics (quinolones versus aminoglycosides)

One study (60 participants) compared topical ciprofloxacin versus gentamicin injected intramuscularly. No aural toileting was reported. Resolution of ear discharge was not measured at one to two weeks. The study did not report any 'side effects' from which we assumed that no ear pain, suspected ototoxicity or serious complications occurred (very low-certainty evidence). The study stated that "no worsening of the audiometric function related to local or parenteral therapy was observed".

3. Topical versus systemic administration of different types of antibiotics (quinolones versus amoxicillin-clavulanic acid)

One study compared topical ofloxacin with amoxicillin-clavulanic acid with all participants receiving suction ear cleaning at the first visit. It is uncertain if there is a difference between the two groups in resolution of ear discharge at one to two weeks due to study limitations and the very small sample size (RR 2.93, 95% CI 1.50 to 5.72; 56 participants; very low-certainty evidence). It is unclear if there is a difference between topical quinolone compared with oral amoxicillin-clavulanic acid with regards to ear pain, hearing or suspected ototoxicity (very low-certainty evidence). No studies reported the outcome of serious complications.

Authors' conclusions

There was a limited amount of low-quality evidence available, from studies completed over 15 years ago, to examine whether topical or systemic antibiotics are more effective in achieving resolution of ear discharge for people with CSOM. However, amongst this uncertainty there is some evidence to suggest that the topical administration of antibiotics may be more effective than systemic administration of antibiotics in achieving resolution of ear discharge (dry ear). There is limited evidence available regarding different types of antibiotics. It is not possible to determine with any certainty whether or not topical quinolones are better or worse than systemic 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

Local antibiotics or antibiotics that target the whole body: which works better to treat chronic suppurative otitis media (persistent or recurring ear infection with discharge)?

Why is this question important?

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

Antibiotics (medicines that fight bacterial infections) are the most common treatment for CSOM. Antibiotics can:

- be applied to part of the body (locally) in the form of drops, sprays, ointments or creams (topical antibiotics); or
- treat the whole body (systemic antibiotics) when injected, or taken orally (by mouth).

To find out whether topical or systemic antibiotics are better for treating CSOM, and whether they have different adverse (unwanted) effects, we reviewed the evidence from research studies.

How did we identify and evaluate the evidence?

First, we searched the medical literature for studies that followed adults or children with CSOM for at least one week and compared:

- the topical and systemic forms of the same antibiotic; or
- a topical antibiotic against a different, systemic antibiotic.

We then compared the results and summarised the evidence from all the studies. Finally, we rated our confidence in the evidence, based on factors such as study methods and sizes, and the consistency of findings across studies.

What did we find?

We found six studies that involved a total of 445 people. People were treated with antibiotics for between five days and two weeks, and were followed for up to 21 days. Studies were conducted in Spain (three studies), Italy (two studies) and Hong Kong (one study). Three studies provided information about how they were funded or who supplied medicines: one study received funding from a university, and medicines were provided by pharmaceutical companies in two studies.

Studies compared:

- quinolone ear drops against oral quinolone (four studies);
- quinolone ear drops against injected aminoglycosides (one study);
- ofloxacin ear drops against oral amoxicillin-clavulanic acid (one study).

Quinolone ear drops compared to quinolone taken orally

Compared to oral quinolone, quinolone ear drops may slightly increase the chances of ear discharge resolving after one to two weeks. We do not know if there is a difference between the two treatments for:

- hearing;
- ear pain;
- serious complications such as facial palsy (weakness of the muscles in the face);
- meningitis (an inflammation of fluid and membranes in the brain); or
- ototoxicity (when a person develops hearing or balance problems due to a medicine).

This is because either no studies reported information about these effects, or we have too little confidence in the evidence available.

Quinolone ear drops compared to injected aminoglycosides

We do not know if quinolone ear drops are better or worse than injected aminoglycosides for treating CSOM. Only one study investigated this and it provided insufficient robust evidence.

Ofloxacin ear drops against oral amoxicillin-clavulanic acid

We do not know if ofloxacin ear drops are better or worse than oral amoxicillin-clavulanic acid for treating CSOM. Only one study investigated this and it provided insufficient robust evidence.

No study reported information about the effects of different treatments on ear discharge after four weeks or health-related quality of life.

What does this mean?

Topical antibiotics may be more effective than systemic antibiotics at resolving ear discharge. We do not know whether systemic or topical antibiotics are better for improving hearing. We need more evidence from robust studies to be able to compare the effects of topical and systemic antibiotics on aspects such as health-related quality of life or ear pain. We also need more information about adverse effects.

How up-to-date is this review?

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

Summary of findings 1. Topical quinolone compared to oral quinolone for chronic suppurative otitis media

Topical quinolone compared to oral quinolone for chronic suppurative otitis media

Patient or population: people (of any age) with CSOM
Setting: various; general hospital in Spain (de Miguel 1999; Povedano 1995), three tertiary hospitals in Spain (Ramos 2003) and university clinic in Italy (Esposito 1990)
Intervention: topical quinolone
Comparison: oral quinolone

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Without topical (ear drops)	With topical (ear drops)	Difference		
Resolution of ear discharge - 1 to 2 weeks Assessed with: 2 studies otoscopically confirmed, 2 studies unclear method Follow-up: 1 to 2 weeks	RR 1.48 (1.24 to 1.76)	285 (3 RCTs)	Study population			⊕⊕⊖⊖ **low** [1,2]	Topical antibiotics (quinolones) may slightly increase the resolution of ear discharge at 1 to 2 weeks.
			57.1%	84.6% (70.9 to 100)	27.5% more (13.8% more to 42.9% more)		
Resolution of ear discharge - after 4 weeks	No study reported this outcome.						
Health-related quality of life	No study reported this outcome.						
Ear pain (otalgia) or discomfort or local irritation	No study reported this outcome.						
Hearing	No study reported results for this outcome, despite three studies mentioning it as an outcome of interest.						
Serious complications	No studies reported this outcome.						
Suspected ototoxicity Assessed with: unclear method Follow-up: 10 to 15 days	—	265 (3 RCTs)	Three studies reported that they did not suspect ototoxicity in any participants, but it is unclear how this was measured (de Miguel 1999; Esposito 1990; Ramos 2003).			⊕⊖⊖⊖ **very low** [3,4]	It is unclear if there is a difference in ototoxicity between topical and systemic quinolones.

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

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

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

[1]Downgraded to low certainty: downgraded by one level for risk of bias (study limitations) as all studies had no blinding of participants and did not provide any descriptions of randomisation and allocation concealment methods. Outcomes were not well-defined and were subjective.
[2]Downgraded to low certainty: downgraded by one level due to imprecision as they were very small studies, with a small total sample size.
[3]Downgraded by two levels for risk of bias (study limitations) as the studies did not blind participants and did not provide any descriptions of randomisation and allocation concealment methods. It was also unclear whether the outcome was assessed appropriately as insufficient information was provided.
[4]Downgraded by one level due to imprecision as numeric results were not reported.

Summary of findings 2. Topical quinolone compared to intramuscular gentamicin for chronic suppurative otitis media

Topical quinolone compared to intramuscular gentamicin for chronic suppurative otitis media

Patient or population: adults with CSOM
Setting: university clinic, Italy
Intervention: topical quinolone
Comparison: intramuscular gentamicin

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Without topical quinolone	With topical quinolone	Difference		
Resolution of ear discharge at 1 to 2 weeks	This study did not report this outcome.						
Resolution of ear discharge after 4 weeks	The study did not report this outcome.						
Health-related quality of life	The study did not report this outcome.						
Ear pain (otalgia) or discomfort or local irritation	—	60 (1 RCT)	The authors of the study reported that "no side effect was recorded in any patient", but it is not clear whether ear pain was included as a side effect.			⊕⊖⊖⊖ **very low** [1,2]	It is unclear if there is a difference between topical quinolone compared with intramuscular gentamicin with regards to ear pain.

Assessed with: self-reported Follow-up: 21 days					
Hearing Assessed with: audiometry Follow-up: 21 days	—	60 (1 RCT)	One study indicated that audiometry was performed after treatment, but only reported that "no worsening of the audiometric function related to local or parenteral therapy was observed".	⊕⊖⊖⊖ **very low** [1,2]	It is unclear if there is a difference between topical quinolone compared with intramuscular gentamicin with regards to hearing.
Serious complications Assessed with: self-reported Follow-up: 21 days	—	60 (1 RCT)	The authors of the study reported that "no side effect was recorded in any patient".	⊕⊖⊖⊖ **very low** [1,2]	It is unclear if there is a difference between topical quinolone compared with intramuscular gentamicin with regards to serious complications.
Suspected ototoxicity Assessed with: audiometric and vestibular tests Follow-up: 21 days	—	60 (1 RCT)	Audiometric measurement and vestibular tests were performed before and 24 hours after the end of the therapy, the authors stating that "no side effect was recorded".	⊕⊖⊖⊖ **very low** [1,3,4]	It is unclear if there is a difference between topical quinolone compared with intramuscular gentamicin with regards 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

[1]Downgraded by two levels for imprecision as it was a single study, with very small sample size (60). Results were only provided as a narrative description.
[2]Downgraded by two levels for risk of bias (study limitations) as the study had no blinding of participants and did not provide any descriptions of randomisation and allocation concealment methods, and it was unclear whether the outcome was measured appropriately.
[3]Downgraded by one level for risk of bias as the study had no blinding of participants and did not provide any descriptions of randomisation and allocation concealment methods.
[4]Downgraded by one level for indirectness as it was unclear whether the outcome was assessed appropriately - no information was provided regarding assessment of tinnitus, or whether bone conduction studies were used.

Summary of findings 3. Topical quinolone compared to oral amoxicillin-clavulanic acid combination for chronic suppurative otitis media

Topical quinolone compared to oral amoxicillin-clavulanic acid combination for chronic suppurative otitis media

Patient or population: adults with CSOM
Setting: otorhinolaryngology outpatient clinic of a university hospital, Hong Kong
Intervention: topical quinolone
Comparison: oral amoxicillin-clavulanic acid combination

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
			Without topical quinolone (ear drops)	With topical quinolone (ear drops)	Difference		
Resolution of ear discharge - 1 to 2 weeks Assessed with: unclear if otoscopically confirmed Follow-up: 1 to 2 weeks	RR 2.93 (1.50 to 5.72)	56 (1 RCT)	Study population 25.9%	76.0% (38.9 to 100)	50.0% more (13 more to 122.4 more)	⊕⊖⊖⊖ **very low** [1,2]	It is uncertain if there is a difference between topical quinolone (ear drops) and oral combination of amoxicillin-clavulanic acid in resolution of ear discharge at 1 to 2 weeks.
Resolution of ear discharge after 4 weeks	The study did not report this outcome.						
Health-related quality of life	The study did not report this outcome.						
Ear pain (otalgia) or discomfort or local irritation Assessed with: self-reported Follow-up: 2 weeks	—	56 (1 RCT)	The study reported that "no patient of the ofloxacin-treated group complained of adverse side effects. There was no hypersensitivity reaction to the topical ofloxacin". It is not clear whether ear pain was specifically assessed.			⊕⊖⊖⊖ **very low** [1,3]	It is unclear if there is a difference between topical quinolone compared with oral amoxicillin-clavulanic acid with regards to ear pain.
Hearing Assessed with: bone conduction Follow-up: 2 weeks	—	56 (1 RCT)	The study reported that "there were no significant differences between the pre-treatment and post-treatment audiograms of bone conduction thresholds at frequencies of 0.5, 1, 2 and 4KHz".			⊕⊖⊖⊖ **very low** [1,3]	It is unclear if there is a difference between topical quinolone compared with oral amoxicillin-clavulanic acid with regards to hearing.

Serious complications	The study did not report this outcome.				
Suspected ototoxicity Assessed with: bone conduction Follow-up: 2 weeks	—	56 (1 RCT)	Bone conduction studies were completed and the study authors reported that "there were no significant differences between the pre-treatment and post-treatment pure-tone audiograms of bone conduction thresholds at frequencies of 0.5, 1, 2, and 4kHz". No further details were provided for the results of patient diaries on dizziness or tinnitus.	⊕⊖⊖⊖ **very low** [1,3]	It is unclear if there is a difference between topical quinolone compared with oral amoxicillin-clavulanic acid with regards to 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

[1]Downgraded by one level for risk of bias (study limitations) as there was no blinding of participants (although outcome assessors were blinded).
[2]Downgraded by two levels for imprecision as there was only one study with a very small sample size (56 participants).
[3]Downgraded by two levels due to imprecision as this was a single study with only 56 participants and the data were only reported narratively.

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, systemic antibiotics, topical antiseptics and aural toileting (ear cleaning) methods (Table 1).

This review compares the effectiveness of topical antibiotics (without corticosteroids) against systemic antibiotics for CSOM.

Description of the condition

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

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

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

Definition of disease

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

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

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

At-risk populations

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

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

Treatment

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

Description of the intervention

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

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, it is necessary to administer treatment for at least five days, 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 their use and others may provide guidance on their 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.

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

Why it is important to do this review

Although topical antibiotics are widely recommended as a first-line treatment for CSOM, systemic antibiotics are still used in situations where the delivery of drops to the middle ear is difficult. These include the treatment of young children and people with small perforations and/or copious ear discharge. Some antibiotics may be unsuitable for formulation as a topical ear drop so systemic antibiotics remain a viable option for the delivery of broad-spectrum antibiotics. In some regions and countries topical antibiotic drops are less available than systemic antibiotics. Evidence-based knowledge of the relative effectiveness of the different routes of administration of antibiotics could help to optimise their use.

OBJECTIVES

To assess the effects of topical versus systemic antibiotics for people with chronic suppurative otitis media (CSOM).

METHODS

Criteria for considering studies for this review

Types of studies

We included studies with the following design characteristics:

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

We excluded studies with the following design characteristics:

- Cross-over trials, because CSOM is not expected to be a stable chronic condition. Unless data from the first phase were available, we excluded such studies.
- Studies that randomised participants by ear (within-patient controlled) because by definition the effects of systemic interventions are not localised.

Types of participants

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

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

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

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

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

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

majority (80% or more), we analysed them in a subgroup analysis (see Subgroup analysis and investigation of heterogeneity).

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

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

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

Types of interventions

Intervention

We included all topical and systemic antibiotics. Topical antibiotics are applied directly into the ear canal. The most common formulations are ear drops but we have also included other formulations such as sprays. Systemic antibiotics are administered orally or parenterally (intramuscular or intravenous).

We excluded studies that selected an antibiotic based upon results of a microbial culture and antibiotic sensitivity testing of the ear discharge.

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

For topical antibiotics there was no limitation on the dose, concentration, volume or frequency of application.

For systemic antibiotics there was no limitation on the dose or frequency of administration.

Comparisons

The following were the comparators:

- The same antibiotic administered systemically (topical antibiotic A versus systemic antibiotic A).
- A different antibiotic administered systemically (topical antibiotic A versus systemic antibiotic B).

We planned to analyse three main scenarios depending on which common therapy was applied in the background:

- **Topical versus systemic antibiotics as a single treatment (main therapy):** this included studies where all participants in both treatment groups either received no other treatment or only received aural toileting. This has also included situations where antiseptics were applied only once (e.g. as part of microsuction at the start of treatment).
- **Topical versus systemic antibiotics as an add-on therapy to antiseptics:** this included studies where all participants in both treatment groups also used a daily antiseptic, with or without aural toileting.
- **Topical versus systemic antibiotics as an add-on therapy to other systemic or topical antibiotics:** this included studies where all participants (in the intervention and comparator groups) received antibiotics as a background therapy - this may have been topical or systemic antibiotics, but was identical for both groups. Participants in the two groups were then randomised to receive either topical or systemic antibiotics in addition to the background treatment.

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

- topical antibiotic versus the **same** antibiotic administered systemically;
- topical antibiotic versus a **different** antibiotic administered systemically; and
- topical antibiotic versus the **same** antibiotic administered systemically, where topical antiseptics were used in both arms.

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 brain 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 (search to 16 March 2020);
- Web of Knowledge, Web of Science (1945 to 16 March 2020);
- ClinicalTrials.gov, 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 2020; Brennan-Jones 2020a; Brennan-Jones 2020b; Chong 2021; Chong 2018b; Head 2020a; Head 2020b). Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011).

Searching other resources

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

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

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

Data collection and analysis

Selection of studies

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

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

Data extraction and management

At least two review authors (KH/LYC/CBJ/MB) independently extracted data from each study using a standardised data collection form (see Appendix 2). Whenever a study had more than one publication, we retrieved all publications to ensure complete extraction of data. Where there were discrepancies in the data extracted by different review authors, we checked these against the original reports and resolved any differences by discussion and consensus, with the involvement of a third author or a methodologist where appropriate. We contacted the original study authors for clarification or for missing data whenever possible. If differences were found between multiple 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 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 of 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 studies on an available case analysis basis, i.e. we included all available data from patients at the time points specified, and

irrespective of whether patients had complied with or received the treatment as planned.

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

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

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 raw values. When raw values were not provided, we extracted information from the graphs using an online data extraction tool, and 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/MJB) 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' tables, we expressed the results as absolute numbers based on the pooled results and compared to the assumed risk. We also planned to calculate 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 had been found, and if appropriate, we would have also presented 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

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

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

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

The patient as the unit of randomisation

Some studies randomised by patient and those with bilateral CSOM received the same intervention for both ears. In some studies the

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

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

Dealing with missing data

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

Assessment of reporting biases

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

Outcome reporting bias (within-study reporting bias)

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

Publication bias (between-study reporting bias)

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

Data synthesis

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

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 measurement, we did not pool change and endpoint data.

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

Subgroup analysis and investigation of heterogeneity

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

We planned to conduct subgroup analyses regardless of whether statistical heterogeneity was observed for studies that included **patients identified as high-risk** (i.e. thought to be less responsive to treatment and more likely to develop CSOM, recurrence or complications) and patients with ventilation tubes (grommets). 'High-risk' patients included 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 following 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 a single 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 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 (e.g. discharge for more than six weeks) is more refractory to treatment compared with discharge of a shorter duration (e.g. less than six weeks).
- **Patient age**: patients who were younger than two years old versus patients up to six years old, versus adults. Patients under two years are widely considered to be more difficult to treat.

We presented the results as subgroups regardless of the presence of statistical heterogeneity based on the following two factors:

- Class of antibiotics. We grouped by pharmacological class, e.g. quinolones, aminoglycosides, penicillins etc. The rationale for this was that different classes may have had different effectiveness and side effect profiles.
- Spectrum of activity against *Pseudomonas aeruginosa* (groups with known activity against *Pseudomonas aeruginosa* versus groups without activity against *Pseudomonas aeruginosa)*. This is the most commonly found bacteria in patients with CSOM and its presence is associated with tissue damage.

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

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

Sensitivity analysis

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

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

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

Summary of findings and assessment of the certainty of the evidence

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 texts for eligibility, of which we excluded 221 references; we excluded 137 of these references (115 studies) with reasons recorded in the review (see Excluded studies).

We included six references (six studies). There are two studies (two references) awaiting classification, because we were uncertain if the participants were randomised in these studies and are waiting to get a response from the authors (Mehboob 2019; Samarei 2014). See Characteristics of studies awaiting classification. We did not identify any ongoing studies.

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

Figure 1. Study flow diagram.

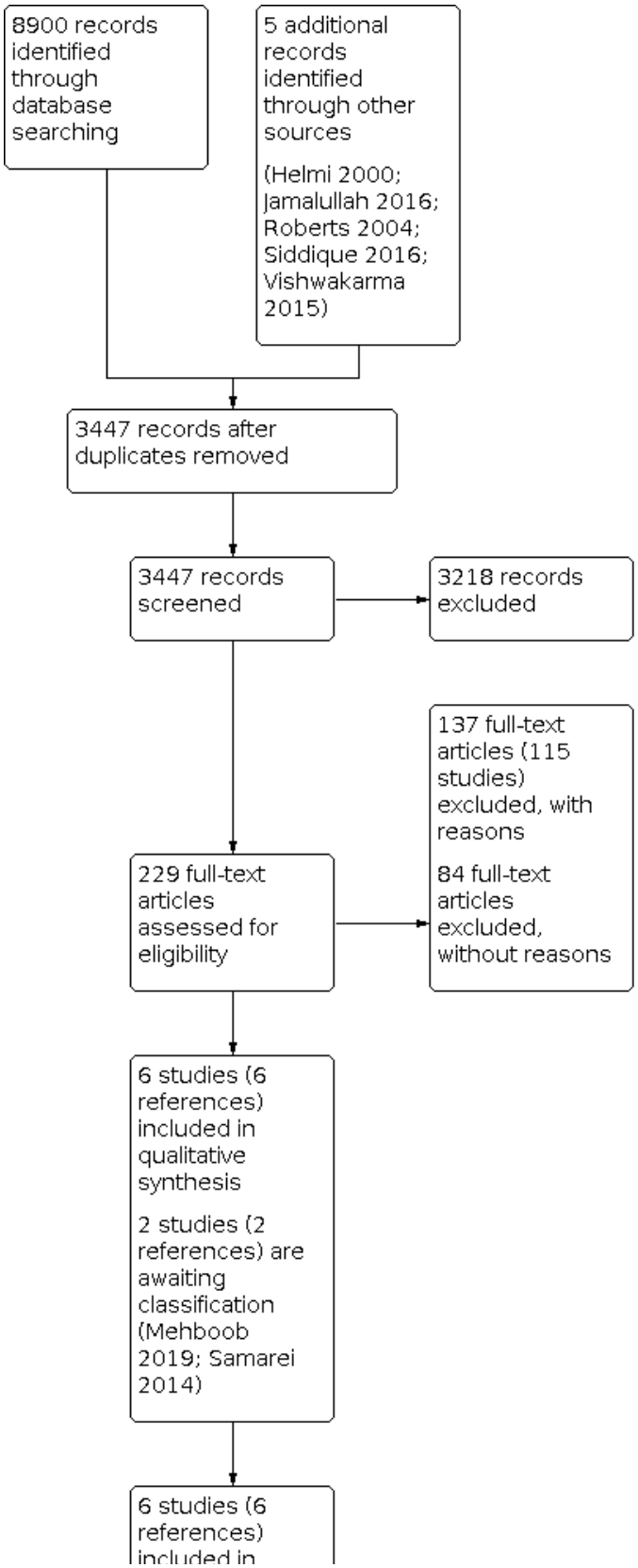
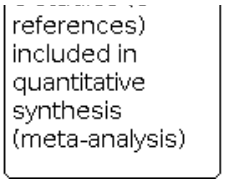


Figure 1. (Continued)



Included studies

We included six studies (de Miguel 1999; Esposito 1990; Esposito 1992; Povedano 1995; Ramos 2003; Yuen 1994). There were two studies that appeared to report on the same set of participants due to the same study design, inclusion criteria, location of study and overlap in key authors (de Miguel 1999; Ramos 2003). Ramos 2003 had 50 participants, rather than 25 per treatment arm, and had an additional treatment arm (six versus five). The proportion of patients achieving resolution of ear discharge was identical. We wrote to the authors to clarify whether these data were obtained from the same set of participants and the authors clarified that these are separate studies. We therefore included both studies in the review.

Table 3 provides a summary of the included studies.

Study design

Three studies were two-arm trials (Esposito 1992; Povedano 1995; Yuen 1994). The remaining three studies were multi-arm trials: Esposito 1990 (three arms), de Miguel 1999 (five arms) and Ramos 2003 (six arms). For this review, only the data that relate to the comparison of topical and systemic antibiotics were included from multi-arm trials. Details of other study arms can be found in the Characteristics of included studies table.

All studies were parallel-group and were reported as "randomised controlled trials". Four studies were from single centres (de Miguel 1999; Esposito 1990; Esposito 1992; Yuen 1994). One was a multicentre study (Ramos 2003). It was unclear in how many centres the remaining study was conducted (Povedano 1995).

Sample size

The total sample size for all of the studies was 445 participants. The sample size by study ranged from 40 to 150, with three of the six studies having 60 participants included.

Unit of randomisation

All studies randomised according to the number of participants, rather than the number of ears. None of the studies provided information regarding methods for assessing ear discharge outcomes in individuals with bilateral disease.

Location

Three studies were conducted in Spain (de Miguel 1999; Povedano 1995; Ramos 2003), two were conducted in Italy (Esposito 1990; Esposito 1992), and one was conducted in Hong Kong (Yuen 1994). See Table 3 for further details.

Setting of trial

Two trials were described as taking place within a university clinic (Esposito 1990; Esposito 1992), and a third was described as being conducted in the otorhinolaryngology outpatient clinic of a university hospital (Yuen 1994). Two trials were conducted in a general hospital (de Miguel 1999; Povedano 1995). The final trial was a multicentre study, conducted at three tertiary hospitals (Ramos 2003).

The years in which the studies were conducted was not always well reported. One study was most likely to have been conducted in the 1980s (Esposito 1990). Four further studies were published in the 1990s (de Miguel 1999; Esposito 1992; Povedano 1995; Yuen 1994). The final study was published in 2003 (Ramos 2003). See Table 3 for additional information.

Population

Age and sex

Two studies included a mixture of adults and children. The mean age in de Miguel 1999 was reported as 39.6 years, although 17/125 participants were children. The mean age was not reported by Ramos 2003, but ages ranged from 5 to 73 years old, and 36/300 participants were children.

Four studies included only adult participants (Esposito 1990; Esposito 1992; Povedano 1995; Yuen 1994). The age of participants was reported as a mean of 38 years for Esposito 1990, 44 years for Povedano 1995 and a median of 35 years for Yuen 1994. The mean age was not reported in Esposito 1992.

All studies reported the inclusion of both male and female participants. Five studies reported the characteristics of all individuals randomised in the study (de Miguel 1999; Esposito 1990; Esposito 1992; Povedano 1995; Ramos 2003). Of the 605 individuals included in these trials, 287 (47.4%) were female and 318 (52.6%) were male, with the percentage of females in studies ranging from 44.7% to 58%. One study reported the baseline characteristics for those who completed the trial, excluding those who provided no outcome data, and included 58.9% female and 41.4% male participants (Yuen 1994).

High-risk populations

None of the studies reported the inclusion of any of the 'high-risk' populations as defined by our inclusion criteria (cleft palate, Down syndrome, Indigenous groups, immunocompromised patients). Esposito 1990 stated that "no patient had diabetes or any other comorbidities".

Diagnosis

CSOM was the main diagnosis for inclusion in four studies (Esposito 1990; Esposito 1992; Povedano 1995; Yuen 1994). Ramos 2003 and de Miguel 1999 included patients with chronic ear discharge, but on a breakdown of the participants more than 50% had CSOM and so we included in the results of this review.

Three studies provided the method for confirmation of diagnosis of tympanic membrane perforation or presence of mucopurulent discharge via otoscopy or microscopic examination (de Miguel 1999; Esposito 1992; Ramos 2003). One further study provided information on the size of the tympanic perforation, therefore we presumed it to have used otoscopic examination (Yuen 1994). The two remaining studies did not describe the diagnostic method used for identifying tympanic membrane perforation (Esposito 1990; Povedano 1995).

Duration of ear discharge

Esposito 1992 reported that participants had the presence of discharge for at least 15 days before entering the study. Ramos 2003 stated that discharge was present for "more than 6 weeks or sporadically with 3 or more episodes in the last year". Four studies did not report the duration of ear discharge (de Miguel 1999; Esposito 1990; Povedano 1995; Yuen 1994).

Other important effect modifiers

One study did not report on any important effect modifiers (Povedano 1995).

Three studies reported on the number of participants with alternative diagnoses for ear discharge (de Miguel 1999 (n = 17, 13.6%); Ramos 2003 (n = 42, 14%); Yuen 1994 (n = 0, 0%)). Two studies reported on the number of participants who had previously had grommets inserted (Ramos 2003 (n = 12, 4%); Yuen 1994 (n = 0, 0%)).

Two studies reported on the number of participants who had previously had ear surgery (de Miguel 1999; Ramos 2003). The study by de Miguel 1999 reported that 31 participants (24.8%) had ear discharge that occurred after surgery, and Ramos 2003 reported that 73 participants (24.3%) had previous ear surgery. The reasons and type of surgery were not reported in either study. Four studies reported on the number of participants who had received antibiotics for CSOM previously (de Miguel 1999; Esposito 1990; Esposito 1992; Ramos 2003), which ranged from 63% to 67%.

Intervention

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

Systemic antibiotics

Four studies included an oral quinolone (ciprofloxacin) as the systemic antibiotic, in doses ranging from 250 mg to 500 mg twice daily (de Miguel 1999; Esposito 1990; Povedano 1995; Ramos 2003).

Esposito 1992 used intramuscular gentamicin (80 mg twice daily) and Yuen 1994 used oral amoxicillin-clavulanic acid (375 mg three times daily).

Topical antibiotics

All of the included studies used topical quinolones. Five studies used topical ciprofloxacin drops. Povedano 1995 used twice daily drops (concentration 250 µg/mL, five drops per dose), as did Esposito 1990 (concentration 250 µg/mL, three drops per dose) and Esposito 1992 (concentration 250 mg/mL, four drops per dose). Two studies used two different concentrations of topical ciprofloxacin ear drops (0.2% and 0.5% three times daily). For the purposes of this review we have combined the data from the two groups for analysis (de Miguel 1999; Ramos 2003).

One study used topical ofloxacin ear drops (0.3%, three times daily; Yuen 1994).

Background treatment

Two studies reported aural toileting at baseline. This included aspiration and cleaning of secretions in one study (de Miguel 1999), and suction clearance of aural pus under microscopy for the second study (Yuen 1994). The remaining four studies did not mention the use of any aural toileting (Esposito 1990; Esposito 1992; Povedano 1995; Ramos 2003).

Duration of intervention

All six studies had a duration of intervention of two weeks or less. Three studies treated participants for seven days (de Miguel 1999; Ramos 2003; Yuen 1994). Two studies treated participants for a minimum of five days; patients who were not 'cured' by five days continued treatment until they were cured, up to a maximum of 10 days (Esposito 1990; Esposito 1992). The final study treated participants for 10 days (Povedano 1995).

Comparisons

Four studies compared topical quinolones to oral quinolones:

- de Miguel 1999 - topical ciprofloxacin versus oral ciprofloxacin.
- Esposito 1990 - topical ciprofloxacin versus oral ciprofloxacin.
- Povedano 1995 - topical ciprofloxacin versus oral ciprofloxacin.
- Ramos 2003 - topical ciprofloxacin versus oral ciprofloxacin.

One study compared a topical quinolone to an intramuscular aminoglycoside:

- Esposito 1992 - topical ciprofloxacin versus intramuscular gentamicin.

One study compared a topical quinolone to an oral penicillin with beta-lactamase inhibitor:

- Yuen 1994 - topical ofloxacin versus oral amoxicillin-clavulanic acid.

Outcomes

Resolution of ear discharge

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

Health-related quality of life using a validated instrument

No studies reported on health-related quality of life.

Ear pain (otalgia) or discomfort or local irritation

No studies specifically reported on ear pain, discomfort or local irritation. Two studies reported that no side effects were reported by any participant, but it is unclear whether this included ear pain, discomfort or irritation (Esposito 1990; Esposito 1992).

Hearing

Four studies indicated that they measured hearing after treatment, but did not provide information on the frequencies that were

tested, or any data on the outcome (Esposito 1990; Esposito 1992; Ramos 2003; de Miguel 1999). One study indicated the frequencies at which hearing was tested (0.5 kHz, 1 kHz, 2 kHz and 4 kHz), but only reported the results narratively (Yuen 1994).

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

No study reported any serious complications.

Suspected ototoxicity

Four studies reported on ototoxicity in some way, but there was a lack of clarity over the methods used to assess this (de Miguel 1999; Esposito 1992; Ramos 2003; Yuen 1994). Three studies indicated that post-treatment audiometry was performed to assess ototoxicity, but no definition of ototoxicity was provided (de Miguel 1999; Esposito 1992; Ramos 2003). One study reported carrying out pre- and post-treatment audiograms of bone conduction thresholds at frequencies of 0.5 kHz, 1 kHz, 2 kHz and 4 kHz but it was not clear if there was a difference between groups in the results, which were reported narratively (Yuen 1994).

Funding

Esposito 1990 and Esposito 1992 reported receiving the intervention medication from a pharmaceutical company. One study reported financial support from a research grant, but no pharmaceutical funding (Yuen 1994). The remaining three studies did not provide any information on funding sources (de Miguel 1999; Povedano 1995; Ramos 2003).

Declarations of interest

None of the included studies provided any information on declarations of interest from the authors.

Excluded studies

We excluded 137 papers (115 studies) after reviewing the full text. Further details for the reasons for exclusion can be found in the Characteristics of excluded studies table. These are the main reasons for exclusion:

We excluded 35 studies (52 references) as the comparisons were not appropriate for this review but were relevant to another review in this suite (Asmatullah 2014; Eason 1986; Fliss 1990; Fradis 1997; Ghosh 2012; Gupta 2015; Gyde 1978; I-HEAR-BETA (in-progress study); Jamallulah 2016; Jaya 2003; Kasemsuwan 1997; Kaygusuz 2002; Legent 1994; Liu 2003; Loock 2012; Lorente 1995; Macfadyen 2005; Minja 2006; Mira 1993; Nawasreh 2001; Nwokoye 2015; Onali 2018; Papastavros 1989; Renuknanada 2014; Rotimi 1990; Sanchez Gonzales 2001; Siddique 2016; Somekh 2000; Tong 1996; Tutkun 1995; van der Veen 2007; van Hasselt 1997; van Hasselt 1998a; Vishwakarma 2015).

We excluded 33 studies (34 references) on the basis of their study design (Agro 1998; Arguedas 1993; Aslan 1998; Baba 1986; Baba 2008; Baba 2008a; Bakir 2013; Brook 1979; Brook 1980; Browning 1984; Deguchi 1985; Deguchi 1986; Deitmer 2002; Esposito 2000; Gehanno 1997; Hwang 2015; Jahn 1984; Jang 2004; Kadar 2003; Kenna 1986; Kothari 1969; Liu 1990; Merifield 1993; Morgon 1976; Poliakova 1991; Singhal 1992; Sugiyama 1981; Sultan 2017; Sumitsawan 1995; Supiyaphun 1995; Tachibana 1986; Van de Heyning 1986; Wintermeyer 1997).

We excluded 32 studies (35 references) due to the population characteristics included in their study (Abbott 2016; Adler 2000; Baba 1982b; Baba 1983; Baba 1983b; Baba 1983c; Baba 1987; Berman 1990; Block 2000; Bogomil'skii 1999; Bross Soriano 1996; Clayton 1990; Garcia-Rodriguez 1993; Granath 2007; Gyde 1981; Gyde 1982; IRCT20130427013136N6; IRCT2016082313136N4; Kovacic 1999; Kurilin 1976; Lancaster 1999; Lancaster 2003; Lang 1992; Lautala 1983; Mesure 1973; Principi 1995; Quick 1973; Quick 1975; Roberts 2004; Saez-Llorens 2005; Stenstrom 1991; van Dongen 2014).

We excluded nine studies (10 references) as the interventions were outside of our protocol (Browning 1983; Browning 1983b; Connolly 1997; CTRI/2019/09/021197; Dellamonica 1995; ISRCTN12149720; ISRCTN84220089; Jiang 2016; Khanna 2000; Li 2004).

Six studies (six references) had multiple reasons for exclusion (Baba 1980; Fombeur 1994; Hemlin 1997; Kashiwamura 2004; Khon 2012; 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.

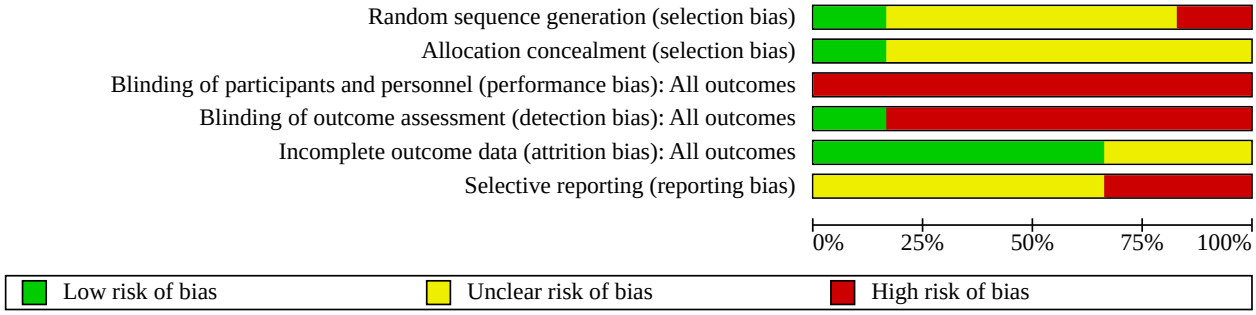
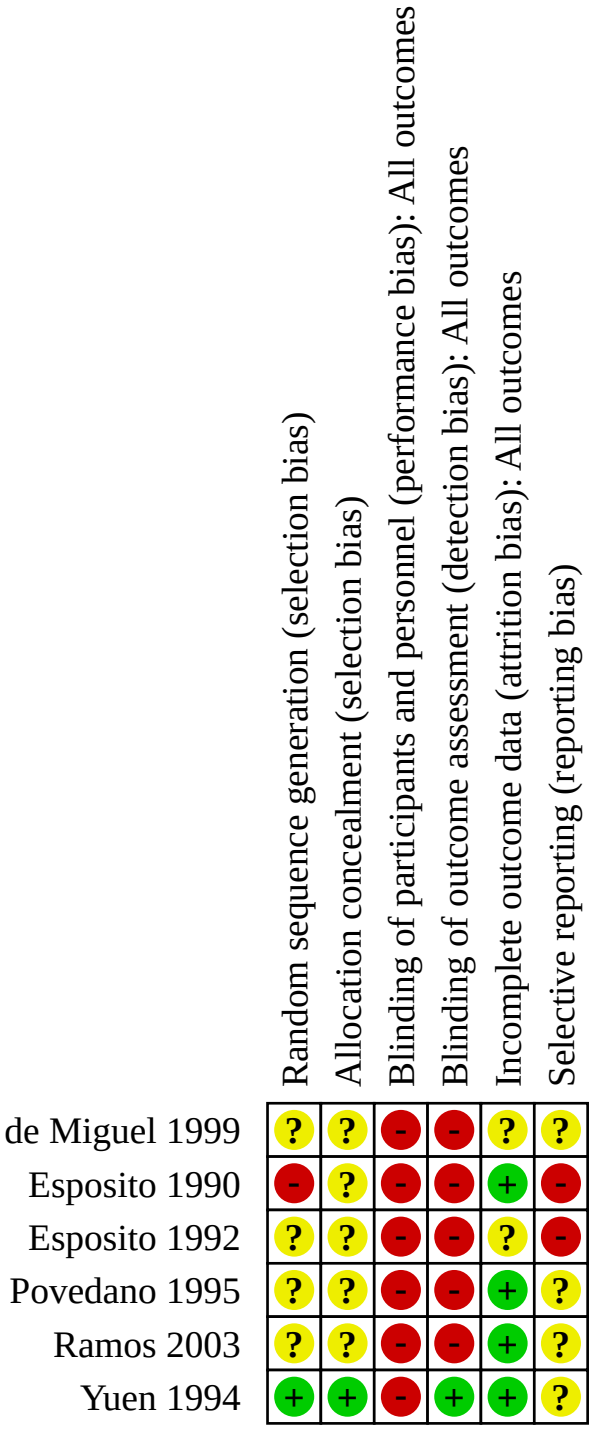


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Randomisation

We judged one study to have had adequate sequence generation (Yuen 1994). We assessed one study as having a high risk of bias as more than half of the patients (38/60) were previously unsuccessfully treated with at least five days of antibiotics, and it was unclear whether this was distributed across groups in a balanced manner (Esposito 1990). In addition, a higher proportion of patients (12/20) in the oral ciprofloxacin only group had *Pseudomonas* compared to the other groups (8/20), introducing a high risk of bias. The remaining four studies did not describe the method of sequence generation and we considered all of these to have unclear risk of bias.

Allocation concealment

We assessed one study to be at low risk of bias (Yuen 1994). We judged the remaining five studies as being at unclear risk of bias as they did not describe the methods used for allocation concealment.

Blinding

Performance bias

All six of the studies were non-blinded and treatments were administered by the patients. Therefore, we assessed the risk of performance bias as high.

Detection bias

We assessed one study as having low risk of bias, as they described how they had attempted to blind the outcome assessors (Yuen 1994). We assessed the remaining five studies as being at high risk as they did not describe any attempts to blind outcome assessors and the outcomes assessed were subjective.

Incomplete outcome data

We assessed the risk of attrition bias as low for four studies (Esposito 1992; Povedano 1995; Ramos 2003; Yuen 1994). We assessed two studies as being at unclear risk of bias as the number of dropouts was not reported (de Miguel 1999; Esposito 1992).

Selective reporting

No protocols were available for any of the six studies. We assessed two studies as being at high risk of bias as some of the results mentioned in the methods section were not fully presented in the results section (Esposito 1990; Esposito 1992). For Esposito 1990, "cure" or resolution of discharge was only reported at one time point, most likely at 14 days after the end of treatment, but the results at other time points are described in the methods section of the paper (24 hours after the end of treatment, i.e. 6 to 11 days) and these were not reported. Similarly, Esposito 1992 showed a table of the number of people who were "cured", "improved" or "failed" treatment, but did not indicate the time point of measurement, and two of the time points measured were not reported. We assessed the remaining four studies as being at unclear risk of bias for selective reporting.

Other potential sources of bias

The studies did not describe how outcomes were measured and defined for patients with bilateral ear disease. Based on the information reported and the nature of the comparison, we assumed that the studies had randomised by patient and the number of events corresponds to patients rather than ears.

Effects of interventions

See: **Summary of findings 1** Topical quinolone compared to oral quinolone for chronic suppurative otitis media; **Summary of findings 2** Topical quinolone compared to intramuscular gentamicin for chronic suppurative otitis media; **Summary of findings 3** Topical quinolone compared to oral amoxicillin-clavulanic acid combination for chronic suppurative otitis media

Comparison 1: Topical quinolone versus oral quinolone

Four studies (325 participants) were included in this comparison (Table 3):

- de Miguel 1999 (75 participants): topical ciprofloxacin (0.2% or 0.5%, three drops three times daily) against oral ciprofloxacin (500 mg twice daily) for 7 days.
- Esposito 1990 (40 participants): topical ciprofloxacin (250 µg/mL, three drops twice daily) against oral ciprofloxacin (250 mg twice daily) for up to 10 days.
- Povedano 1995 (60 participants): topical ciprofloxacin (250 µg/mL, five drops twice daily) against oral ciprofloxacin (500 mg twice daily) for 10 days.
- Ramos 2003 (150 participants): topical ciprofloxacin (0.2%/0.5%, 0.5 mL three times daily) against oral ciprofloxacin (500 mg twice daily) for 7 days.

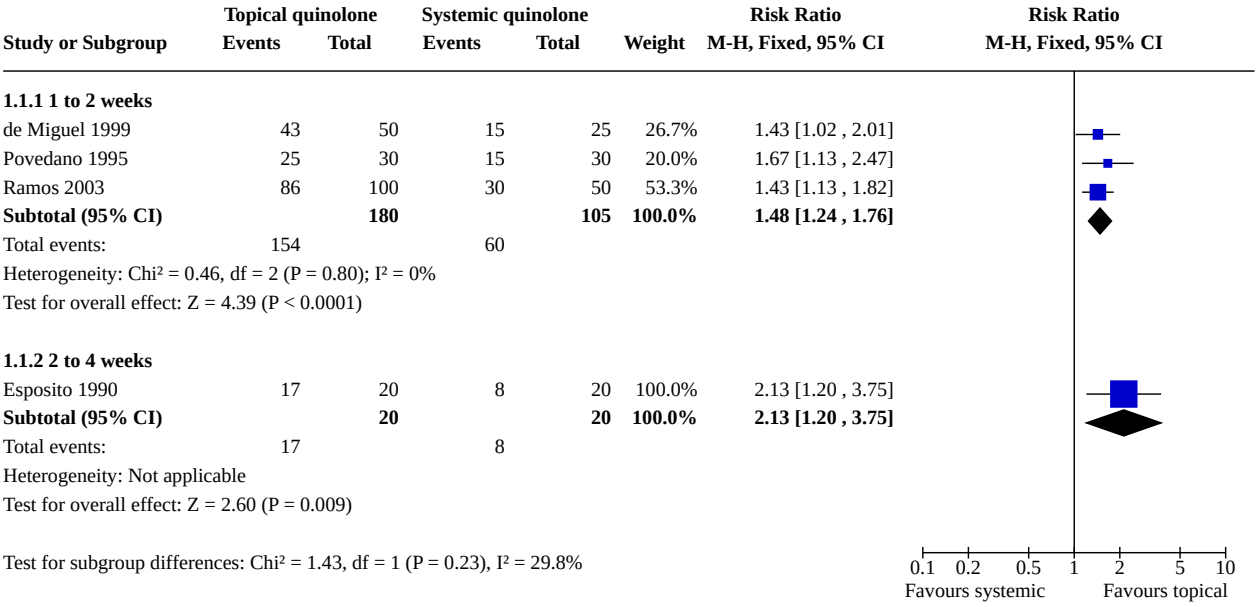
In these studies, aural toileting was either not mentioned or limited to the first visit. See Summary of findings 1.

Resolution of ear discharge or 'dry ear'

Between one week and up to two weeks

Topical quinolones may be slightly more effective at resolving ear discharge at one to two weeks than oral quinolones (risk ratio (RR) 1.48, 95% confidence interval (CI) 1.24 to 1.76; 285 participants; 3 studies; I^2 = 0%; low-certainty evidence; Figure 4; Analysis 1.1).

Figure 4. Forest plot of comparison: 1 Topical quinolone versus oral quinolone, outcome: 1.1 Resolution of ear discharge.



Two weeks to up to four weeks

Esposito 1990 reported resolution of ear discharge at two to four weeks (RR 2.13, 95% CI 1.20 to 3.75; 40 participants).

After four weeks

None of the studies reported results after four weeks.

Health-related quality of life using a validated instrument

None of the studies reported this outcome.

Ear pain (otalgia) or discomfort or local irritation

None of the studies reported this outcome.

Hearing

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

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

None of the studies reported this outcome.

Suspected ototoxicity

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

de Miguel 1999 reported that the data did not show cochleovestibular dysfunction during treatment or further follow-up. They also stated that all post-treatment audiometry showed no evidence of ototoxicity, either for the oral or topical routes. However, no definition of 'ototoxicity' was provided and it is likely to be standard audiometry rather than bone conduction studies.

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

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

Subgroup analysis

We did not undertake any subgroup analysis as there were no differences in any of the identified studies with regards to the planned subgroups.

Comparison 2: Topical quinolone versus intramuscular gentamicin

Only one study (Esposito 1992; 60 participants) compared topical ciprofloxacin (250 mg/mL, twice daily) with intramuscular gentamicin injections (80 mg twice daily) for up to 10 days. No concurrent treatments or aural toileting were reported (see Summary of findings 2).

Resolution of ear discharge or 'dry ear'

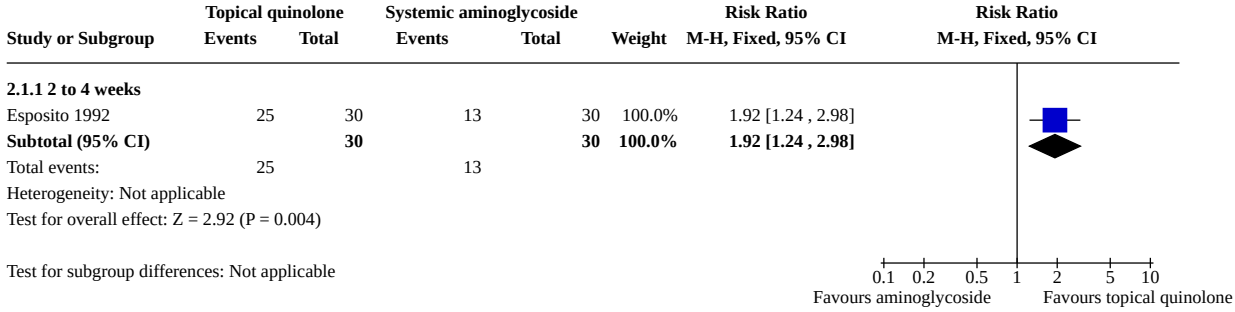
Between one week and up to two weeks

The study did not report results for this time point.

Between two weeks and up to four weeks

Topical ciprofloxacin may increase the resolution of ear discharge at two to four weeks compared to intramuscular gentamicin, but the evidence is very uncertain (RR 1.92, 95% CI 1.24 to 2.98; 60 participants; Figure 5; Analysis 2.1).

Figure 5. Forest plot of comparison: 3 Topical quinolone versus intramuscular (IM) gentamicin, outcome: 3.1 Resolution of ear discharge.



After four weeks

The study did not report results for this time point.

Health-related quality of life using a validated instrument

Esposito 1992 did not report this outcome.

Ear pain (otalgia) or discomfort or local irritation

Although this outcome was not specifically reported by Esposito 1992, the authors reported that "no side effect was recorded in any patient" (very low-certainty evidence).

Hearing

Esposito 1992 indicated that audiometry was performed after treatment, but only reported that "no worsening of the audiometric function related to local or parenteral therapy was observed" (very low-certainty evidence).

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

Esposito 1992 reported that "no side effect was recorded" and did not report that any participant died or had any intracranial or extracranial complications (very low-certainty evidence).

Suspected ototoxicity

Audiometric measurement and vestibular tests were performed before and 24 hours after the end of the therapy and "no side effect was recorded" (very low-certainty evidence).

Subgroup analysis

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

Comparison 3: Topical quinolone versus (oral) systemic beta-lactams

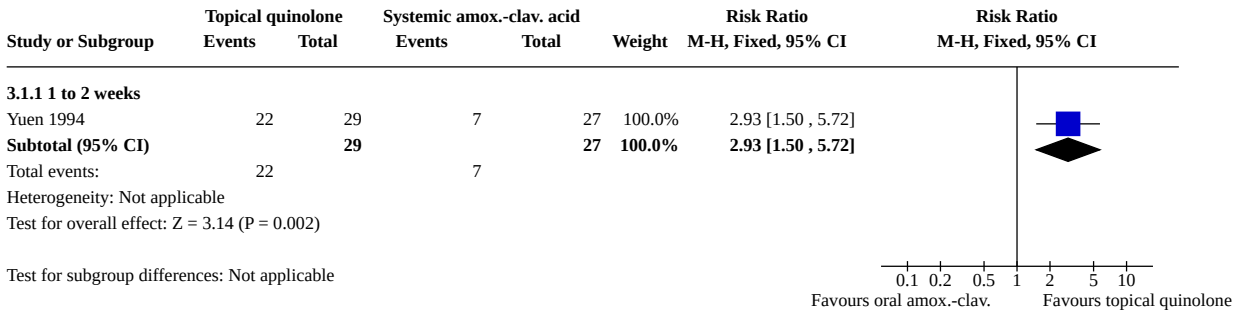
Only one study (Yuen 1994; 60 participants) compared ofloxacin ear drops (0.3% three times daily) with oral amoxicillin-clavulanic acid (375 mg, three times daily) for seven days. All participants underwent ear cleaning at the first treatment but no other concurrent treatments were mentioned (see Summary of findings 3).

Resolution of ear discharge

Between one week and up to two weeks

We are uncertain if topical ofloxacin ear drops increase resolution of ear discharge compared with oral amoxicillin-clavulanic acid as although Yuen 1994 (56 participants) reported an increase in resolution with topical ofloxacin, the limitations in the study and small sample size reduce our certainty in the result (RR 2.93, 95% CI 1.50 to 5.72; 56 participants, very low-certainty evidence; Figure 6; Analysis 3.1).

Figure 6. Forest plot of comparison: 2 Topical quinolone versus oral amoxicillin-clavulanic acid, outcome: 2.1 Resolution of ear discharge.



One participant was excluded from this analysis as they discontinued treatment. We conducted a sensitivity analysis to assess the effect of re-including this participant, with the assumption that they were not cured by the intervention. The results remained in favour of topical ofloxacin (RR 3.03, 95% CI 1.55 to 5.95; Analysis 3.2).

Two weeks to up to four weeks

The study did not report results for resolution of ear discharge at this time point.

After four weeks

The study did not report results for this time point.

Health-related quality of life using a validated instrument

Yuen 1994 did not report this outcome.

Ear pain (otalgia) or discomfort or local irritation

Although this outcome was not specifically reported, Yuen 1994 reported that "no patient of the ofloxacin-treated group complained of adverse side effects. There was no hypersensitivity reaction to the topical ofloxacin" (very low-certainty evidence).

Hearing

Yuen 1994 reported that "there were no significant differences between the pre-treatment and post-treatment pure-tone audiograms of bone conduction thresholds at frequencies of 0.5, 1, 2, and 4kHz" (very low-certainty evidence). No further details were provided.

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

Yuen 1994 did not report did not report this outcome.

Suspected ototoxicity

Although Yuen 1994 reported the use of patient diaries to record tinnitus and dizziness, the results for this were not reported. Bone conduction studies were also completed and the study authors reported that "there were no significant differences between the pre-treatment and post-treatment pure-tone audiograms of bone conduction thresholds at frequencies of 0.5, 1, 2, and 4kHz" (very low-certainty evidence). No further details were provided.

Subgroup analysis

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

DISCUSSION

Summary of main results

We included six studies reporting on three different comparisons. Due to the choice of outcome measures used in these studies and the incomplete reporting of results, for many of the proposed comparisons we were not able to find a substantial amount of evidence.

Comparison 1. Topical versus systemic administration of the same type of antibiotics (quinolones)

We included four studies (325 participants), which compared topical versus systemic (oral) administration of ciprofloxacin and found that topical administration may slightly increase resolution of ear discharge at one to two weeks compared with systemic administration (risk ratio (RR) 1.48, 95% confidence interval (CI) 1.24 to 1.76; 285 participants; 3 studies; I^2 = 0%; low-certainty evidence). In these studies, aural toileting was either not mentioned or limited to the first visit. Resolution at two to four weeks was also higher for the topical quinolone group (RR 2.13, 95% CI 1.20 to 3.75; 40 participants; 1 study). The studies did not report outcomes beyond four weeks. Two studies reported otoscopic confirmation of CSOM, whilst the other two studies were unclear. Three studies reported that they did not suspect ototoxicity in any participants, but it is unclear how this was measured (very low-certainty evidence). No studies reported on health-related quality of life, ear pain/discomfort/irritation or serious complications, and no data were presented for hearing outcomes despite three studies describing it as having been measured. See Summary of findings 1.

Comparison 2. Topical versus systemic administration of different types of antibiotics (topical quinolones versus systemic aminoglycosides)

We included one study (60 participants), which compared topical ciprofloxacin against gentamicin injected intramuscularly. No aural toileting was reported. No results for resolution of ear discharge were presented at either one to two weeks or after four weeks. At two to four weeks of follow-up, although the authors reported a higher resolution rate in the topical quinolone group (RR 1.92, 95% CI 1.24 to 2.98; 60 participants), we are very uncertain about this finding due to study limitations and imprecision. It was unclear if this study used otoscopic confirmation of CSOM. The study did not report any "side effects", from which we assumed no ear pain, suspected ototoxicity or serious complications occurred (very low-certainty evidence). The study stated that "no worsening of the audiometric function related to local or parenteral therapy was observed" (very low-certainty evidence). Health-related quality of life was not reported. See Summary of findings 2.

Comparison 3. Topical versus systemic administration of different types of antibiotics (topical quinolones versus systemic amoxicillin-clavulanic acid)

One study compared topical ofloxacin versus oral amoxicillin-clavulanic acid, where all participants underwent suction clearance at the first visit. This study found that topical quinolones may result in more people having resolution of ear discharge at one to two weeks of follow-up (RR 2.93, 95% CI 1.50 to 5.72; 56 participants, very low-certainty evidence), but the very small sample size and study limitations reduced our certainty in the results. It was unclear if this study used otoscopic confirmation of CSOM. The study reported no adverse events in the topical antibiotic group, including otalgia (ear pain) and hypersensitivity reactions. There were no significant differences in hearing (air-conduction hearing levels) reported (very low-certainty evidence). Potential ototoxicity was measured in the topical antibiotic group with bone-conduction audiometry and it was reported that there was no difference between pre- and post-treatment bone-conduction hearing levels. Participants were asked to record any tinnitus, dizziness or suspected hearing loss symptoms, but reporting was

limited to a statement that "none complained of adverse side effects" in the topical antibiotic group. Health-related quality of life and serious complications were either not measured or not reported. See Summary of findings 3.

Overall completeness and applicability of evidence

The overall completeness of the evidence base was very limited. Only six studies were available over the three comparisons, and only a single study was included for each of the second and third comparisons. All studies were conducted at tertiary or secondary care centres including hospital departments and specialist clinics. All studies were published at least 15 years ago (and up to 30 years ago). Two studies reported otoscopic confirmation of CSOM whilst for four studies this was unclear. Although we planned subgroup analyses for different participant characteristics (age, high-risk, ventilation tubes), treatment duration and spectrum of antibiotic activity, these were not carried out because the data were not available, data were not clearly reported or heterogeneity was not observed. No studies examined children under two years of age and this leaves us with no information on this important patient group. No studies included participants classed as 'high-risk' in our protocol. 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. All studies were conducted in high-resource settings in Western European and East Asian countries (five in Western Europe, one in China (Hong Kong)), which have a below average estimated incidence of CSOM of fewer than four cases per thousand people (Monasta 2012). Disease in low-resource settings may be more severe as well as more prevalent.

Two of the commonly used topical antibiotics were quinolones and aminoglycosides. Although we have limited evidence showing that topical application of quinolones may be slightly more effective with respect to resolution of ear discharge than systemic (oral) quinolones at one to two weeks, we have not found any studies comparing topical versus systemic aminoglycosides. Therefore, we are unable to generalise with regard to whether topical administration of antibiotics is always better than systemic administration when the same type or class of antibiotics is used. The spectrum of activity and bioavailability of antibiotics are factors that might influence their effectiveness by different routes of administration.

We are also unable to compare the safety of topical versus systemic aminoglycosides regarding the risk of ototoxicity. Whilst there were no significant differences reported in mean hearing levels or suspected worsening of audiological measurements, the outcome was poorly reported across all studies. The efficacy of topical compared to systemic antibiotics is likely to be influenced by the sensitivity of the micro-organisms present to the antibiotic used. We were unable to carry out a subgroup analysis of the spectrum of antibiotic activity as the data were either not in the included studies or heterogeneity was not observed, which leaves us with no information on this aspect of antibiotic treatment. Aural toileting prior to application of topical antibiotics may also influence the effectiveness of topical antibiotic treatment. All the studies included had limited use of aural toileting, either only mentioning microsuction in the initial assessment (two studies), or not mentioning any form of aural toileting (four studies).

There were very few data for outcomes other than resolution of ear discharge. No studies reported health-related quality of life. Adverse events, suspected ototoxicity and serious complications were all poorly reported. The length of follow-up in all studies was between one and four weeks, meaning that there was limited evidence regarding the long-term effectiveness of topical versus systemic antibiotics for the resolution of discharge for people with CSOM.

Quality of the evidence

The certainty of the evidence for all outcomes in these comparisons was low or very low (GRADE assessment). This was mainly due to two factors: the **risk of bias** in the studies and **imprecision**. In many cases the results were imprecise due to the small number of participants available for analysis (resulting in large confidence intervals). There were important limitations in the methods of study conduct and reporting in nearly all of the studies. Five (of six) of the studies had unclear randomisation and allocation concealment and none of the studies blinded participants or study personnel to treatment group.

Accuracy of the diagnosis was also a potential issue throughout the studies included in this review. Of the six included studies, only two described the use of otoscopic confirmation of resolution of discharge. This may have impacted on the accuracy of the diagnostic outcome and therefore the response to treatment.

Potential biases in the review process

Within this series of CSOM Cochrane Reviews the potential for publication bias has been identified as an issue. In some reviews, unpublished studies were found and included in the review (Brennan-Jones 2020a; Head 2020a; Head 2020b), and there is a suspicion that further unpublished trials may have been completed. It is unknown whether this is a risk with this review.

Agreements and disagreements with other studies or reviews

This review is part of a series of reviews on CSOM (Bhutta 2020; Brennan-Jones 2020a; Brennan-Jones 2020b; Head 2020a; Head 2020b). A companion review looks at the effectiveness of systemic antibiotics for the treatment of CSOM (Chong 2021).

Two other reviews evaluated whether topical and systemic antibiotics are effective for the treatment of CSOM (Brennan-Jones 2020a and Chong 2021, respectively), and provided information that is complementary to the findings of this review. The potential ototoxicity of topical quinolones versus topical aminoglycosides was also compared in another review in this series (Brennan-Jones 2020a). In Brennan-Jones 2020a, topical antibiotics were compared against placebo and other types of topical antibiotics. Despite the serious limitations of the evidence (very low-certainty), the review suggested that topical antibiotics (aminoglycosides and quinolones) may be effective (compared to a placebo) as a single treatment, and when used on top of systemic antibiotics. The efficacy of the addition of topical steroids to topical antibiotics for the treatment of CSOM was also included in this suite of reviews. Given the very low certainty of the evidence included, it was not clear whether there was any benefit to adding a steroid to topical antibiotics alone, in terms of resolution of ear discharge (Brennan-Jones 2020b).

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

AUTHORS' CONCLUSIONS

Implications for practice

There is a limited amount of low-quality evidence available to examine whether topical or systemic antibiotics are more effective in achieving resolution of ear discharge for people with CSOM. However, amongst this uncertainty there is some evidence to suggest that the topical administration of antibiotics may be slightly more effective than systemic administration in achieving resolution of ear discharge (dry ear) at one to two weeks. There is limited evidence available regarding different types of antibiotics. It is not possible to determine with any certainty whether 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, show that there is low-certainty evidence that, for people with CSOM, treatment with topical antibiotics may be beneficial in improving the short-term resolution of ear discharge when compared to a systemic antibiotic. Potential adverse effects and hearing outcomes were poorly reported and the impact of background treatment with aural toileting is also unclear. The low certainty of the evidence for CSOM treatments in this review is common throughout this suite of seven reviews of CSOM treatments.

There is insufficient evidence to address the efficacy and harms of antibiotics for high-risk groups such as immunocompromised patients or Indigenous populations.

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

- What are the relative effects of topical antibiotics compared with the same systematic antibiotics?

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

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

Suggestions for future trials

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

Design and methods

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

Population

- Diagnosis of CSOM should be according to the World Health Organization criteria (WHO 2004), be otoscopically confirmed, include an assessment of hearing level, and record the duration of discharge.
- Potentially important patient characteristics (such as presence of ear grommets) should be recorded and presented in the report.
- If patients from 'high-risk' groups are included, these characteristics should be accounted for and explored in the design of the study.

Interventions

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

used across the treatment groups (including aural toileting), should be provided.

Outcomes

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

ACKNOWLEDGEMENTS

We are grateful to Mr Iain Swan for peer reviewing the protocol and review, and to consumer referee Joan Blakely for her helpful comments at all stages. We would also like to thank Dr Adrian James, as Acting Co-ordinating Editor for Cochrane ENT, for his insightful comments and advice, and the other members of the Cochrane ENT editorial board for their input and encouragement.

We would like to sincerely thank Jenny Bellorini and Samantha Cox from the Cochrane ENT team for their invaluable help, which has enabled the completion of this suite of reviews. In addition, we thank Professor Amanda Leach for her contributions towards the project and we are grateful to Takashi Fujiwara, Maria Paula Garcia and Rina Shoki for assisting with the data extraction and risk of bias assessments.

We would also like to thank the following clinicians, scientists and consumers who provided comments on the initial scoping review and prioritisation exercise for this suite of reviews into CSOM: Amanda Leach, Chris Perry, Courtney McMahen, De Wet Swanepoel, Deborah Lehmann, Eka Dian Safitri, Francis Lannigan, Harvey Coates, Has Gunasekera, Ian Williamson, Jenny Reath, Kathy Brooker, Kathy Currie, Kelvin Kong, Matthew Brown, Pavanee Intakorn, Penny Abbott, Samantha Harkus, Sharon Weeks, Shelly Chadha, Stephen O'Leary, Victoria Stroud and Yupitri Pitoyo.

We are also indebted to Erika Ota from Cochrane Japan for organising a group of MSc students, Shunka Cho, Kiriko Sasayama, Asuka Ohashi, Noyuri Yamaji and Mika Kato, to help with translating and identifying primary studies for inclusion or exclusion for this suite of reviews.

This project was funded by the NHMRC Centre of Research Excellence in Ear and Hearing Health of Aboriginal and Torres Strait Islander Children (NHMRC CRE_ICHEAR). The contents of the publications arising from this work are solely the responsibility of the authors and do not reflect the views of NHMRC.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to Cochrane ENT. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

de Miguel 1999 *{published data only}*

De Miguel Martinez I, Vasallo Morillas JR, Ramos Macias A. Antimicrobial therapy in chronic suppurative otitis media [Terapeutica antimicrobiana en otitis media cronica supurada]. *Acta Otorrinolaringologica Espanola* 1999;**50**(1):15-9. [CENTRAL: CN-00161091] [PMID: 10091344]

Esposito 1990 *{published data only}*

Esposito S, D'Errico G, Montanaro C. Topical and oral treatment of chronic otitis media with ciprofloxacin. A preliminary study. *Archives of Otolaryngology - Head & Neck Surgery* 1990;**116**(5):557-9. [CENTRAL: CN-00067110] [PMID: 2328112]

Esposito 1992 *{published data only}*

Esposito S, Noviello S, D'Errico G, Montanaro C. Topical ciprofloxacin vs intramuscular gentamicin for chronic otitis media. *Archives of Otolaryngology--Head & Neck Surgery* 1992;**118**(8):842-4. [CENTRAL: CN-00086057] [PMID: 1642836]

Povedano 1995 *{published data only}*

Povedano Rodriguez V, Seco Pinero MJ, Jurado Ramos A, Lopez Villarejo P. Efficacy of topical ciprofloxacin in the treatment of chronic otorrhea [Eficacia del ciprofloxacino topico en el tratamiento de la otorrea cronica]. *Acta Otorrinolaringologica Espanola* 1995;**46**(1):15-8. [CENTRAL: CN-00113534] [PMID: 7734157]

Ramos 2003 *{published data only}*

Ramos A, Ayudarte F, de Miguel I, Cuyas JM, Cenjor C. Use of topical ciprofloxacin in chronic suppurating otitis media [Utilizacion del ciprofloxacino topico en la otitis media cronica supurada]. *Acta Otorrinolaringologica Espanola* 2003;**54**(7):485-90. [CENTRAL: CN-00614808] [PMID: 14671920]

Yuen 1994 *{published data only}*

Yuen PW, Lau SK, Chau PY, Hui Y, Wong SF, Wong S, et al. Ofloxacin eardrop treatment for active chronic suppurative otitis media: prospective randomized study. *American Journal of Otology* 1994;**15**(5):670-3. [CENTRAL: CN-00122894] [EMBASE: 1994288260] [PMID: 8572070]

References to studies excluded from this review

Abbott 2016 *{published data only}*

Abbott P, Gunasekera H, Leach AJ, Askew D, Walsh R, Kong K, et al. A multi-centre open-label randomised noninferiority trial comparing watchful waiting to antibiotic treatment for acute otitis media without perforation in low-risk urban Aboriginal and Torres Strait Islander children (the WATCH trial): study protocol for a randomised controlled trial. *Trials* 2016;**17**(1):119. [CENTRAL: CN-01297248] [EMBASE: 613896996]

Adler 2000 *{published data only}*

Adler M, McDonald PJ, Trostmann U, Keyserling C, Tack K. Cefdinir versus amoxicillin/clavulanic acid in the treatment of suppurative acute otitis media in children. *European Journal of Clinical Microbiology & Infectious Diseases* 1997;**16**(3):214-9. [CENTRAL: CN-00139087] [PMID: 9131324]

Adler M, McDonald PJ, Trostmann U, Keyserling C, Tack K. Cefdinir vs. amoxicillin/clavulanic acid in the treatment of suppurative acute otitis media in children. *Pediatric Infectious Disease Journal* 2000;**19**(12 Suppl):S166-70. [CENTRAL: CN-00327730] [EMBASE: 2001001391] [PMID: 11144399]

Agro 1998 *{published data only}*

Agro AS, Garner ET, Wright III JW, De Escobar IC, Villeda B, Seidlin M. Clinical trial of ototopical ofloxacin for treatment of chronic suppurative otitis media. *Clinical Therapeutics* 1998;**20**(4):744-59. [CENTRAL: CN-00893582] [EMBASE: 1998310491]

Arguedas 1993 *{published data only}*

Arguedas AG, Herrera JF, Faingezicht I, Mohs E. Ceftazidime for therapy of children with chronic suppurative otitis media without cholesteatoma. *Pediatric Infectious Disease Journal* 1993;**12**(3):246-8.

Aslan 1998 *{published data only}*

Aslan A, Altuntas A, Titiz A, Arda HN, Nalca Y. A new dosage regimen for topical application of ciprofloxacin in the management of chronic suppurative otitis media. *Otolaryngology - Head and Neck Surgery* 1998;**118**(6):883-5. [CENTRAL: CN-00362566]

Asmatullah 2014 *{published data only}*

Asmatullah, Khan Q, Nawaz G, Ullah G, Iqbal J, Khan M, et al. Comparison of efficacy of topical ofloxacin and gentamycin in tubotympanic type of chronic suppurative otitis media. *Medical Forum Monthly* 2015;**25**(12):68-71. [CENTRAL: CN-01084518] [EMBASE: 2015070065]

Baba 1980 *{published data only}*

Baba S, Hondo J, Wada K. Evaluation of cefroxadine (CGP-9000) in acute tonsillitis, acute suppurative otitis media and acute exacerbation of chronic otitis media. A comparative double blind study with cephalexin. *Japanese Journal of Chemotherapy* 1980;**28**(Suppl 3):590-618. [CENTRAL: CN-00333804] [EMBASE: 1981031803]

Baba 1982b *{published data only}*

Baba S, Ito H, Kinoshita H. A well controlled comparative study on cefmetazole and cefazolin in the treatment of suppurative otitis media. *Japanese Journal of Antibiotics* 1982;**35**(6):1523-52.

Baba 1983 *{published data only}*

Baba S, Murai K, Kinoshita H. Evaluation of BRL25000 (clavulanic acid-amoxicillin) in acute purulent otitis media and acute exacerbation of chronic purulent otitis media. A comparative double blind study with amoxicillin. *Chemotherapy* 1983;**31**(Suppl 2):97-112. [CENTRAL: CN-00174613] [EMBASE: 1983209351]

Baba 1983b *{published data only}*

Baba S, Murai K, Kinoshita H, Kawai T, Koyama K, Tsukiyama M, et al. The double-blind trial of cefroxadine and cephalexin in the treatment of acute suppurative otitis media and acute exacerbation of chronic suppurative otitis media. *Japanese Journal of Antibiotics* 1983;**36**(9):2595-634. [CENTRAL: CN-00334158] [EMBASE: 1984002024]

Baba 1983c *{published data only}*

Baba S, Murai K, Kinoshita H, Kawai T, Koyama K, Tsukiyama M, et al. The double-blind trial of cefroxadine and cephalexin in the treatment of acute suppurative otitis media and acute exacerbation of chronic suppurative otitis media. *Japanese Journal of Antibiotics* 1983;**36**(9):2595-634. [CENTRAL: CN-00334158] [EMBASE: 1984002024]

Baba 1986 *{published data only}*

Baba S, Kinoshita H, Mori Y, Suzuki K, Furuuchi C, Baba K, et al. Efficacy evaluation of aztreonam for suppurative otitis media. *Japanese Journal of Antibiotics* 1986;**39**(1):159-76.

Baba 1987 *{published data only}*

Baba S, Kinoshita H, Mori Y, Suzuki K, Shimada J, Kawamura S, et al. A parallel comparative double blind study of cefixime with cefaclor in the treatment of acute suppurative otitis media in children. *Japanese Journal of Antibiotics* 1987;**40**(1):1-24. [CENTRAL: CN-00048250] [PMID: 3295321]

Baba 2008 *{published data only}*

Baba S, Suzuki K, Yamanaka N, Yamashita H, Kurono Y, Hori S. Efficacy and safety of sitafloxacin in patients with otorhinolaryngological infections and its tissue distribution in the otorhinolaryngological field. *Japanese Journal of Chemotherapy* 2008;**56**(Suppl 1):110-20.

Baba 2008a *{published data only}*

Baba S, Suzuki K, Yamanaka N, Yamashita H, Kurono Y, Hori S. Efficacy and safety of sitafloxacin in patients with otorhinolaryngological infections and its tissue distribution in the otorhinolaryngological field. *Japanese Journal of Chemotherapy* 2008;**56**(Suppl 1):110-20.

Bakir 2013 *{published data only}*

Bakir S, Kinis V, Bez Y, Gun R, Yorgancilar E, Ozbay M, et al. Mental health and quality of life in patients with chronic otitis media. *European Archives of Oto-rhino-laryngology* 2013;**270**(2):521-6. [PMID: 22566178]

Berman 1990 *{published data only}*

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

Block 2000 *{published data only}*

Block SL, McCarty JM, Hedrick JA, Nemeth MA, Keyserling CH, Tack KJ. Comparative safety and efficacy of cefdinir vs amoxicillin/clavulanate for treatment of suppurative acute otitis media in children. *Pediatric Infectious Disease Journal* 2000;**19**(12 Suppl):S159-65. [CENTRAL: CN-00327731] [EMBASE: 2001001390] [PMID: 11144398]

Bogomil'skii 1999 *{published data only}*

Bogomil'skii MR, Minasian VS. Co-amoxiclav antibiotic therapy of acute otitis media, exacerbation of otitis media chronica and sinusitis in children [Antibiotikoterapiia ko-amoksiklavom pri ostrom i obostrenii khronicheskogo srednego otita i sinusita u detei]. *Vestnik Otorinolaringologii* 1999;(4):22-4. [CENTRAL: CN-00166594] [PMID: 10453230]

Brook 1979 *{published data only}*

Brook I. Bacteriology and treatment of chronic otitis media. *Laryngoscope* 1979;**89**(7 Pt 1):1129-34. [PMID: 449555]

Brook 1980 *{published data only}*

Brook I. Clindamycin in treatment of chronic recurrent suppurative otitis media in children. *Journal of Laryngology and Otology* 1980;**94**(6):607-15.

Bross Soriano 1996 *{published data only}*

Bross Soriano D, Arrieta Gomez JR, Corvera Behar G, Ledon Perez LE. Comparison of the efficacy and safety of ceftibuten and cefaclor in the treatment of acute otitis medica and of the exacerbation of chronica otitis media in children [Comparacion de la eficacia y seguridad del ceftibuten y el cefaclor en el tratamiento de la otitis media aguda y la otitis media cronica agudizada en ninos]. *Anales de Otorrinolaringologia Mexicana: Anales de la Sociedad Mexicana de Otorrinolaringologia* 1996;**41**(1):18-23. [CENTRAL: CN-01050653]

Browning 1983 *{published data only}*

Browning GG, Picozzi GL, Calder IT, Sweeney G. Controlled trial of medical treatment of active chronic otitis media. *British Medical Journal (Clinical Research Ed.)* 1983;**287**(6398):1024. [CENTRAL: CN-00032195] [PMID: 6412934]

Picozzi CL, Calder I, Browning GG, Sweeney G. Controlled trial of medical treatment of active chronic otitis media. *Clinical Otolaryngology and Allied Sciences* 1982;**7**:137-8. [CENTRAL: CN-00262047]

Browning 1983b *{published data only}*

Browning GG, Picozzi G, Sweeney G, Calder IT. Role of anaerobes in chronic otitis media. *Clinical Otolaryngology and Allied Sciences* 1983;**8**(1):47-51. [CENTRAL: CN-00262083] [PMID: 6831755]

Browning 1984 *{published data only}*

Browning GG. Medical management of chronic mucosal otitis media [editorial]. *Clinical Otolaryngology and Allied Sciences* 1984;**9**(3):141-4.

Clayton 1990 *{published data only}*

Clayton MI, Osborne JE, Rutherford D, Rivron RP. A double-blind, randomized, prospective trial of a topical antiseptic versus a topical antibiotic in the treatment of otorrhoea. *Clinical Otolaryngology and Allied Sciences* 1990;**15**(1):7-10. [CENTRAL: CN-00066816] [PMID: 2323085]

Connolly 1997 *{published data only}*

Connolly AA, Picozzi GL, Browning GG. Randomized trial of neomycin/dexamethasone spray vs drop preparation for the treatment of active chronic mucosal otitis media. *Clinical Otolaryngology and Allied Sciences* 1997;**22**(6):529-31. [CENTRAL: CN-00147553] [PMID: 9466064]

CTRI/2019/09/021197 *{published data only}*

CTRI/2019/09/021197. Treatment for ear discharge using kushtadi taila and ciprofloxacin ear drops. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=31448 2019.

Deguchi 1985 *{published data only}*

Deguchi K, Fukayama S, Nishimura Y, Nishike A, Oda S, Sato S, et al. Study of clinical bacteriological efficacy of cefmenoxime ototopical solution. *Japanese Journal of Antibiotics* 1985;**38**(7):1739-49. [CENTRAL: CN-00357486] [EMBASE: 1986002477]

Deguchi 1986 *{published data only}*

Deguchi K, Yokota N, Tanaka S, Fukayama S, Nishimura Y, Yoshihara H, et al. A clinical bacteriological efficacy study on a fosfomycin otic solution. *Japanese Journal of Antibiotics* 1986;**39**(9):2344-54. [CENTRAL: CN-00045975] [PMID: 3099028]

Deitmer 2002 *{published data only}*

Deitmer T. Topical and systemic treatment for chronic suppurative otitis media. *Ear, Nose, & Throat Journal* 2002;**81**(8 Suppl 1):16-7.

Dellamonica 1995 *{published data only}*

Dellamonica P, Choutet P, Lejeune JM, Lucht F, Morgon A, Pessey JJ, et al. Efficacy and safety of cefotiam hexetil in the treatment of chronic otitis media. A comparative double blind randomized study versus cefuroxime axetil [Efficacite et tolerance du cefotiam hexetil dans le traitement des otites moyennes chroniques. etude randomisee, en double aveugle, comparaison au cefuroxime axetil]. *Medecine et Maladies Infectieuses* 1995;**25**(5):733-9. [CENTRAL: CN-00169813] [EMBASE: 1995207381]

Eason 1986 *{published data only}*

Eason RJ, Harding E, Nicholson R, Nicholson D, Pada J, Gathercole J. Chronic suppurative otitis media in the Solomon Islands: a prospective, microbiological, audiometric and therapeutic survey. *New Zealand Medical Journal* 1986;**99**:812-5. [CENTRAL: CN-00045614] [PMID: 3466089]

Esposito 2000 *{published data only}*

Esposito S, Noviello S, Ianniello F, D'Errico G. Ceftazidime for outpatient parenteral antibiotic therapy (OPAT) of chronic suppurative otitis media due to Pseudomonas aeruginosa. *Journal of Chemotherapy (Florence, Italy)* 2000;**12**(1):88-93.

Fliss 1990 *{published data only}*

Fliss DM, Dagan R, Houri Z, Leiberman A. Medical management of chronic suppurative otitis media without cholesteatoma in children. *Journal of Pediatrics* 1990;**116**(6):991-6. [CENTRAL: CN-00067997] [PMID: 2189979]

Leiberman A, Fliss DM, Dagan R. Medical treatment of chronic suppurative otitis media without cholesteatoma in children--a two-year follow-up. *International Journal of Pediatric Otorhinolaryngology* 1992;**24**(1):25-33. [PMID: 1399301]

Fombeur 1994 *{published data only}*

Fombeur JP, Barrault S, Koubbi G, Laurier JN, Ebbo D, Lecomte F, et al. Study of the efficacy and safety of ciprofloxacin in the treatment of chronic otitis. *Chemotherapy* 1994;**40**(Suppl 1):29-34. [CENTRAL: CN-00108584] [PMID: 7805428]

Fradis 1997 *{published data only}*

Fradis M, Brodsky A, Ben-David J, Srugo I, Larboni J, Podoshin L. Chronic otitis media treated topically with ciprofloxacin or tobramycin. *Archives of Otolaryngology--Head & Neck Surgery* 1997;**123**(10):1057-60. [CENTRAL: CN-00144425] [PMID: 9339980]

Podoshin L, Brodzki A, Fradis M, Ben-David J, Larboni J, Srugo I. Local treatment of purulent chronic otitis media with ciprofloxacin. *Harefuah* 1998;**134**(1):32-6, 78. [CENTRAL: CN-00682735] [PMID: 9517277]

Garcia-Rodriguez 1993 *{published data only}*

Garcia Rodriguez JA, Garcia Sanchez JE, Garcia Garcia MI, Garcia Sanchez E, Munoz Bellido JL, Ramos Macias A. Efficacy of topical ciprofloxacin in the treatment of ear infections in adults. *Journal of Antimicrobial Chemotherapy* 1993;**31**(3):452-3. [CENTRAL: CN-00092937] [PMID: 8486586]

Gehanno 1997 *{published data only}*

Gehanno P. Multicenter study of the efficacy and safety of oral ciprofloxacin in the treatment of chronic suppurative otitis media in adults. The French Study Group. *Otolaryngology - Head and Neck Surgery* 1997;**117**(1):83-90. [CENTRAL: CN-00141764] [PMID: 9230329]

Ghosh 2012 *{published data only}*

CTRI/2011/10/002079. Comparison of effectiveness of ciprofloxacin and cefpodoxime in patients with acute attack of chronic middle ear infection. http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=3489 (first received 19 October 2011). [CENTRAL: CN-01013255]

Ghosh A, Jana U, Khaowas A, Das S, Mandal A, Das N. Comparison of the effectiveness and safety of cefpodoxime and ciprofloxacin in acute exacerbation of chronic suppurative otitis media: a randomized, open-labeled, phase IV clinical trial. *Journal of Pharmacology & Pharmacotherapeutics* 2012;**3**(4):320-4. [CENTRAL: CN-00905716] [EMBASE: 2013360430] [PMID: 23326103]

Granath 2007 *{published data only}*

Granath A, Lindberg K, Rynnel-Dagoo B. Tube associated otorrhea in children with recurrent otitis media: results of a prospective randomized treatment study. In: 9th International Symposium on Recent Advances in Otitis Media; 2007 Jun 3-7; St. Pete Beach (FL). St. Pete Beach (FL), 2007. [CENTRAL: CN-00614760]

Gupta 2015 *{published data only}*

Gupta C, Agrawal A, Gargav ND. Role of acetic acid irrigation in medical management of chronic suppurative otitis media: a comparative study. *Indian Journal of Otolaryngology - Head & Neck Surgery* 2015;**67**(3):314-8. [CENTRAL: CN-01098823] [PMID: 26405670]

Gyde 1978 *{published data only}*

Gyde MC, Randall RF. Double-blind comparative study of trimethroprim-sulphacetamide-polymyxin b and gentamicin in the treatment of otorrhoea [Etude comparative a double insu de la trimethorprime-sulfacetamide=polymyxine B et de la gentamicine dans le traitement de l'otorrhee]. *Annales d'Oto-laryngologie et de Chirurgie Cervico Faciale* 1978;**95**(1-2):43-55. [CENTRAL: CN-00018235] [PMID: 207210]

Gyde 1981 *{published data only}*

Gyde MC. A double-blind comparative study of trimethoprim-polymyxin B versus trimethoprim-sulfacetamide-polymyxin B otic solutions in the treatment of otorrhea. *Journal of Laryngology and Otology* 1981;**95**(3):251-9. [CENTRAL: CN-00024381] [PMID: 6257815]

Gyde MC. Double-blind comparative trial of trimethoprim-polymyxin B and trimethoprim-sulphacetamide-polymyxin B ear drops in the treatment of otorrhoea [Etude comparative a double insu sur les solutions otiques de trimethoprime - polymyxine B et de trimethoprime - sulfacetamide - polymyxine B dans le traitement de l'otorrhee]. *Annales d'Oto-laryngologie et de Chirurgie Cervico Faciale* 1981;**98**(1-2):37-40. [CENTRAL: CN-00026056] [EMBASE: 1982037351] [PMID: 6269476]

Gyde 1982 *{published data only}*

Gyde MC, Norris D, Kavalec EC. The weeping ear: clinical re-evaluation of treatment. *Journal of International Medical Research* 1982;**10**(5):333-40. [CENTRAL: CN-00029419] [PMID: 6754505]

Hemlin 1997 *{published data only}*

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

Hwang 2015 *{published data only}*

Hwang JH, Lee JH, Hwang JH, Chung KM, Lee EJ, Yoon YJ, et al. Comparison of arbekacin and vancomycin in treatment of chronic suppurative otitis media by methicillin resistant staphylococcus aureus. *Journal of Korean Medical Science* 2015;**30**(6):688-93. [CENTRAL: CN-01257881] [PMID: 26028918]

Lee JH, Hwang JH, Moon MK, Kim JS, Lee CS. Comparison of the usefulness of arbekacin and vancomycin in treating chronic suppurative otitis media due to methicillin resistant staphylococcus aureus. *International Journal of Antimicrobial Agents* 2015;**45**(52):S60-1.

I-HEAR-BETA *{published data only}*

* ACTRN12614000234617. Among Aboriginal children (2 months of age and up to 17 years of age) with chronic suppurative otitis media, is 4 months of povidone-iodine ear wash and/or oral cotrimoxazole in addition to standard treatment (cleaning and dry mopping with tissue spears plus topical ciprofloxacin) superior to standard treatment alone for resolving ear discharge? A 2x2 factorial randomised controlled trial. www.anzctr.org.au (first received 25 March 2014). [ACTRN12614000234617]

Wigger C, Leach AJ, Beissbarth J, Oguoma V, Lennox R, Nelson S, et al. Povidone-iodine ear wash and oral cotrimoxazole for chronic suppurative otitis media in Australian aboriginal children: study protocol for factorial design randomised controlled trial. *BMC Pharmacology & Toxicology* 2019;**20**(1):46. [CENTRAL: CN-01954293] [PMID: 31351491]

IRCT20130427013136N6 *{published data only}*

IRCT20130427013136N6. The efficacy of ceftazidime on bacterial otitis. http://en.irct.ir/trial/45218 (first received 13 February 2020).

IRCT2016082313136N4 *{published data only}*

IRCT2016082313136N4. The effect clotrimazole ointment comparison to ceftizoxime powder and clotrimazole ointment in the treatment of patients with fungal otitis media. https://en.irct.ir/trial/13058 (first received 13 October 2016).

ISRCTN12149720 *{published data only}*

ISRCTN12149720. Treatment of chronic suppurative otitis media with the antimicrobial peptide OP-145 (AMP60.4Ac) in adults. http://www.isrctn.com/isrctn12149720 (first received 13 October 2015). [CENTRAL: CN-01601160]

ISRCTN84220089 *{published data only}*

ISRCTN84220089. An interventional, randomized, double-blind, placebo-controlled, parallel-assignment, safety/efficacy study for treatment of chronic middle ear infection in adult patients with the antimicrobial peptide OP-145. http://isrctn.org/ISRCTN84220089 (first received 18 January 2008). [CENTRAL: CN-01013171]

Jahn 1984 *{published data only}*

Jahn AF, Abramson M. Medical management of chronic otitis media. *Otolaryngologic Clinics of North America* 1984;**17**(4):673-7.

Jamallulah 2016 *{published data only}*

Jamalullah M, Babat M, Choudhury IM. Comparison of efficacy of topical gentamycin 0.3% with topical ciprofloxacin 0.6% in patients with active tubotympanic type of chronic suppurative otitis media. *Isra Medical Journal* 2016;**8**(1):14-8. [CENTRAL: CN-01601161]

Jang 2004 *{published data only}*

Jang CH, Song CH, Wang PC, Wang PC. Topical vancomycin for chronic suppurative otitis media with methicillin-resistant Staphylococcus aureus otorrhoea. *Journal of Laryngology and Otology* 2004;**118**(8):645-7. [CENTRAL: CN-00497367]

Jaya 2003 *{published data only}*

Jaya C, Job A, Mathai E, Antonisamy B. Evaluation of topical povidone-iodine in chronic suppurative otitis media. *Archives of*

Otolaryngology--Head & Neck Surgery 2003;**129**(10):1098-100. [CENTRAL: CN-00452670] [EMBASE: 37248310] [PMID: 14568795]

Jiang 2016 *{published data only}*

Jiang S-L, Li H-Y, Gong Q-H. Efficacy and safety compare of two antibiotics combined with Chinese patent medicine for chronic suppurative otitis media in children. *International Journal of Clinical and Experimental Medicine* 2016;**9**(2):4089-94. [CENTRAL: CN-01199922] [EMBASE: 20160256082]

Kadar 2003 *{published data only}*

Kadar AA, Usman M, Tirmizi S. Topical quinolones versus topical aminoglycosides in the medical management of chronic suppurative otitis media: a comparative trial. *Journal of Surgery Pakistan* 2003;**8**(4):6-9. [CENTRAL: CN-00597098]

Kasemsuwan 1997 *{published data only}*

Kasemsuwan L, Clongsuesuek P. A double blind, prospective trial of topical ciprofloxacin versus normal saline solution in the treatment of otorrhoea. *Clinical Otolaryngology and Allied Sciences* 1997;**22**(1):44-6. [CENTRAL: CN-00138220] [PMID: 9088679]

Kashiwamura 2004 *{published data only}*

Kashiwamura M, Chida E, Matsumura M, Nakamaru Y, Suda N, Terayama Y, et al. The efficacy of Burow's solution as an ear preparation for the treatment of chronic ear infections. *Otology & Neurotology* 2004;**25**(1):9-13.

Kaygusuz 2002 *{published data only}*

Kaygusuz I, Karlidag T, Gok U, Yalcin S, Keles E, Demirbag E, et al. Efficacy of topical ciprofloxacin and tobramycin in combination with dexamethasone in the treatment of chronic suppurative otitis media [Kronik supuratif otitis media tedavisinde topikal siprofloksasin ve tobramisinin deksametazon ile kullanimi]. *Kulak Burun Bogaz Ihtisas Dergisi: KBB [Journal of Ear, Nose, and Throat]* 2002;**9**(2):106-11. [CENTRAL: CN-00397704] [PMID: 12122630]

Kenna 1986 *{published data only}*

Kenna MA, Bluestone CD, Reilly JS, Lusk RP. Medical management of chronic suppurative otitis media without cholesteatoma in children. Laryngoscope 1986;**96**(2):146-51. [PMID: 3945144]

Khanna 2000 *{published data only}*

Khanna V, Chander J, Nagarkar NM, Dass A. Clinicomicrobiologic evaluation of active tubotympanic type chronic suppurative otitis media. *Journal of Otolaryngology* 2000;**29**(3):148-53. [CENTRAL: CN-00331653] [PMID: 10883827]

Khon 2012 *{published data only}*

Khon EM, Dzhenzhera GE, Ovchinnikov AI. Local antibacterial therapy for the inflammatory diseases of the external and middle ear. *Vestnik Otorinolaringologii* 2012;(3):92-4. [CENTRAL: CN-00850158] [EMBASE: 365865807] [PMID: 22951697]

Kothari 1969 *{published data only}*

Kothari A. Treatment of 'resistant' otorrhea with acetic acid. *Laryngoscope* 1969;**79**(3):494-8. [PMID: 5776741]

Kovacic 1999 *{published data only}*

Kovacic M, Dzelalija B. Clinical success of treatment of chronic otitis media using topical and peroral administration of ofloxacin. *Lijecnicki Vjesnik* 1999;**121**(6):185-7.

Kurilin 1976 *{published data only}*

Kurilin IA, Mokhort NA, Iurina RV, Garankina LA. Complex conservative method of treatment of chronic suppurative otitis media with the use of mefenamine sodium salt [Kompleksnyi konservativnyi metod lecheniia khronicheskikh gnoinykh srednykh otitov s primeneniem mefenamina natrievoi soli]. *Zhurnal Ushnykh, Nosovykh I Gorlovykh Boleznei [Journal of Otology, Rhinology, and Laryngologie [sic]]* 1976;(2):64-70. [PMID: 1266398]

Lancaster 1999 *{published data only}*

Lancaster JL, Makura ZG, Porter G, McCormick M. Topical aminoglycosides in the management of active mucosal chronic suppurative otitis media. *Journal of Laryngology and Otology* 1999;**113**(1):10-2.

Lancaster 2003 *{published data only}*

Lancaster J, Matthews J, Williams RS, Thussey C, Kent SE. Comparison of compliance between topical aural medications. *Clinical Otolaryngology and Allied Sciences* 2003;**28**(4):331-4.

Lang 1992 *{published data only}*

Lang R, Goshen S, Raas-Rothschild A, Raz A, Ophir D, Wolach B, et al. Oral ciprofloxacin in the management of chronic suppurative otitis media without cholesteatoma in children: preliminary experience in 21 children. *Pediatric Infectious Disease Journal* 1992;**11**(11):925-9. [PMID: 1454433]

Lautala 1983 *{published data only}*

Lautala P, Vare M, Vuorinen O, Kaar ML. Ceftazidime in the treatment of chronic suppurative otitis media in children. *Journal of Antimicrobial Chemotherapy* 1983;**12 Suppl A**:365-7.

Legent 1994 *{published data only}*

Legent F, Bordure P, Beauvillain C, Berche P, Bordure PH. Controlled prospective study of oral ciprofloxacin versus amoxycillin/clavulanic acid in chronic suppurative otitis media in adults. *Chemotherapy* 1994;**40**(Suppl 1):16-23. [CENTRAL: CN-00108583] [EMBASE: 1994301734] [PMID: 7805426]

Li 2004 *{published data only}*

Li KY, Zhao NJ, Zhu JC. Clinical observation on treatment of chronic suppurative otitis media caused large tympanic membranes perforation by ear-dropping with combined Chinese and Western drugs. *Zhongguo Zhong Xi Yi Jie He za Zhi [Chinese Journal of Integrated Traditional and Western Medicine]* 2004;**24**(11):989-91. [CENTRAL: CN-00504865] [PMID: 15609596]

Liu 1990 *{published data only}*

Liu SL. Therapeutic effects of borneol-walnut oil in the treatment of purulent otitis media. *Zhong Xi Yi Jie He za Zhi [Chinese Journal of Modern Developments in Traditional Medicine]* 1990;**10**(2):93-5, 69. [PMID: 2364470]

Liu 2003 *{published data only}*

Liu J. The curative effect of Rifampicin solution in the treatment of chronic suppurative otitis media. *Journal of Preclinical Medicine College of Shangdong University* 2003;**17**(1):8-9. [CENTRAL: CN-00475923]

Loock 2012 *{published data only}*

Loock J. Strategies in the medical treatment of active mucosal chronic otitis media suitable for all levels of healthcare: a randomized controlled trial. *Clinical Otolaryngology* 2012;**37**(Suppl 1):165-6. [CENTRAL: CN-01008068] [EMBASE: 71023646]

Loock JW. A randomised controlled trial of active chronic otitis media comparing courses of eardrops versus one-off topical treatments suitable for primary, secondary and tertiary healthcare settings. *Clinical Otolaryngology* 2012;**37**(4):261-70. [CENTRAL: CN-00850193] [EMBASE: 365535141] [PMID: 22804826]

Lorente 1995 *{published data only}*

Lorente J, Sabater F, Maristany M, Jimenez R, Menem J, Vinas J, et al. Multicenter study comparing the efficacy and tolerance of topical ciprofloxacin (0.3%) versus topical gentamicin (0.3%) in the treatment of simple, non-cholesteatomaous chronic otitis media in the suppurative phase [Estudio multicentrico comparativo de la eficacia y tolerancia de ciprofloxacino topico (0.3%) versus gentamicina topica (0.3%) en el tratamiento de la otitis media cronica simple no colesteatomatosa en fase supurativa]. *Anales Otorrinolaringologicos Ibero-americanos* 1995;**22**(5):521-33. [CENTRAL: CN-00120014] [PMID: 7485860]

Sabater F, Maristany M, Mensa J, Villar E, Traserra J. Prospective double-blind randomized study of the efficacy and tolerance of topical ciprofloxacin vs topical gentamicin in the treatment of simple chronic otitis media and diffuse external otitis [Estudio prospectivo doble-ciego randomizado de la eficacia y tolerancia de ciprofloxacino topico versus gentamicina topica en el tratamiento de la otitis media cronica supurada simple y de la otitis externa difusa]. *Acta Otorrinolaringologica Espanola* 1996;**47**(3):217-20. [CENTRAL: CN-00129550] [PMID: 8924287]

Macfadyen 2005 *{published data only}*

Macfadyen C, Gamble C, Garner P, Macharia I, Mackenzie I, Mugwe P, et al. Topical quinolone vs. antiseptic for treating chronic suppurative otitis media: a randomized controlled trial. *Clinical Otolaryngology* 2005;**30**(2):193-4. [CENTRAL: CN-00521519] [EMBASE: 2005185914] [PMID: 15839875]

Macfadyen C, Gamble C, Garner P, Macharia I, Mackenzie I, Mugwe P, et al. Topical quinolone vs. antiseptic for treating chronic suppurative otitis media: a randomized controlled trial. *Tropical Medicine & International Health* 2005;**10**(2):190-7. [CENTRAL: CN-00502876] [EMBASE: 2005088099] [PMID: 15679563]

Merifield 1993 *{published data only}*

Merifield DO, Parker NJ, Nicholson NC. Therapeutic management of chronic suppurative otitis media with otic drops. *Otolaryngology - Head & Neck Surgery* 1993;**109**(1):77-82. [CENTRAL: CN-00343156] [PMID: 8393167]

Mesure 1973 *{published data only}*

Mesure R. Double-blind study of the association of sulfamethoxazole and trimethoprim in otorhinolaryngological infections [Essai en double aveugle de l'association de sulfamethoxazole et de trimethoprime dans les infections oto-rhino-laryngologiques]. *Acta Oto-rhino-laryngologica Belgica* 1973;**27**(1):27-33. [CENTRAL: CN-00008422] [PMID: 4697134]

Minja 2006 *{published data only}*

Minja BM, Moshi NH, Ingvarsson L, Bastos I, Grenner J. Chronic suppurative otitis media in Tanzanian school children and its effects on hearing. *East African Medical Journal* 2006;**83**(6):322-5. [CENTRAL: CN-00568108] [PMID: 16989377]

Mira 1993 *{published data only}*

Mira E, Benazzo M, Mira E, Benazzo M. Ceftizoxime as local therapy in the treatment of recurrences of chronic suppurative otitis media. *Journal of Drug Development Supplement* 1993;**6**(Suppl 2):39-44. [CENTRAL: CN-00362597]

Mira E, Benazzo M, Mira E, Benazzo M. Clinical evaluation of ceftizoxime (EposerinR) as local therapy in the treatment of recurrences of chronic suppurative otitis media [Uso topico delle cefalosporine nel trattamento delle otiti medie purulente: valutazione della ceftizoxima (eposerin R)]. *Rivista Italiana di Otorinolaringologia Audiologia e Foniatria* 1992;**12**(4):219-25. [CENTRAL: CN-00624623]

Morgon 1976 *{published data only}*

Morgon A. Role of antibiotic therapy with clindamycin in the treatment of chronic suppurative otitis media [Place de l'antibiotherapie par la clindamycine dans le traitement des otites moyennes suppurees chroniques]. *JFORL. Journal Francais d'Oto-rhino-laryngologie; Audiophonologie et Chirurgie Maxillo-faciale* 1976;**25**(4):353-4. [PMID: 135074]

Nawasreh 2001 *{published data only}*

Nawasreh O, Fraihat A. Topical ciprofloxacin versus topical gentamicin for chronic otitis media. *La Revue de Sante de la Mediterranee Orientale / Al-Majallah Al-sihhiyah Li-sharq Al-mutawassit [Eastern Mediterranean Health Journal]* 2001;**7**(1-2):26-30. [CENTRAL: CN-00413339] [12596948]

Nwokoye 2015 *{published data only}*

Bakshi SS. Occurrence of otitis media in children and assessment of treatment options. *Journal of Laryngology and Otology* 2015;**129**(12):1253. [PMID: 26429519]

Nwokoye NN, Egwari LO, Olubi OO. Occurrence of otitis media in children and assessment of treatment options. *Journal of Laryngology and Otology* 2015;**129**(8):779-83. [PMID: 26072993]

Onali 2018 *{published data only}*

Onali MA, Bareeqa SB, Zia S, Ahmed SI, Owais A, Ahmad AN. Efficacy of empirical therapy with combined ciprofloxacin versus topical drops alone in patients with tubotympanic chronic suppurative otitis media: a randomized double-blind controlled trial. *Clinical Medicine Insights. Ear Nose & Throat* 2018;**11**:1179550617751907. [CENTRAL: CN-01445979] [PMID: 29348711]

Papastavros 1989 *{published data only}*

Papastavros T, Giamarellou H, Varlejides S. Preoperative therapeutic considerations in chronic suppurative otitis media. *Laryngoscope* 1989;**99**(6 Pt 1):655-9. [CENTRAL: CN-00060222] [PMID: 2725163]

Poliakova 1991 *{published data only}*

Poliakova TS, Voznesenskii NL, Mironov AA. "Otinum" in the therapy of middle ear diseases. *Vestnik Otorinolaringologii* 1991; (2):56-8. [PMID: 2048256]

Principi 1995 *{published data only}*

Principi N. Multicentre comparative study of the efficacy and safety of azithromycin compared with amoxicillin/clavulanic acid in the treatment of paediatric patients with otitis media. *European Journal of Clinical Microbiology & Infectious Diseases* 1995;**14**(8):669-76. [CENTRAL: CN-00120943] [EMBASE: 1995280756] [PMID: 8565983]

Quick 1973 *{published data only}*

Quick CA, Wagner D. Trimethoprim-sulfamethoxazole in the treatment of infections of the ears, nose, and throat. *Journal of Infectious Diseases* 1973;**128**(Suppl):S696-700. [CENTRAL: CN-00009316] [PMID: 4202209]

Quick 1975 *{published data only}*

Quick CA. Comparison of penicillin and trimethoprim-sulfamethoxazole in the treatment of ear, nose and throat infections. *Canadian Medical Association Journal* 1975;**112**(13 Spec No):83-6. [CENTRAL: CN-00697942] [PMID: 805651]

Renuknanada 2014 *{published data only}*

Renukananda GS, Santosh UP, George NM. Topical vs combination ciprofloxacin in the management of discharging chronic suppurative otitis media. *Journal of Clinical and Diagnostic Research* 2014;**8**(6):KC01-4. [CENTRAL: CN-00995335] [EMBASE: 2014430779] [PMID: 25121008]

Roberts 2004 *{published data only}*

Iseh KR, Amutta SB, Mohammed A, Aliyu D, Osisi K, Salihu A, et al. Aural toileting and dressing—important intervention measures in the management of acute suppurative otitis media. *International Journal of Otolaryngology and Head & Neck Surgery* 2014;**3**(5):233-8.

Rotimi 1990 *{published data only}*

Rotimi VO, Olabiyi DA, Banjo TO, Okeowo PA. Randomised comparative efficacy of clindamycin, metronidazole, and lincomycin, plus gentamicin in chronic suppurative otitis media. *West African Journal of Medicine* 1990;**9**(2):89-97. [CENTRAL: CN-00072366] [PMID: 2268574]

Saez-Llorens 2005 *{published data only}*

Saez-Llorens X, Rodriguez A, Arguedas A, Hamed KA, Yang J, Pierce P, et al. Randomized, investigator-blinded, multicenter study of gatifloxacin versus amoxicillin/clavulanate treatment of recurrent and nonresponsive otitis media in children. *Pediatric Infectious Disease Journal* 2005;**24**(4):293-300. [CENTRAL: CN-00515218] [EMBASE: 2005176460] [PMID: 15818287]

Sanchez Gonzales 2001 *{published data only}*

Sanchez Gonzalez A, Gonzalez Galindo T. An open, comparative study of treatment of chronic middle ear otitis with levofloxacine vs amoxicillin/clavulanate [Estudio abierto comparativo del tratamiento de otitis media cronica con levofloxacino vs amoxicilina/clavulanato]. *Investigacion Medica Internacional* 2001;**28**(1):33-6. [CENTRAL: CN-00425055] [EMBASE: 2001355708]

Siddique 2016 *{published data only}*

Siddique W, Hakeem A, Ashfaq K, Khan M, Gul AA. Comparison between the efficacy of topical ciprofloxacin with neomycin in the management of chronic suppurative otitis media. *Pakistan Armed Forces Medical Journal* 2016;**66**(2):235-9. [CENTRAL: CN-01601188]

Singhal 1992 *{published data only}*

Singhal S, Sharma SC, Singhal KC. Adverse reactions to gentamycin in patients with ear, nose or throat infections. *Indian Journal of Physiology and Pharmacology* 1992;**36**(3):189-98.

Somekh 2000 *{published data only}*

Somekh E, Cordova Z. Ceftazidime versus aztreonam in the treatment of pseudomonal chronic suppurative otitis media in children. *Scandinavian Journal of Infectious Diseases* 2000;**32**(2):197-9. [CENTRAL: CN-00296955] [PMID: 10826908]

Stenstrom 1991 *{published data only}*

Stenstrom C, Lundgren K, Ingvarsson L, Bertilson SO. Amoxycillin/clavulanate versus amoxycillin in recurrent otitis media and therapeutic failure in children. Acta Oto-Laryngologica 1991;**111**(1):120-9. [CENTRAL: CN-00074552] [EMBASE: 1991091483] [PMID: 1901686]

Sugiyama 1981 *{published data only}*

Sugiyama M, Tanabe K, Chang KC, Nakai Y, Nakai Y. Variation in bacterial count in otorrhea from cases of chronic otitis media depending upon the method of antibiotic administration. *Acta Otolaryngologica* 1981;**92**(3-4):285-91. [CENTRAL: CN-00270770]

Sultan 2017 *{published data only}*

Sultan SSN, Alsaady MA. Role of levofloxacin for treatment of chronic suppurative otitis media: sample of Iraqi patients. *Asian Journal of Pharmaceutical and Clinical Research* 2017;**10**(9):358-60. [EMBASE: 618371938]

Sumitsawan 1995 *{published data only}*

Sumitsawan Y, Tharavichitkul P, Prawatmuang W, Ingsuwan B, Sriburi P. Ofloxacin otic solution as treatment of chronic suppurative otitis media and diffuse bacterial otitis externa. *Chotmaihet Thangphaet [Journal of the Medical Association of Thailand]* 1995;**78**(9):455-9. [PMID: 7561571]

Supiyaphun 1995 *{published data only}*

Supiyaphun P, Chochaipanichnon L, Tonsakulrungruang K, Chongtateong A, Samart Y. The treatment of chronic suppurative otitis media and otitis externa with 0.3 per cent ofloxacin otic solution: a clinico-microbiological study. *Chotmaihet Thangphaet [Journal of the Medical Association of Thailand]* 1995;**78**(1):18-21.

Tachibana 1986 *{published data only}*

Tachibana M, Ohshima W, Mizukoshi O, Yanohara K, Nishimura T. Clinical trial of BRL 28500 (clavulanic acid-ticarcillin) in the treatment of chronic suppurative otitis media. *Chemotherapy* 1986;**34**(Suppl 4):1120-4.

Thomsen 1976 *{published data only}*

Thomsen VF, Olsen JS, Sorensen H, Thomsen J. Bacteriology and antibiotics in acute suppurative otitis media. *Journal of Otolaryngology* 1976;**5**(4):289-97.

Tong 1996 *{published data only}*

Tong MC, Woo JK, van Hasselt CA. A double-blind comparative study of ofloxacin otic drops versus neomycin-polymyxin B-hydrocortisone otic drops in the medical treatment of chronic suppurative otitis media. *Journal of Laryngology and Otology* 1996;**110**(4):309-14. [CENTRAL: CN-00127151] [PMID: 8733449]

Tutkun 1995 *{published data only}*

Ozagar A, Koc A, Ciprut A, Tutkun A, Akdas F, Sehitoglu MA. Effects of topical otic preparations on hearing in chronic otitis media. *Otolaryngology - Head and Neck Surgery* 1997;**117**(4):405-8. [CENTRAL: CN-00144419] [PMID: 9339804]

Tutkun A, Ozagar A, Koc A, Batman C, Uneri C, Sehitoglu MA. Treatment of chronic ear disease. Topical ciprofloxacin vs topical gentamicin. *Archives of Otolaryngology--Head & Neck Surgery* 1995;**121**(12):1414-6. [CENTRAL: CN-00121174] [PMID: 7488373]

Van de Heyning 1986 *{published data only}*

Van de Heyning PH, Pattyn SR, Valcke HD. Ciprofloxacin in oral treatment of ear infections. *Pharmaceutisch Weekblad. Scientific Edition* 1986;**8**(1):63-6. [PMID: 2938071]

van der Veen 2007 *{published data only}*

Boonacker CW, van der Veen EL, van der Wilt GJ, Schilder AG, Rovers MM. Trimethoprim-sulfamethoxazole in children with chronic otitis media: a randomized comparison of costs and effects. *Otology & Neurotology* 2008;**29**(7):961-4. [CENTRAL: CN-00666283] [PMID: 18758386]

Miller JL, Honey BL, Johnson PN, Hagemann TM. Effectiveness of trimethoprim/sulfamethoxazole for children with chronic active otitis media. *Pediatrics* 2007;**120**(6):1403. [PMID: 18055693]

NCT00189098. Effectiveness of sulfamethoxazole-trimethoprim in the treatment of chronic otitis media. https://clinicaltrials.gov/show/nct00189098 (first received 16 September 2005). [CENTRAL: CN-01039521]

van der Veen EL, Rovers MM, Albers FW, Sanders EA, Schilder AG. Effectiveness of trimethoprim/sulfamethoxazole for children with chronic active otitis media: a randomized, placebo-controlled trial. *Pediatrics* 2007;**119**(5):897-904. [CENTRAL: CN-00588516] [PMID: 17473089]

van der Veen EL, Schilder AG, Timmers TK, Rovers MM, Fluit AC, Bonten MJ, et al. Effect of long-term trimethoprim/sulfamethoxazole treatment on resistance and integron prevalence in the intestinal flora: a randomized, double-blind, placebo-controlled trial in children. *Journal of Antimicrobial Chemotherapy* 2009;**63**(5):1011-6. [CENTRAL: CN-00697186] [PMID: 19297377]

Verhoeff M, Rovers MM, Sanders EAM, Schilder AGM. The COCO-study: a randomized clinical trial of the efficacy of trimethoprim-sulfamethoxazole (co-trimoxazole) in children with chronic suppurative otitis media. *Clinical Otolaryngology and Allied Sciences* 2004;**29**(4):460. [CENTRAL: CN-00874123]

van Dongen 2014 *{published data only}*

NTR1481. Comparison of ototopical antibiotic-steroid drops or oral antibiotics versus watchful waiting in children with acute tympanostomy tube otorrhea [Comparison of Bacicoline-B eardrops or oral Augmentin versus watchful waiting in children with acute tympanostomy tube otorrhea]. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1481 (first received 6 October 2008). [CENTRAL: CN-00974948]

van Dongen TMA, van der Heijden GJMG, Venekamp RP, Rovers MM, Schilder AGM. A trial of treatment for acute otorrhea in children with tympanostomy tubes. *New England Journal of Medicine* 2014;**370**(8):723-33. [CENTRAL: CN-00982484] [EMBASE: 2014119997] [PMID: 24552319]

van Hasselt 1997 *{published data only}*

van Hasselt P, van Kregten E. Treatment of chronic suppurative otitis media with ofloxacin in hydroxypropyl methylcellulose ear drops: a clinical/bacteriological study in a rural area of Malawi. *International Journal of Pediatric Otorhinolaryngology* 2002;**63**(1):49-56. [CENTRAL: CN-00519676]

van Hasselt P. Pilot trial of treatment of chronic suppurative otitis media (CSOM) with several types of ear drops in Nkota Kota District, Malawi. Internal Report of the Christian Blind Mission International 1997. [CENTRAL: CN-00519675]

van Hasselt 1998a *{published data only}*

van Hasselt P, van Kregten E. Treatment of chronic suppurative otitis media with ofloxacin in hydroxypropyl methylcellulose ear drops: a clinical/bacteriological study in a rural area of Malawi. *International Journal of Pediatric Otorhinolaryngology* 2002;**63**(1):49-56. [CENTRAL: CN-00519676]

van Hasselt P. A controlled trial of the treatment of CSOM in rural Malawi. In: Conference of the Pan-African Federation of Otorhinolaryngological Societies (PAFOS); 1998; Nairobi. Nairobi, 1998. [CENTRAL: CN-00519673]

Vishwakarma 2015 *{published data only}*

Vishwakarma K, Khan FA, Nizamuddin S, Signh P, Yadav L. Role of topical acetic acid in comparison to gentamicin for the management of chronic suppurative otitis media. *International Archives of Biomedical and Clinical Research* 2015;**1**(1):13-6. [CENTRAL: CN-01601165]

Wintermeyer 1997 *{published data only}*

Wintermeyer SM, Hart MC, Nahata MC. Efficacy of ototopical ciprofloxacin in pediatric patients with otorrhea. *Otolaryngology - Head & Neck Surgery* 1997;**116**(4):450-3.

References to studies awaiting assessment

Mehboob 2019 *{published data only}*

Mehboob S, Rafi ST, Ahmed N, Mehjabeen. Association of hearing loss with depression, anxiety and stress in patients suffering from chronic suppurative otitis media. *Pakistan Journal of Medical Sciences* 2019;**35**(2):510-4. [PMID: 31086542]

Samarei 2014 *{published data only}*

Samarei R. Comparison of local and systemic ciprofloxacin ototoxicity in the treatment of chronic media otitis. *Global Journal of Health Science* 2014;**6**(7 Spec No):144-9.

Additional references

Baumann 2011

Baumann I, Gerendas B, Plinkert PK, Praetorius M. General and disease-specific quality of life in patients with chronic suppurative otitis media--a prospective study. *Health and Quality of Life Outcomes* 2011;**9**:48. [DOI: 10.1186/1477-7525-9-48]

Bhutta 2011

Bhutta MF, Williamson IG, Sudhoff HH. Cholesteatoma. *BMJ* 2011;**342**:d1088. [DOI: 10.1136/bmj.d1088]

Bhutta 2016

Bhutta MF. Evolution and otitis media: a review, and a model to explain high prevalence in indigenous populations. *Human Biology* 2016;**87**(2):92-108.

Bhutta 2020

Bhutta MF, Head K, Chong LY, Daw J, Schilder AGM, Burton MJ, Brennan-Jones CG. Aural toilet (ear cleaning) for chronic suppurative otitis media. *Cochrane Database of Systematic Reviews* 2020, Issue 9. Art. No: CD013057. [DOI: 10.1002/14651858.CD013057.pub2]

Brennan-Jones 2020a

Brennan-Jones CG, Head K, Chong LY, Tu N, Burton MJ, Schilder AGM, et al. Topical antibiotics for chronic suppurative otitis media. *Cochrane Database of Systematic Reviews* 2020, Issue 1. Art. No: CD013051. [DOI: 10.1002/14651858.CD013051.pub2]

Brennan-Jones 2020b

Brennan-Jones CG, Chong LY, Head K, Burton MJ, Schilder AGM, Bhutta MF. Topical antibiotics with steroids for chronic suppurative otitis media. *Cochrane Database of Systematic Reviews* 2020, Issue 9. Art. No: CD013054. [DOI: 10.1002/14651858.CD013054.pub2]

Chong 2021

Chong L-Y, Head K, Webster KE, Daw J, Richmond P, Snelling T, Bhutta MF, et al. Systemic antibiotics for chronic suppurative otitis media. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No: CD013052. [DOI: 10.1002/14651858.CD013052.pub2]

Dubey 2007

Dubey SP, Larawin V. Complications of chronic suppurative otitis media and their management. *Laryngoscope* 2007;**117**(2):264-7.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629-34.

Elbourne 2002

Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140-9.

Elemraid 2010

Elemraid MA, Brabin BJ, Fraser WD, Harper G, Faragher B, Atef Z, et al. Characteristics of hearing impairment in Yemeni children with chronic suppurative otitis media: a case-control study. *International Journal of Pediatric Otorhinolaryngology* 2010;**74**(3):283-6.

Gates 2002

Gates GA, Klein JO, Lim DJ, Mogi G, Ogra PL, Pararella MM, et al. Recent advances in otitis media. 1. Definitions, terminology, and classification of otitis media. *Annals of Otology, Rhinology & Laryngology. Supplement* 2002;**188**:8-18.

Gilbert 2007

Gilbert JG, Dawes PJ, Mahadevan M, Baber WJ, Hall F. Use of ototoxic eardrops: a position statement from the New Zealand Society of Otolaryngology Head and Neck Surgery. *New Zealand Medical Journal* 2007;**120**(1258):84-93.

Handbook 2011

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

Head 2020a

Head K, Chong LY, Bhutta MF, Morris PS, Vijayasekaran S, Burton MJ, et al. Topical antiseptics for chronic suppurative otitis media. *Cochrane Database of Systematic Reviews* 2020, Issue 1. Art. No: CD013055. [DOI: 10.1002/14651858.CD013055.pub2]

Head 2020b

Head K, Chong LY, Bhutta MF, Morris PS, Vijayasekaran S, Burton MJ, et al. Antibiotics versus topical antiseptics for chronic suppurative otitis media. *Cochrane Database of Systematic Reviews* 2020, Issue 1. Art. No: CD013056. [DOI: 10.1002/14651858.CD013056.pub2]

Jensen 2013

Jensen RG, Koch A, Homøe P. The risk of hearing loss in a population with a high prevalence of chronic suppurative otitis media. *International Journal of Pediatric Otorhinolaryngology* 2013;**77**(9):1530-5. [DOI: 10.1016/j.ijporl.2013.06.025]

Mahadevan 2012

Mahadevan M, Navarro-Locsin G, Tan HK, Yamanaka N, Sonsuwan N, Wang PC, et al. A review of the burden of disease due to otitis media in the Asia-Pacific. *International Journal of Pediatric Otorhinolaryngology* 2012;**76**(5):623-35. [DOI: 10.1016/j.ijporl.2012.02.031]

Mittal 2015

Mittal R, Lisi CV, Gerring R, Mittal J, Mathee K, Narasimhan G, et al. Current concepts in the pathogenesis and treatment of chronic suppurative otitis media. *Journal of Medical Microbiology* 2015;**64**(10):1103-16. [DOI: 10.1099/jmm.0.000155]

Monasta 2012

Monasta L, Ronfani L, Marchetti F, Montico M, Vecchi Brumatti L, Bavcar A, et al. Burden of disease caused by otitis media: systematic review and global estimates. *PloS One* 2012;**7**(4):e36226.

Nadol 2000

Nadol JB Jr, Staecker H, Gliklich RE. Outcomes assessment for chronic otitis media: the Chronic Ear Survey. *Laryngoscope* 2000;**110**(3 Pt 3):32-5. [DOI: 10.1097/00005537-200003002-00009]

Olatoke 2008

Olatoke F, Ologe FE, Nwawolo CC, Saka MJ. The prevalence of hearing loss among schoolchildren with chronic suppurative otitis media in Nigeria, and its effect on academic performance. *Ear, Nose, & Throat Journal* 2008;**87**(12):E19.

Orji 2013

Orji F. A survey of the burden of management of chronic suppurative otitis media in a developing country. *Annals of Medical and Health Sciences Research* 2013;**4**(3):598-601. [DOI: 10.4103/2141-9248.122126]

Phillips 2007

Phillips JS, Yung MW, Burton MJ, Swan IR. Evidence review and ENT-UK consensus report for the use of aminoglycoside-containing ear drops in the presence of an open middle ear. *Clinical Otolaryngology* 2007;**32**(5):330-6.

Phillips 2014a

Phillips JS, Yung MW. COMQ-12 scores in adult patients without chronic middle ear disease. *Clinical Otolaryngology* 2014;**39**(6):362-7. [DOI: 10.1111/coa.12306]

Phillips 2014b

Phillips JS, Haggard M, Yung M. A new health-related quality of life measure for active chronic otitis media (COMQ-12): development and initial validation. *Otology & Neurotology* 2014;**35**(3):454-8. [DOI: 10.1097/mao.0000000000000205]

RevMan 2014 [Computer program]

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

Schilder 2016

Schilder AG, Chonmaitree T, Cripps AW, Rosenfeld RM, Casselbrant ML, Haggard MP, et al. Otitis media. *Nature Reviews Disease Primers* 2016;**2**:16063. [DOI: 10.1038/nrdp.2016.63]

Stedman 2011

Stedman MR, Curtin F, Elbourne DR, Kesselheim AS, Brookhart MA. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2011;**40**(6):1732-4.

van der Veen 2006

van der Veen EL, Schilder AG, van Heerbeek N, Verhoeff M, Zielhuis GA, Rovers MM. Predictors of chronic suppurative otitis media in children. *Archives of Otolaryngology--Head & Neck Surgery* 2006;**132**(10):1115-8. [DOI: 10.1001/archotol.132.10.1115]

van Dinther 2015

van Dinther J, Droessaert V, Camp S, Vanspauwen R, Maryn Y, Zarowski A, et al. Validity and test-retest reliability of the Dutch Version of the Chronic Otitis Media Questionnaire 12 (COMQ-12). *Journal of International Advanced Otology* 2015;**11**(3):248-52. [DOI: 10.5152/iao.2015.1701]

Verhoeff 2006

Verhoeff M, van der Veen EL, Rovers MM, Sanders EA, Schilder AG. Chronic suppurative otitis media: a review. *International Journal of Pediatric Otorhinolaryngology* 2006;**70**(1):1-12.

WHO 2004

World Health Organization. Chronic Suppurative Otitis Media (CSOM): Burden of Illness and Management Options. Geneva, Switzerland: World Health Organization, 2004.

Yorgancılar 2013

Yorgancılar E, Yildirim M, Gun R, Bakir S, Tekin R, Gocmez C, et al. Complications of chronic suppurative otitis media: a retrospective review. *European Archives of Oto-rhino-laryngology* 2013;**270**(1):69-76. [DOI: 10.1007/s00405-012-1924-8]

References to other published versions of this review

Chong 2018b

Chong LY, Head K, Richmond P, Snelling T, Schilder AGM, Burton MJ, et al. Topical versus systemic antibiotics for chronic suppurative otitis media. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No: CD013053. [DOI: 10.1002/14651858.CD013053]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

de Miguel 1999

Study characteristics	
Methods	5-arm, non-blinded, parallel-group RCT, with 7 days duration of treatment and 15 days duration of follow-up

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

Interventions	**Group A (n = 25):** oral ciprofloxacin, 500 mg/12 hours for 7 days **Group B (n = 25):** topical ciprofloxacin 0.2%, 3 ear drops/8 hours for 7 days

de Miguel 1999 *(Continued)*

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "125 patients were analysed for two years attending to health system with chronic otorrhea as the mean symptom" Comment: insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomized to five therapeutic groups" Comment: insufficient information about allocation concealment method provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no information provided about blinding method or use of placebo. The treatment arms involved different dosage forms (oral versus ear drops) – blinding of these interventions impossible without 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, hearing test or adverse events) it is probable that the knowledge of treatment group has influenced the results.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no dropouts or missing data reported; no statements about missing data
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk'; protocol for trial not available

Esposito 1990

Study characteristics	
Methods	3-arm, non-blinded, parallel-group RCT, with 5 to 10 days of treatment and 24 hours and 14 days follow-up after end of treatment

Participants	**Location:** Naples, Italy, 1 site
	
	Setting of recruitment and treatment: Clinic of Infectious Diseases and Otolaryngology, University of Naples
	
	Sample size:
	
	• Number randomised: 20 in each intervention
	• Number completed: 20 in each intervention
	
	Participant (baseline) characteristics:
	
	• Age: mean 38 years
	• Gender (F/M): 29 (48%)/31 (52%)
	• Main diagnosis: mild or moderate CSOM in the acute stage
	• High-risk population: no
	  * Cleft palate (or other craniofacial malformation): not reported
	  * Down syndrome: not reported
	  * Indigenous groups (Australian Aboriginals/Greenland natives): not reported
	  * Immunocompromised: "no patients had diabetes or any other comorbidities"
	• Diagnosis method:
	  * Confirmation of perforated tympanic membrane: not reported
	  * Presence of mucopurulent discharge: not reported
	  * Duration of symptoms (discharge): not specified
	• Other important effect modifiers:
	  * Alternative diagnosis of ear discharge: not reported
	  * Number who have previously had grommets inserted: not reported
	  * Number who have had previous ear surgery: not reported
	  * Number who had previous antibiotic treatment for CSOM: 38/60 (63%) had at least 5 days of antibiotics and did not respond
	• Inclusion criteria:
	  * Mild to moderate chronic otitis media in acute stage without cholesteatoma or mastoiditis
	• Exclusion criteria:
	  * Younger than 18 years old
	  * Cholesteatoma
	  * Mastoiditis

Interventions	**Topical plus systemic ciprofloxacin (n = 20):** 3 drops topical ciprofloxacin 250 µg/mL in saline solution locally twice a day PLUS oral ciprofloxacin 250 mg twice a day until cure or up to 10 days **Topical ciprofloxacin (n = 20):** 3 drops topical ciprofloxacin 250 µg/mL in saline solution locally twice a day until cure or up to 10 days **Oral ciprofloxacin (n = 20):** oral ciprofloxacin 250 mg twice a day until cure or up to 10 days All interventions given for at least 5 days; those not cured at 5 days carried on up to 10 days **Concurrent treatment:** not reported
Outcomes	Outcomes of interest in the review:

Esposito 1990 *(Continued)*

	Primary outcomes: • Resolution of ear discharge at 1 week (5 to 11 days) and 2 to 4 weeks (19 to 24 days). Unclear if otoscopically confirmed. **Secondary outcomes:** • Suspected ototoxicity (audiometric and vestibular function) • 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
Funding sources	"The ciprofloxacin tablets and powder used in this study were kindly provided by Bayer Italia Spa, Milan, Italy."
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported

Risk of bias

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

Esposito 1990 *(Continued)*

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

Esposito 1992

Study characteristics	
Methods	2-arm, non-blinded, parallel-group RCT, with 5 to 10 days of treatment and follow-up at 12 hours, 14 days and 21 days after interruption of treatment

Participants	**Location:** Naples, Italy, 1 site
	
	Setting of recruitment and treatment: Institutes of Infectious Diseases and Otolaryngology, University of Naples
	
	Sample size:
	
	• **Number randomised:** 30 in intervention, 30 in comparison
	• **Number completed:** 30 in intervention, 30 in comparison
	
	Participant (baseline) characteristics:
	
	• Age: adults, mean 39 (range 18 to 65)
	• Gender (F/M): 33 (55%)/27 (45%)
	• Main diagnosis: mild to moderate chronic otitis media in acute stage with perforation of tympanic membrane
	• 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: otoscopy assessment before, during and after the therapy
	  * Presence of mucopurulent discharge: 60/60 (100%)
	  * Duration of symptoms (discharge): ≥ 15days
	• 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: 40/60 (67%)
	
	Inclusion criteria:
	
	• "The otitis media had lasted at least 3 years, purulent otorrhea had recurred at least once annually, and recurrent episodes of purulent otorrhea had been constant for at least 15 days"
	
	Exclusion criteria:
	
	• Pregnant women
	• Previous allergy to quinolone or aminoglycosides
	• Younger than 18 years old
	• Cholesteatoma or mastoiditis

Interventions	**Intervention (n = 30):** topical ciprofloxacin hydrochloride 250 mg/mL, 12-hourly for 5 to 10 days **Comparator group (n = 30):** intramuscular gentamicin sulphate 80 mg 12-hourly for 5 to 10 days

Esposito 1992 *(Continued)*

	Concurrent treatment: aural toileting not mentioned
Outcomes	Outcomes of interest in the review: **Primary outcomes:** • Clinical and bacteriological resolution 12 hours, 14 days and 21 days after treatment **Secondary outcomes:** • Ototoxicity
Funding sources	No information provided
Declarations of interest	Ciprofloxacin powder was provided by Bayer Italia Spa, Milan, Italy; gentamicin by Schering Plough, Milan
Notes	**Unit of randomisation:** not reported **Methods for including patients with bilateral disease:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Ciprofloxacin was randomly given according to the following schedules" Comment: method of selection was not specific
Allocation concealment (selection bias)	Unclear risk	Comment: no specific information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: both treatments are by different routes of administration and given that no placebo was used, masking the intervention arms would not be achievable
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no indication that outcomes assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no dropouts reported
Selective reporting (reporting bias)	High risk	Quote: "the clinical and bacteriological evaluation was stated 12 hours and 14 and 21 days (follow-up) after the interruption of treatment" Comment: study protocol not available for assessment. Although the methods section indicates that 3 time points were measured, only one time point (unclear which one) was reported. The other 2 time points were not reported.

Povedano 1995

Study characteristics

Povedano 1995 *(Continued)*

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

Participants	**Location:** Spain, unclear how many sites
	
	Setting: otolaryngology department, general hospital, Spain, 1994
	
	Sample size:
	
	• **Number randomised:** 30 in group A, 30 in group B
	• **Number completed:** 30 in group A, 30 in group B
	
	Participant (baseline) characteristics:
	
	• Age: mean 45 ± 2 years, range 18 to 65
	• Gender (F/M): 35 (58%)/25 (42%)
	• Main diagnosis: active phase of chronic otorrhoea
	• High-risk population: not reported
	  * Cleft palate (or other craniofacial malformation): not reported
	  * Down syndrome: not reported
	  * Indigenous groups (Australian Aboriginals/Greenland natives): not reported
	  * Immunocompromised: not reported
	• Diagnosis method:
	  * Confirmation of perforated tympanic membrane: unclear
	  * Presence of mucopurulent discharge: 60/60 (100%)
	  * 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:
	
	• Patients with chronic active otorrhoea in the active phase (diagnostic criteria used not reported)
	
	Exclusion criteria:
	
	• Age < 18 years
	• Allergy to fluoroquinolones
	• Medical comorbidities (diabetes mellitus, cardiomyopathy, etc.)

Interventions	**Group A (n = 30):** oral ciprofloxacin, 500 mg/12 hours, for 10 days **Group B (n = 30)**: topical ciprofloxacin 250 µg/mL, 5 ear drops/12 hours, for 10 days **Concurrent treatment:** not reported
Outcomes	Outcomes of interest in the review: **Primary outcomes:** • Resolution of ear discharge ("dry ear"), measured at between 1 to 2 weeks. Unclear if otoscopically confirmed.
Funding sources	No information provided
Declarations of interest	No information provided
Notes	**Unit of randomisation:** not reported

Povedano 1995 *(Continued)*

Methods for including patients with bilateral disease: not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: patients were "allocated randomly" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Quote: "Ciprofloxacin was randomly administered to two groups" Comment: no information was provided to determine adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no indication of use of placebo; different methods of administration
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: no indication of blinding of outcomes assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients finished the study, without reporting of attrition during follow-up"
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient information to permit judgement of 'low risk' or 'high risk' (no protocol available or pre-specified outcomes)

Ramos 2003

Study characteristics	
Methods	6-arm, open-label, parallel-group RCT, with 7-day duration of treatment and 10 days of follow-up; follow-up to 3 days after finishing the treatment
Participants	**Location:** Spain **Setting of recruitment and treatment:** 3 ENT departments of 3 tertiary hospitals **Sample size:** 300 patients • **Number randomised:** 50 in each group • **Number completed:** 50 in each group **Participant (baseline) characteristics:** • Age (mean, range): 5 to 73, n = 36 (12%) were children (< 14 years) • Gender (F/M): 134 (44.7%)/166 (55.3%)

Ramos 2003 *(Continued)*

- Main diagnosis: chronic ear discharge, which comprised the following groups:
  - Simple chronic otitis media (n = 128): no lesions of the ossicular chain, erosion of the tympanic frame, absence of tympanosclerosis and no evidence of cholesteatoma
  - Chronic otitis media with osteolysis (OMCO) (n = 57): osteolytic lesions and alterations of the mucosa of medium type, types of pansclerosis, granulomatous lesions, atelectasis or marginal perforation, without signs of cholesteatoma
  - Chronic cholesteatoma (n = 42): signs of infection of middle cholesteatoma
  - Chronic otorrhoea in operated ears (n = 73): radical mastoidectomy (n = 40), tympanoplasty infection (n = 21), transtympanic grommets (n = 12)
- High-risk population:
  - Cleft palate (or other craniofacial malformation): not reported
  - Down syndrome: not reported
  - Indigenous groups (Australian Aboriginals/Greenland natives): not reported
  - Immunocompromised: not reported
- Diagnosis method:
  - Confirmation of perforated tympanic membrane*:* all had otoscopic examination at baseline; 62.3% had perforation confirmed (marginal perforation: 1.43% non-marginal perforation: 42% attical perforation)
  - Presence of mucopurulent discharge: otoscopic examination
  - Duration of symptoms (discharge): "for more than 6 weeks or sporadically with 3 or more episodes in the last year"
- Other important effect modifiers
  - Alternative diagnosis of ear discharge: cholesteatoma (n = 42)
  - Number who have previously had grommets inserted: 12
  - Number who have had previous ear surgery: 73
  - Number who had previous antibiotic treatment for CSOM: 65.6% (n = 197)

Inclusion criteria:

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

Exclusion criteria:

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

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

Ramos 2003 *(Continued)*

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

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

Risk of bias

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

Yuen 1994

Study characteristics

Yuen 1994 *(Continued)*

Methods	Non-blinded, parallel-group RCT, with 1 week of treatment and a total of 2 weeks follow-up

Participants	**Location:** Hong Kong, 1 site
	
	Setting of recruitment and treatment: outpatient clinic of the Otorhinolaryngology Unit, the University of Hong Kong, Queen Mary Hospital between October 1991 and February 1993
	
	Sample size: 60
	
	• **Number randomised:** 30 in ofloxacin group, 30 in amoxicillin-clavulanic acid group
	• **Number completed:** 29 in ofloxacin group, 27 in amoxicillin-clavulanic acid group
	
	Participant (baseline) characteristics:
	
	• Age: 18 to 70 years with a median of 35 years
	• Gender (F/M): 33 (55%)/23 (45%)
	• Main diagnosis: active chronic suppurative otitis media with central perforation
	• 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: size of perforation documented
	  * Presence of mucopurulent discharge: 39/60
	  * Duration of symptoms (discharge): not reported
	• 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: not reported
	  * Number who had previous antibiotic treatment for CSOM: not reported
	
	Inclusion criteria:
	
	• Active chronic suppurative otitis media with central perforation
	
	Exclusion criteria:
	
	• Cholesteatoma
	• Discharging mastoid cavity
	• Large aural polyp
	• Acute traumatic perforation
	• Acute otitis media
	• Presence of a grommet
	• History of radiotherapy of temporal bone and otomycosis
	• All patients had no prior antibiotic treatment for at least 1 week before commencement of treatment

Interventions	**Intervention (n = 30):** 0.3% ofloxacin ear drops 3 times daily for 1 week **Comparator group (n = 30)**: oral amoxicillin-clavulanic acid (375 mg) 3 times daily for 1 week **Concurrent treatment:** suction clearance of aural pus under microscopy (conducted after obtaining microbiology sample at baseline)
Outcomes	Outcomes of interest in the review: **Primary outcomes:** • Complete resolution of ear discharge, measured at between 1 to 2 weeks

Yuen 1994 *(Continued)*

	• Pain (otalgia) **Secondary outcomes:** • Hearing loss (pure-tone audiograms were carried out before commencement and after completion of treatment) • Suspected ototoxicity (tinnitus, hearing loss, dizziness)
Funding sources	"This study was supported in part by a grant (No. 335/048/0040) from the committee on research and conference grants of the University of Hong Kong."
Declarations of interest	No information provided
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized to two groups by drawing concealed envelopes." Comment: adequate randomisation sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomized to two groups by drawing concealed envelopes." Comment: no further information about how the allocation was concealed (e.g. opaque envelope) but should be adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: no blinding or placebo mentioned – should be unblinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The patients were instructed for the documentation of the degree of severity (graded into mild, moderate, and severe) of symptoms of otalgia, tinnitus, hearing loss, dizziness, and aural discharge daily for 2 weeks on a card…" Comment: patients were the main assessors of outcomes – not blinded and most outcomes were subjective
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 1/30 (3%) in the ofloxacin group and 2/30 (7%) in the amoxicillin-clavulanic acid group defaulted visits. One patient in the amoxicillin-clavulanic acid group stopped treatment early due to adverse effects. The attrition percentage was small and clearly documented.
Selective reporting (reporting bias)	Unclear risk	Comment: no published protocol was found. Some of the outcomes described as collected in the methods section were not fully reported, e.g. otalgia, degree of severity.

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

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

Study	Reason for exclusion
Abbott 2016	POPULATION: not CSOM (acute otitis media without perforation)
Adler 2000	POPULATION: acute otitis media with effusion for less than a week; patients with chronic or sub-chronic otitis media, or acute exacerbation of otitis media were specifically excluded
Agro 1998	STUDY DESIGN: not a RCT (current practice versus history control)
Arguedas 1993	STUDY DESIGN: not a RCT (all patients had the same intervention)
Aslan 1998	STUDY DESIGN: no description of randomisation INTERVENTION: low-dose versus high-dose topical antibiotics
Asmatullah 2014	COMPARISON: variety of topical antibiotics (see CSOM-1)
Baba 1980	INTERVENTION: comparison of antibiotics within same class and spectrum of activity (cefraxadine versus cephalexin); cefraxadine a withdrawn drug DURATION: only 6 days of follow-up
Baba 1982b	POPULATION: acute suppurative otitis media, including acute otitis media
Baba 1983	POPULATION: acute suppurative otitis media
Baba 1983b	POPULATION: acute suppurative otitis media
Baba 1983c	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 a RCT (all patients received the same intervention)
Baba 2008a	STUDY DESIGN: not a RCT (all patients received the same intervention)
Bakir 2013	STUDY DESIGN: not a RCT (prospective case-control study)
Berman 1990	POPULATION: middle ear effusion, not CSOM
Block 2000	POPULATION: not CSOM (acute otitis media without perforation of tympanic membrane)
Bogomil'skii 1999	POPULATION: less than half were COM. Not able to distinguish COM patients from other types of diagnosis - data not reported separately
Brook 1979	STUDY DESIGN: not a RCT - (alternative treatment) aminoglycosides only added when Gram-negative organisms present in large numbers
Brook 1980	STUDY DESIGN: not a RCT (all patients received the same intervention, additional intervention only added based on bacteriological findings)
Bross Soriano 1996	POPULATION: AOM; patients with CSOM were excluded
Browning 1983	INTERVENTION: standard antibiotics were not given, the choice was dependent on cultures
Browning 1983b	INTERVENTION: culture sensitivity-based prescribing versus empirical treatment with metronidazole

Study	Reason for exclusion
Browning 1984	STUDY DESIGN: not a RCT
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
CTRI/2019/09/021197	INTERVENTION: ayurvedic preparation is not an intervention under investigation
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)
Eason 1986	COMPARISON: systemic antibiotics versus none (see CSOM-2), topical steroids versus none (see CSOM-4), antiseptics versus none (see CSOM-5), and aural toilet versus none (see CSOM-7)
Esposito 2000	STUDY DESIGN: not a RCT (all patients had the same intervention - ceftazidime)
Fliss 1990	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Fombeur 1994	STUDY DESIGN: not a RCT (no mention of randomisation) INTERVENTION: high-dose versus low-dose ciprofloxacin
Fradis 1997	COMAPRISON: variety of topical antibiotics (see CSOM-1) and topical antiseptic versus none (see CSOM-6)
Garcia-Rodriguez 1993	POPULATION: mixture of patients, less than half had CSOM; patients were not stratified by diagnosis
Gehanno 1997	STUDY DESIGN: not a RCT (all patients had the same intervention)
Ghosh 2012	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Granath 2007	POPULATION: not CSOM (patients with recurrent acute otitis media with discharge through tympanostomy tube)
Gupta 2015	COMPARISON: antibiotic versus antiseptic (see CSOM-6)
Gyde 1978	COMPARISON: variety of topical antibiotics (see CSOM-1)
Gyde 1981	POPULATION: less than 50% (27/68) had CSOM
Gyde 1982	POPULATION: less than 50% had CSOM
Hemlin 1997	POPULATION: unilateral or bilateral secretory otitis media (COME) INTERVENTION: systemic corticosteroids
Hwang 2015	STUDY DESIGN: not a RCT (case-control study)

Study	Reason for exclusion
I-HEAR-BETA	COMPARISON: systemic antibiotic versus none (see CSOM-2), topical antiseptic versus none (see CSOM-5), topical antiseptic versus topical antibiotic (see CSOM-6)
IRCT20130427013136N6	POPULATION: patients had otitis externa
IRCT2016082313136N4	POPULATION: patients had otomycosis
ISRCTN12149720	INTERVENTION: antimicrobial peptide OP145
ISRCTN84220089	INTERVENTION: antimicrobial peptide OP145
Jahn 1984	STUDY DESIGN: not a RCT
Jamallulah 2016	COMPARISON: variety of topical antibiotics (see CSOM-1)
Jang 2004	STUDY DESIGN: not a RCT (mentioned use of a "control group", no mention of randomisation)
Jaya 2003	COMPARISON: topical antibiotic versus topical antiseptic (see CSOM-6)
Jiang 2016	INTERVENTION: comparison of two agents of the same class of antibiotics (erythromycin versus azithromycin) used in addition to a Traditional Chinese Medicine product
Kadar 2003	STUDY DESIGN: not a RCT
Kasemsuwan 1997	COMPARISON: topical antibiotic versus none (see CSOM-1)
Kashiwamura 2004	STUDY DESIGN: cohort (no comparison group) POPULATION: less than 50% with CSOM
Kaygusuz 2002	COMPARISON: topical antibiotics versus none (see CSOM-1) and variety of topical antibiotics plus steroids (see CSOM-4)
Kenna 1986	STUDY DESIGN: not a RCT; cohort study (no comparison group)
Khanna 2000	INTERVENTION: culture sensitivity-based prescribing
Khon 2012	POPULATION: not CSOM - either diffuse otitis externa or acute otitis externa STUDY DESIGN: no evidence of randomisation
Kothari 1969	STUDY DESIGN: not a RCT (no comparison)
Kovacic 1999	STUDY DESIGN: not a RCT (compared ofloxacin in patients who had previous ear surgery versus no previous ear surgery)
Kurilin 1976	STUDY DESIGN: not a RCT (no mention of RCT design or control group included for comparison)
Lancaster 1999	STUDY DESIGN: not a RCT (cross-sectional survey)
Lancaster 2003	STUDY DESIGN: not a RCT (compared compliance)
Lang 1992	STUDY DESIGN: not a RCT (case series)
Lautala 1983	STUDY DESIGN: not a RCT (case series)
Legent 1994	COMPARSION: variety of systemic antibiotics (see CSOM-2)

Study	Reason for exclusion
Li 2004	INTERVENTION: not an intervention of interest to the review (self-prepared Chinese herbal medicine ear drops)
Liu 1990	STUDY DESIGN: not a RCT
Liu 2003	COMPARISON: variety of topical antibiotics (see CSOM-1)
Loock 2012	COMPARISON: variety of topical antiseptics (see CSOM-5) and topical antibiotic versus topical antiseptic (see CSOM-6)
Lorente 1995	COMPARISON: variety of topical antibiotics (see CSOM-1)
Macfadyen 2005	COMPARISON: topical antibiotic versus topical antiseptic (see CSOM-6)
Merifield 1993	STUDY DESIGN: not a RCT (case series)
Mesure 1973	POPULATION: in clinical trial part of study (part 2) only one case of chronic otitis media
Minja 2006	COMPARISON: systemic antibiotic versus none (see CSOM-2) and topical antiseptic versus none (see CSOM-5)
Mira 1993	COMPARISON: adding topical antibiotic to systemic antibiotic (see CSOM-1)
Morgon 1976	STUDY DESIGN: single arm study
Nawasreh 2001	COMPARISON: variety of topical antibiotics (see CSOM-1)
Nwokoye 2015	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Onali 2018	COMPARISON: systemic antibiotic versus none (see CSOM-2)
Papastavros 1989	COMPARISON: topical antiseptic versus none (see CSOM-5)
Poliakova 1991	STUDY DESIGN: not a RCT
Principi 1995	POPULATION: acute and recurrent otitis media
Quick 1973	POPULATION: not CSOM (included acute tonsillitis, acute pharyngitis, acute sinusitis, acute otitis media, chronic sinusitis and peritonsillar abscess)
Quick 1975	POPULATION: not CSOM (only 6/145 patients had otitis media)
Renuknanada 2014	COMPARISON: systemic antibiotics added to topical antibiotics (see CSOM-2)
Roberts 2004	POPULATION: acute suppurative otitis media (duration of discharge less than 2 weeks)
Rotimi 1990	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Saez-Llorens 2005	POPULATION: AOM
Sanchez Gonzales 2001	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Siddique 2016	COMPARISON: variety topical antibiotics (see CSOM-1)
Singhal 1992	STUDY DESIGN: not a RCT (no comparison group)

Study	Reason for exclusion
Somekh 2000	COMPARISON: variety of systemic antibiotics (see CSOM-2)
Stenstrom 1991	POPULATION: acute otitis media; not CSOM
Sugiyama 1981	STUDY DESIGN: not a RCT (no indication of randomisation)
Sultan 2017	STUDY DESIGN: not a RCT - single intervention (oral levofloxacin) studied
Sumitsawan 1995	STUDY DESIGN: not a RCT - single intervention (ofloxacin drops) studied
Supiyaphun 1995	STUDY DESIGN: not a RCT (cohort - all patients received same treatment)
Tachibana 1986	STUDY DESIGN: not a RCT (all patients received same treatment)
Thomsen 1976	STUDY DESIGN: not a RCT POPULATION: acute suppurative otitis media
Tong 1996	COMPARISON: steroids added to topical antibiotics (see CSOM-4)
Tutkun 1995	COMPARISON: variety of topical antibiotics (see CSOM-1)
Van de Heyning 1986	STUDY DESIGN: not a RCT (cohort - all patients received same treatment)
van der Veen 2007	COMPARISON: systemic antibiotics versus none (see CSOM-2)
van Dongen 2014	POPULATION: 1) inclusion of minimum 2 weeks (review defined exclusion of 6 weeks perioperatively); 2) maximum duration of otorrhoea was 1 week
van Hasselt 1997	COMPARISON: variety of topical antibiotics (see CSOM-1) and topical antibiotics versus topical antiseptics (see CSOM-6)
van Hasselt 1998a	COMPARISON: variety of topical antibiotics (see CSOM-1)
Vishwakarma 2015	COMPARISON: topical antiseptic versus topical antibiotic (see CSOM-6)
Wintermeyer 1997	STUDY DESIGN: not a RCT (cohort)

AOM: acute otitis media; COM: chronic otitis media; CSOM: chronic suppurative otitis media; OME: otitis media with effusion; RCT: randomised controlled trial
For CSOM-1 to -7 Cochrane Reviews see Table 1.

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

Mehboob 2019

Methods	3-arm, unclear blinding, single-centre, parallel-group, unclear if RCT, with unclear duration of treatment and unclear duration of follow-up
Participants	**Location:** Pakistan, 1 site **Setting of recruitment and treatment:** ENT department of tertiary health care hospital in Karachi, May to September 2018 **Sample size:** 120 participants (120 ears)

Mehboob 2019 *(Continued)*

- **Number randomised:** 40 treated with ciprofloxacin, 40 treated with amoxicillin-clavulanic acid, 40 untreated (control)
- **Number completed:** not reported

Participant (baseline) characteristics:

- Age: range 18 to 75 years (inclusion criteria)
- Gender (F/M): 60 female (50%)/60 male (50%)
- Main diagnosis: unilateral ear presentation of 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: not reported, otoscopically confirmed
  * Presence of mucopurulent discharge: without fluid discharge at time of pure-tone audiometry
  * 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:

- Patients aged between 18 to 75 years
- Both the genders
- Unilateral ear presentation of CSOM without fluid discharge at the time of pure-tone audiometry

Exclusion criteria:

- Paediatric population
- Patients over 75 years
- History of neurological disorder or profound psychological distress, cardiac arrest, family history of sensorineural hearing loss or using hearing aid

Interventions	**Intervention (n = 40 participants):** ciprofloxacin, method of administration not reported, dosage not reported, duration of treatment not reported **Intervention (n = 40 participants):** amoxicillin-clavulanic acid, method of administration not reported, dosage not reported, duration of treatment not reported **Comparator group (n = 40 participants):** untreated **Concurrent treatment:** not reported
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Not reported **Secondary outcomes** • Hearing: pure-tone audiometry was examined at different frequencies using an audiometer with aural headphones to measure hearing thresholds
Notes	**Funding sources:** "University Research funding committee of JSMU"

Mehboob 2019 *(Continued)*

Unit of randomisation: person

Methods for reporting outcomes of patients with bilateral disease: not reported, only included unilateral presentation of CSOM

Hearing thresholds divided into 7 categories as normal (25 dB), mild (26 to 34 dB) hearing loss (HL), moderate (50 to 64 dB) HL, severe (65 to 79 dB) HL, profound (80 to 94 dB) HL and deaf

Objective: to study the correlation of hearing loss with depression, anxiety and stress in patients suffering from chronic suppurative otitis media in local population of Pakistan

Depression, anxiety and stress were scored taking depression, anxiety and stress scale (DASS) as tool and Likert scale was taken for scoring

Awaiting author reply regarding randomisation

Samarei 2014

Methods	2-arm, non-blinded, single-centre, parallel-group "RCT", with 10 to 17 days duration of treatment and 30 days duration of follow-up

Participants	**Location:** Iran, 1 site
	
	Setting of recruitment and treatment: not reported
	
	Sample size:
	
	• **Number randomised:** unclear – it appears some patients may have been excluded from the study
	• **Number completed:** 40 in topical ciprofloxacin, 32 in systemic ciprofloxacin
	
	Participant (baseline) characteristics:
	
	• Age: not reported
	• Gender (F/M): not reported
	• Main diagnosis: purulent active otorrhoea and perforated tympanic membrane for more than 3 months
	• High-risk population: unclear
	  * Cleft palate (or other craniofacial malformation): not reported
	  * Down syndrome: not reported
	  * Indigenous groups (Australian Aboriginals/Greenland natives): not reported
	  * Immunocompromised: not reported
	• Diagnosis method:
	  * Confirmation of perforated tympanic membrane: unclear (no method described but inclusion criteria implies all patients had perforated membrane)
	  * Presence of mucopurulent discharge: unclear (no method described but inclusion criteria implies all patients had purulent discharge)
	  * Duration of symptoms (discharge): 3 months (inclusion criteria)
	• Other important effect modifiers:
	  * Alternative diagnosis of ear discharge: 0%
	  * Number who have previously had grommets inserted: not reported
	  * Number who have had previous ear surgery: not reported
	  * Number who had previous antibiotic treatment for CSOM: not reported
	
	Inclusion criteria:
	
	• Purulent active otorrhoea and perforated tympanic membrane for more than 3 months
	
	Exclusion criteria:

Samarei 2014 *(Continued)*

	• Age less than 18 years • Pregnancy • Breastfeeding • Recent local drug • "Proposals for viral infections" • Sensitivity to the fluoroquinolone drug group • Use of systemic medications that are ototoxic • Concurrent infection of the middle and external fungal
Interventions	**Intervention (n = 40):** ciprofloxacin ear drops, unclear concentration, 2 drops twice daily, 10 days treatment and additional 7 days if ear not dry at 10 days **Comparator group (n = 32)**: ciprofloxacin orally 500 mg, 1 tablet twice daily, 10 days treatment and additional 7 days if ear not dry at 10 days **Concurrent treatment:** "regular suction for outer middle ear washings." No other concurrent treatment mentioned.
Outcomes	**Outcomes of interest in the review:** **Primary outcomes:** • Adverse effects (reported as measured in the methods but no results given) **Secondary outcomes:** • Hearing loss (measured as change in hearing threshold from baseline or at endpoint) • Adverse effects from treatment (reported as measured in the methods but no results given)
Notes	**Unit of randomisation:** person **Methods for including patients with bilateral disease:** not reported Awaiting author reply regarding randomisation

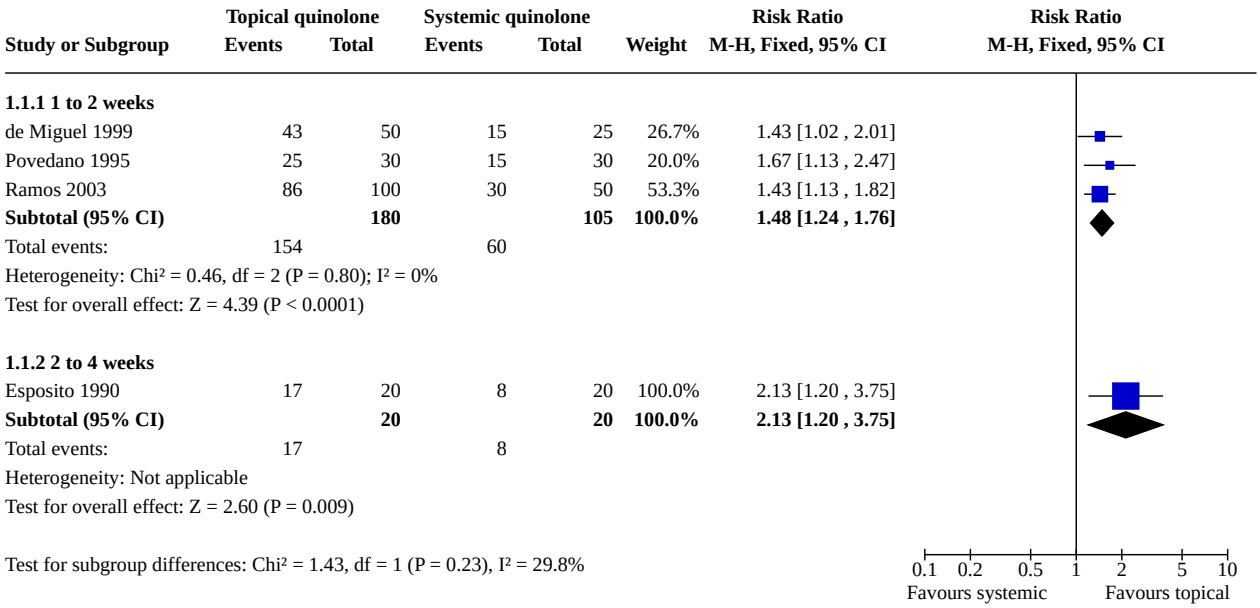
CSOM: chronic suppurative otitis media; F: female; M: male; RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Topical quinolone versus oral quinolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Resolution of ear discharge	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 1 to 2 weeks	3	285	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.24, 1.76]
1.1.2 2 to 4 weeks	1	40	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.20, 3.75]

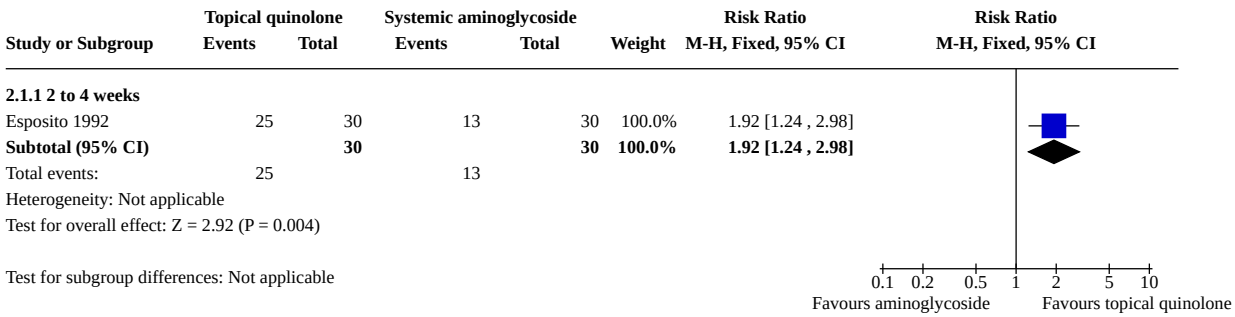
Analysis 1.1. Comparison 1: Topical quinolone versus oral quinolone, Outcome 1: Resolution of ear discharge



Comparison 2. Topical quinolone versus intramuscular gentamicin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Resolution of ear discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1.1 2 to 4 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.24, 2.98]

Analysis 2.1. Comparison 2: Topical quinolone versus intramuscular gentamicin, Outcome 1: Resolution of ear discharge

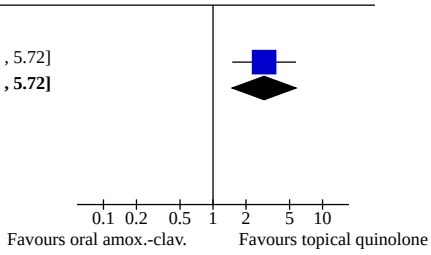


Comparison 3. Topical quinolone versus oral amoxicillin-clavulanic acid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Resolution of ear discharge	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1.1 1 to 2 weeks	1	56	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [1.50, 5.72]
3.2 Resolution of ear discharge - sensitivity analysis, re-including excluded case	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.2.1 1 to 2 weeks	1	57	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [1.55, 5.95]

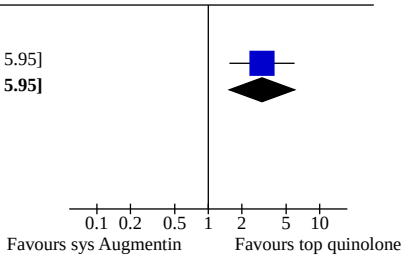
Analysis 3.1. Comparison 3: Topical quinolone versus oral amoxicillin-clavulanic acid, Outcome 1: Resolution of ear discharge

Study or Subgroup	Topical quinolone Events	Total	Systemic amox.-clav. acid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 1 to 2 weeks						
Yuen 1994	22	29	7	27	100.0%	2.93 [1.50 , 5.72]
Subtotal (95% CI)		**29**		**27**	**100.0%**	**2.93 [1.50 , 5.72]**
Total events:	22		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.14 (P = 0.002)						
Test for subgroup differences: Not applicable						



Analysis 3.2. Comparison 3: Topical quinolone versus oral amoxicillin-clavulanic acid, Outcome 2: Resolution of ear discharge - sensitivity analysis, re-including excluded case

Study or Subgroup	Topical quinolone Events	Total	Systemic amox.-clav. acid Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 1 to 2 weeks						
Yuen 1994	22	29	7	28	100.0%	3.03 [1.55 , 5.95]
Subtotal (95% CI)		**29**		**28**	**100.0%**	**3.03 [1.55 , 5.95]**
Total events:	22		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.23 (P = 0.001)						
Test for subgroup differences: Not applicable						



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 2020a).
CSOM-2: Systemic antibiotics for chronic suppurative otitis media (Chong 2021).
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 2020b).
CSOM-5: Topical antiseptics for chronic suppurative otitis media (Head 2020a).
CSOM-6: Antibiotics versus topical antiseptics for chronic suppurative otitis media (Head 2020b).
CSOM-7: Aural toilet (ear cleaning) for chronic suppurative otitis media (Bhutta 2020).

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

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

Table 3. Summary of included studies

Ref ID (no. participants)	Setting	Population	Intervention 1	Intervention 2	Treatment duration	Follow-up	Background Treatment	Notes
1. Topical quinolone versus oral quinolones								
de Miguel 1999 (n = 75)	Spain, general hospital	Chronic otitis media Mean age 39.6 years	Topical ciprofloxacin 0.2%/0.5%, 3 drops/8 hours	Oral ciprofloxacin, 500 mg/12 hours	7 days	15 days	All patients had aspiration and cleaning of ear secretions before beginning treatment Analgesics and antipyretics	Part of a 5-arm trial
Esposito 1990 (n = 40)	Italy, university clinic	Mild or moderate CSOM in the acute stage Mean age 38 years	Topical ciprofloxacin 250 µg/mL in saline solution, 3 drops twice daily	Oral ciprofloxacin 250 mg twice daily	5 days, up to 10 days if not cured	14 days	None	Part of 3-arm trial
Povedano 1995 (n = 60)	Spain, general hospital	Active phase of chronic otorrhoea Mean age 45 years	Topical ciprofloxacin 250 µg/mL, 5 ear drops/12 hours	Oral ciprofloxacin, 500 mg/12 hours	10 days	10 days	None	—
Ramos 2003 Ramos 2003 (n = 150)	Spain, ENT department of 3 tertiary hospitals	Simple chronic otitis media (42.7%), chronic otitis media with osteolysis (19%), chronic cholesteatoma (14%), chronic otorrhoea in operated ears 24.3%) Age range 5 to 73, 12% were children < 14 years	Topical ciprofloxacin 0.2%/0.5%, 0.5 mL/8 hours	Oral ciprofloxacin 500 mg, 12-hourly	7 days	10 days	None	Part of 6-arm trial
2. Topical quinolone versus intramuscular gentamicin								
Esposito 1992 (n = 60)	Italy, university clinic	Mild to moderate otitis media in acute stage with perforation of tympanic membrane Adults > 18 years old	Topical ciprofloxacin hydrochloride, 250 mg/mL, 12-hourly	Intramuscular gentamicin sulphate, 80 mg, 12-hourly	5 to 10 days	21 days after interruption of treatment	None	—

Table 3. Summary of included studies *(Continued)*

3. Topical quinolone versus oral systemic beta-lactams

Yuen 1994 (n = 60)	Hong Kong, university otorhinolaryngology outpatient clinic	Active chronic suppurative otitis media with central perforation Age range 18 to 70, median 35	Topical ofloxacin 0.3%, 3 times daily	Oral amoxicillin-clavulanic acid 375 mg, 3 times daily	1 week	2 weeks	Suction clearance of aural pus under microscopy conducted after obtaining microbiology sample at baseline	—

CSOM: chronic suppurative otitis media

Table 4. Resolution of ear discharge

Reference	Unit of randomisation	Reported	Definition	Otoscopically confirmed?	Time points	Notes
de Miguel 1999	Person	Person	"global index of clinical microbiological cure"	Yes	1 to 2 weeks (7 days)	—
Esposito 1990	Person	Person	"clinically cured"	Unclear	1 to 2 weeks (5 to 11 days), 2 to 4 weeks (19 to 24 days)	Results examined but not reported at 1 to 2 weeks
Esposito 1992	Person	Person	"clinically and bacteriologically cured"	Unclear	2 to 4 weeks (19 to 31 days)	Authors describe follow-up as taking place 14 to 21 days after treatment cessation (treatment was for 5 to 10 days)
Povedano 1995	Person	Person	"healed" ("curation")	Unclear	1 to 2 weeks (10 days)	Results described as healing, improvement or failure "Healing" should correspond with "dry ear" since even patients with "improvement" were described as no longer having otorrhoea
Ramos 2003	Person	Person	"cured" according to "indices de curacion"	Yes	1 to 2 weeks (10 days)	—
Yuen 1994	Person	Person	"dry"	Unclear	1 to 2 weeks (end of second week)	No information provided on whether there were participants with bilateral CSOM and how these data were counted

CSOM: chronic suppurative otitis media

APPENDICES

Appendix 1. Search strategies

CENTRAL (CRS Web)	MEDLINE (Ovid)	Embase (Ovid)
1 MESH DESCRIPTOR Otitis Media EXPLODE ALL AND CENTRAL:TARGET1061 2 ("otitis media" or OME):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET2347 3 MESH DESCRIPTOR Tympanic Membrane Perforation EXPLODE ALL AND CENTRAL:TARGET71 4 MESH DESCRIPTOR Tympanic Membrane EXPLODE ALL AND CENTRAL:TARGET257 5 ("ear drum*" or eardrum* or tympanic):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET967	1 exp Otitis Media/ 2 ("otitis media" or OME).ab,ti. 3 exp Tympanic Membrane Perforation/ 4 exp Tympanic Membrane/	1 exp otitis media/ 2 ("otitis media" or OME).ab,ti. 3 exp eardrum perforation/ 4 exp eardrum/ 5 ("ear drum*" or eardrum* or tympanic).ab,ti. 6 4 or 5

(Continued)

6 #4 OR #5 AND CENTRAL:TARGET967
7 (perforat* or hole or ruptur*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET0
8 #6 AND #7 AND CENTRAL:TARGET0
9 #1 OR #2 OR #3 OR #8 AND CENTRAL:TARGET2386
10 MESH DESCRIPTOR Suppuration EXPLODE ALL AND CENTRAL:TARGET891
11 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or discomfort or earach* or mucopurulen*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET90987
12 (pain):AB,TI,TO AND CENTRAL:TARGET87639
13 #10 or #11 or #12 AND CENTRAL:TARGET165103
14 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND CENTRAL:TARGET11305
15 MESH DESCRIPTOR Recurrence EXPLODE ALL AND CENTRAL:TARGET10431
16 (chronic* or persist* or recurr* or repeat*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET182517
17 #14 OR #15 OR #16 AND CENTRAL:TARGET182523
18 #9 AND #17 AND #13 AND CENTRAL:TARGET378
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:TARGET0
20 ((earach* near (chronic or persist* or recurr* or repeat*))):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET3
21 MESH DESCRIPTOR Otitis Media, Suppurative EXPLODE ALL AND CENTRAL:TARGET104
22 (CSOM):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET88
23 #20 OR #21 OR #22 OR #18 OR #19 AND CENTRAL:TARGET418

5 ("ear drum*" or eardrum* or tympanic).ab,ti.

6 4 or 5

7 (perforat* or hole or ruptur*).ab,ti.

8 6 and 7

9 1 or 2 or 3 or 4 or 8

10 exp Suppuration/ n

11 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or moist or wet or mucopurulen* or discomfort or pain* or earach*).ab,ti.

12 10 or 11

13 exp Chronic Disease/

14 exp Recurrence/

15 (chronic* or persist* or recurr* or repeat*).ab,ti.

16 13 or 14 or 15

17 9 and 12 and 16

18 ((chronic or persist*) adj3 (ear or ears or aural) adj3 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort)).ab,ti.

19 CSOM.ab,ti.

20 exp Otitis Media, Suppurative/

21 (earach* adj6 (chronic or persist* or recurr* or repeat*)).ab,ti.

22 17 or 18 or 19 or 20 or 21

7 (perforat* or hole or ruptur*).ab,ti.

8 6 and 7

9 1 or 2 or 3 or 8

10 exp suppuration/

11 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or moist or wet or mucopurulen* or discomfort or pain* or earach*).ab,ti.

12 10 or 11

13 exp chronic disease/

14 exp recurrent disease/

15 (chronic* or persist* or recurr* or repeat*).ab,ti.

16 13 or 14 or 15

17 9 and 12 and 16

18 exp suppurative otitis media/

19 CSOM.ab,ti.

20 ((chronic or persist*) adj3 (ear or ears or aural) adj3 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort or disease*)).ab,ti.

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

22 17 or 18 or 19 or 20 or 21

Web of Science (Web of Knowledge)	CINAHL (EBSCO)	Cochrane ENT Register (CRS Web)
#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 pu-	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

(Continued)

#2 TOPIC: (("ear drum*" or eardrum* or tympanic) AND (perforat* or hole or ruptur*))

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#3 #2 OR #1

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#4 TOPIC: ((suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or moist or wet or mucopurulen* or discomfort or pain* or earach*) AND (chronic* or persist* or recurr* or repeat*))

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#5 #4 AND #3

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#6 TOPIC: (((chronic or persist*) NEAR/3 (ear or ears or aural) NEAR/3 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort)))

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#7 TOPIC: ((earach* NEAR/3 (chronic or persist* or recurr* or repeat*)))

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#8 #7 OR #6 OR #5

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

rulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort))

S19 TX (earach* N3 (chronic or persist* or recurr* or repeat*))

S18 TX csom

S17 S9 AND S12 AND S16

S16 S13 OR S14 OR S15

S15 TX chronic* or persist* or recurr* or repeat*

S14 (MH "Recurrence")

S13 (MH "Chronic Disease")

S12 S10 OR S11

S11 TX suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or moist or wet or mucopurulen* or discomfort or pain* or earach*)

S10 (MH "Suppuration+")

S9 S1 OR S2 OR S3 OR S8

S8 S6 AND S7

S7 TX perforat* or hole or ruptur*

S6 S4 OR S5

S5 TX "ear drum*" or eardrum* or tympanic

S4 (MH "Tympanic Membrane")

S3 (MH "Tympanic Membrane Perforation")

S2 TX "otitis media" or OME

S1 (MH "Otitis Media+")

3 (perforat* or hole or ruptur*):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER

4 #2 AND #3 AND INREGISTER

5 #4 OR #1 AND INREGISTER

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

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

8 #6 OR #7 AND INREGISTER

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

10 #5 AND #8 AND #9 AND INREGISTER

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

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

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

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

ClinicalTrials.gov (CRS Web)	ICTRP (WHO Portal)	Other
Search 1: (chronic OR persistent OR recurrence OR recurrent) AND (suppuration OR pus OR discharge OR otorrhea or active OR mucopurulent)	otitis media AND chronic OR ear discharge OR earache OR wet ear OR weeping ear OR moist ear OR CSOM OR OME	**LILACS** TW:"otitis media" OR "TW:"ear discharge" OR TW:earache OR ((TW:eardrum OR TW:tympanic) AND

(Continued)

AND Condition: "Otitis Media" OR OME AND Study type: interventional **Search 2:** (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:** ("ear drum" OR eardrum OR "tympanic membrane") AND (hole OR perforation OR rupture) AND Study type: interventional	AND chronic OR tympanic membrane AND perforation OR eardrum AND hole OR eardrum AND perforation	(TW:perforation OR hole)) OR ((TW:wet OR moist OR weeping) AND TW:ear) AND: Filter: Controlled Clinical Trial **IndMed** otitis media OR ear discharge OR csom OR earache OR wet ear OR tympanic membrane perforation OR eardrum hole OR wet ear OR weeping ear or moist ear OR OME **PakMediNet** otitis media | ear discharge | csom | earache | wet ear | tympanic membrane perforation | eardrum hole | wet ear | weeping ear **African Index Medicus** "otitis media" OR "ear discharge" OR CSOM

Appendix 2. Data extraction form

REF ID:	Study title:
Date of extraction:	Extracted by:
Name and email address of correspondence authors:	
General comments/notes (internal for discussion):	

FLOW CHART OF TRIAL:

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

(Continued)

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

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

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

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

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

(Continued)

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

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

(Continued)

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

RISK OF BIAS TABLE:

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

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

FINDINGS OF STUDY

CONTINUOUS OUTCOMES

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

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

DICHOTOMOUS OUTCOMES

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

(Continued)

Time point: [xx]

Dizziness/vertigo/balance

[Measurement method or definition used]

Time point: [xx]

Serious complications:
[State whether the paper had prespecified looking for this event, how it was diagnosed]

Time point: state length of follow-up of the trial

Note down the page number / table where info was found for ease of checking

Otitic meningitis

[How was this diagnosed?]

Lateral sinus thrombosis

[How was this diagnosed?]

Cerebellar abscess

[How was this diagnosed?]

Mastoid abscess/mastoiditis

[How was this diagnosed?]

Postauricular fistula

[How was this diagnosed?]

Facial palsy

[How was this diagnosed?]

Other complications

[How was this diagnosed?]

Death

[How was this diagnosed?]

Multiple serious complications

[How was this diagnosed?]

Comment/additional notes:

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

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

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

HISTORY

Protocol first published: Issue 6, 2018
Review first published: Issue 2, 2021

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

Lee Yee Chong: none known.
Karen Head: none known.
Katie Webster: none known.
Jessica Daw: none known.
Peter Richmond: none known.
Tom Snelling: none known.
Anne GM Schilder: Professor Anne Schilder was joint Co-ordinating Editor of Cochrane ENT until April 2020, but had no role in the editorial process for this review. Her evidENT team at UCL is supported by the National Institute of Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC), with research being funded by the NIHR, Wellcome Trust and EU Horizon2020. She is the National Specialty Lead for the NIHR Clinical Research Network ENT and Surgical Specialty Lead for ENT for the Royal College of Surgeons of England's Clinical Research Initiative. In her role as director of the NIHR UCLH BRC Deafness and Hearing Problems Theme, she acts as an advisor on clinical trial design and delivery to a range of biotech companies in the hearing field.
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.
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.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

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

There is no 'Summary of findings' table for 'Topical antibiotic versus the same antibiotic administered systemically, where topical antiseptics were used in both arms' because no studies addressed this comparison.