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[Intervention Protocol]

Topical versus systemic antibiotics for chronic suppurative otitis media

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

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

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 will compare 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, charac-

terised 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 will use CSOM only to refer to tympanic membrane perforation, with intermittent or continuous ear discharge (Gates 2002). We will use a duration of otorrhoea of two weeks as an inclusion criterion, in accordance with the definition used by the World Health Organization, but we will use 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 will also include, 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 will therefore focus 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, people with cholesteatoma will not be included in these reviews.

Description of the intervention

Antibiotics are the most commonly used treatment for CSOM. They can be administered topically (as drops, ointments, sprays or creams to the affected area) or systemically (either by mouth or by injection into a vein (intravenous) or muscles (intramuscular)). Topical application has the advantage of potentially delivering high concentrations of antibiotic to the affected area, whereas systemic antibiotics are absorbed and distributed throughout the body. However, the penetration of topical antibiotics into the middle ear may be compromised if the perforation in the tympanic membrane is small or there is copious mucopurulent discharge in the ear canal that cannot be cleaned. It may also be difficult to achieve compliance with topical dosing in young children. In these cases, systemic antibiotics may have an advantage.

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 active against the most frequently cultured micro-organisms (*Pseudomonas aeruginosa* and *Staphylococcus aureus*), are therefore commonly used (Mittal 2015) (Table 2). It is possible that antibiotics for CSOM that target *Pseudomonas aeruginosa* may have an advantage over antibiotics that do not. Dose and duration of treatment are also important factors but are less likely to affect relative effectiveness if given within the therapeutic range. Generally, treatment for at least five days is necessary and a duration of one to two weeks is sufficient to resolve uncomplicated infections. However, in some cases it may take more than two weeks for the ear to become dry and therefore longer follow-up (more than four weeks) may be needed to monitor for recurrence of discharge. Some antibiotics (such as aminoglycosides) can be toxic to the inner ear (ototoxicity), which might be experienced as sensorineural hearing loss, dizziness or tinnitus, but this is less likely to be a risk when applied topically in patients with CSOM (Phillips 2007). 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, for example diarrhoea or nausea. However, the risk or incidence of these events is not expected to be different from other common infections since the doses and duration of treatment used are similar in CSOM. A broader concern is the association of the overuse of antibiotics with increasing resistance among community- and hospital-acquired pathogens.

Why it is important to do this review

Although 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. 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 relative effectiveness 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 will include 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 will exclude 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 are available, we will exclude 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 will include studies with patients (adults and children) who had:

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

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

We will define 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 will **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 will record these factors in the patient characteristics section during data extraction from the studies. If any of the included studies mostly recruited these patients (80% or more), we will analyse them in a subgroup analysis (see [Subgroup analysis and investigation of heterogeneity](#)).

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

Types of interventions

Intervention

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

We will exclude studies that conduct swabs and tests for antimicrobial sensitivity and then base the choice of antibiotics for each participant on the results of the laboratory test.

Duration

At least five days of treatment with antibiotics is 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 is no limitation on the dose, concentration, volume or frequency of application.

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

Comparisons

The following are 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 will analyse these as three main scenarios depending on which common therapy is applied in the background:

- **Topical versus systemic antibiotics as a single treatment (main therapy):** this will include studies where all participants in both treatment groups either received no other treatment or only received aural toileting. This will also include situations where antiseptics are 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 will include 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 will include studies where all participants in both treatment groups also received a systemic or topical antibiotic, with or without aural toileting or antiseptics.

Many comparison pairs are possible in this review. The main comparisons of interest that we will summarise and present in the 'Summary of findings' table will be:

- 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 are used in both arms.

Types of outcome measures

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

We will extract and report 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 is not available, we will report the pure-tone average of the thresholds measured.
 - Serious complications, including intracranial complications (such as otitic meningitis, lateral sinus thrombosis and cerebellar abscess) and extracranial complications (such as mastoid abscess, postauricular fistula and facial palsy), and death.
 - Ototoxicity; this will be 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 will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

- the Cochrane Register of Studies ENT Trials Register (search via CRS Web to date);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (search via CRS Web to date);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to present);
- Ovid EMBASE (1974 to date);
- EBSCO CINAHL (1982 to date);
- LILACS (search to date);
- KoreaMed (search to date);
- IndMed (search to date);
- PakMediNet (search to date);
- African Index Medicus (search to date);
- Web of Knowledge, Web of Science (1945 to date);
- ClinicalTrials.gov, www.clinicaltrials.gov (search via the Cochrane Register of Studies to date);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search to date);
- ISRCTN, www.isrctn.com (search to date).

The subject strategies for databases are detailed in [Appendix 1](#). The strategy has been designed to identify all relevant studies for a suite of reviews on various interventions for chronic suppurative otitis media ([Bhutta 2018](#); [Brennan-Jones 2018a](#); [Brennan-Jones 2018b](#); [Chong 2018a](#); [Chong 2018b](#); [Head 2018a](#); [Head 2018](#)). Where appropriate, these will be 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 will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. The Information Specialist will also run non-systematic searches of Google

Scholar to retrieve grey literature and other sources of potential trials.

Data collection and analysis

Selection of studies

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

We will resolve 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) will independently extract data from each study using a standardised data collection form (see [Appendix 2](#)). Whenever a study has more than one publication, we will retrieve all publications to ensure complete extraction of data. Where there are discrepancies in the data extracted by different review authors, we will check these against the original reports and resolve differences by discussion and consensus, with the involvement of a third author or a methodologist where appropriate. We will contact the original study authors for clarification or for missing data whenever possible. If differences are found between publications of a study, we will contact the original authors for clarification. We will use data from the main paper(s) if no further information is found.

We will include 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 will also collect baseline information on prognostic factors or effect modifiers (see [Appendix 2](#)). For this review, this will include the following information whenever available:

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

We will record 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 will extract the findings of the studies on an available case analysis basis, i.e. we will include data from all patients available at the time points based on the treatment randomised whenever possible, irrespective of compliance or whether patients had received the treatment as planned.

In addition to extracting pre-specified information about study characteristics and aspects of methodology relevant to risk of bias, we will extract 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 are not available, we will extract the values for change from baseline. We will analyse 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 experiencing an event and the number of patients assessed at the time point.
- For ordinal scale data: if the data appear to be approximately normally distributed or if the analysis that the investigators performed suggests parametric tests were appropriate, then we will treat the outcome measures as continuous data. Alternatively, if data are available, we plan to convert into binary data.
- Time-to-event outcomes: we are not expecting any outcomes to be measured as time-to-event data. However, if outcomes such as resolution of ear discharge are measured in this way, we will report the hazard ratios.

For resolution of ear discharge, we will extract 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 will report the results from the longest available follow-up period.

Extracting data for pain/discomfort and adverse effects

For these outcomes, there will be variations in how studies have reported the outcomes. For example, some studies will report both 'pain' and 'discomfort' separately whereas others will not. Prior to the commencement of data extraction, we will agree and specify a data extraction algorithm for how data should be extracted.

We will extract data for serious complications as a composite outcome. If a study reports more than one complication and we cannot distinguish whether these occurred in one or more patients, we will extract the data with the highest incidence. This prevents double counting.

Extracting data from figures

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

Assessment of risk of bias in included studies

At least two review authors (KH/LYC/CBJ/MB) will independently assess the risk of bias of each included study. We will follow the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Handbook 2011](#)), using the Cochrane 'Risk of bias' tool. With this tool we will assess 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 will summarise 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 we will present in the 'Summary of findings' table, we will also express the results as absolute numbers based on the pooled results and compared to the assumed risk. We also plan to calculate the number needed to treat to benefit (NNTB) using the pooled results. The assumed baseline risk will typically be 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 are available, and where appropriate, we also plan to present additional data based on the assumed baseline risk in (c) a low-risk population and (d) a high-risk population.

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

Unit of analysis issues

Cross-over studies

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

The patient as the unit of randomisation

Some studies randomise by patient and those with bilateral CSOM will receive 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 is expected to be very high, and if both ears are counted in the analysis this is effectively a form of double counting, which may be especially problematic in smaller studies if the number of people with bilateral CSOM is unequal. We will not exclude these studies, but we will only report the results if the paper presents the data in such a way that we can include the data from each participant only once (one data point per participant) or if we have 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 is not possible we will contact the authors for more information. If there is no response from the authors, then we will not include data from these studies in the analysis. If we find cluster-randomised trials by setting or operator, we will analyse 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 will contact study authors via email whenever the outcome of interest is not reported, if the methods of the study suggest that the outcome had been measured. We will do the same if not all data required for meta-analysis are reported, unless the missing data are standard deviations. If standard deviation data are not available, we will approximate these using the standard estimation methods from P values, standard errors or 95% CIs if these are reported, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). Where it is impossible to estimate these, we will contact the study authors.

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

Assessment of heterogeneity

We will assess 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 will not pool studies where the clinical heterogeneity makes it unreasonable to do so.

We will assess statistical heterogeneity by visually inspecting the forest plots and by considering the Chi² test (with a significance

level set at P value < 0.10) and the I² statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance, with I² values over 50% suggesting substantial heterogeneity (Handbook 2011).

Assessment of reporting biases

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

Outcome reporting bias (within-study reporting bias)

We will assess within-study reporting bias by comparing the outcomes reported in the published report against the study protocol, whenever this can be obtained. If the protocol is not available, we will compare the outcomes reported to those listed in the methods section. If results are mentioned but not reported adequately in a way that allows analysis (e.g. the report only mentions whether the results were statistically significant or not), bias in a meta-analysis is likely to occur. We will try to find further information from the study authors. If no further information can be obtained, we will note this as being a high risk of bias. Where there is insufficient information to judge the risk of bias, we will note this as an unclear risk of bias (Handbook 2011).

Publication bias (between-study reporting bias)

We plan to create funnel plots if sufficient studies (more than 10) are available for an outcome. If we observe asymmetry of the funnel plot, we plan to conduct more formal investigation using the methods proposed by Egger 1997.

Data synthesis

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

For continuous outcomes, if all the data are from the same scale, we plan to pool mean values obtained at follow-up with change outcomes and report this as a MD. However, if the SMD has to be used as an effect measure, we will 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 will subgroup studies where most participants (80% or more) meet the criteria stated below in order to determine whether the effect of the intervention is different compared to other patients. Due to the risks of reporting and publication bias with unplanned subgroup analyses of trials, we will only analyse subgroups reported in studies if these were prespecified and stratified at randomisation. We plan to conduct subgroup analyses regardless of whether statistical heterogeneity is observed for studies that included **patients identified as high risk** (i.e. thought to be less responsive to treatment and more likely to develop CSOM, recurrence or complications) and patients with ventilation tubes (grommets). 'High risk' patients include Indigenous populations (e.g. Australian Aboriginal and Torres Strait Islanders, Native Americans and Inuit populations of Alaska, Canada and Greenland), people with craniofacial malformation (e.g. cleft palate), Down syndrome and people with known immunodeficiency.

We plan 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 applies to the outcomes resolution of ear discharge (dry ear), quality of life, pain/discomfort, development of complications and hearing loss.

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

For this review, effect modifiers include:

- **Diagnosis of CSOM:** it is likely that some studies will include patients with chronic ear discharge but who have not had a diagnosis of CSOM. Therefore, we will subgroup studies where most patients (80% or more) meet the criteria for CSOM diagnosis in order to determine whether the effect of the intervention is different compared to patients where the precise diagnosis is unknown and inclusion into the study is based purely on chronic ear discharge symptoms.

- **Duration of ear discharge:** there is uncertainty about whether the duration of ear discharge prior to treatment has an impact on the effectiveness of treatment and whether more established disease (i.e. discharge for more than six weeks) is more refractory to treatment compared with discharge of a shorter duration (i.e. less than six weeks).

- **Patient age:** patients who are 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 will present the results as subgroups regardless of the presence of statistical heterogeneity based on the following two factors:

- Class of antibiotics. We will group by pharmacological class, e.g. quinolones, aminoglycosides, penicillins etc. The rationale for this is that different classes may have 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 are also used as a common treatment in both the intervention and comparison group, we will investigate the class and antipseudomonal activity when statistical heterogeneity is present and cannot be explained by the other subgroup analyses.

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

Sensitivity analysis

We plan to carry out sensitivity analyses to determine whether the findings are robust to the decisions made in the course of identifying, screening and analysing the trials. We plan 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 will define 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 is statistical heterogeneity, studies that only recruited patients who had previously not responded to one of the treatments under investigation in the RCT. Studies that specifically recruited patients who did not respond to a treatment could potentially have reduced the relative effectiveness of an agent.

If any of these investigations finds a difference in the size of the effect or heterogeneity, we will mention this in the 'Effects of interventions' section and/or present the findings in a table.

GRADE and 'Summary of findings' table

Using the GRADE approach, at least two review authors (KH/LYC) will independently rate the overall quality of evidence using the GDT tool (<http://www.guidelinedevelopment.org/>) for the main comparison pairs listed in the [Types of interventions](#) section. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: 'high', 'moderate', 'low' and 'very low' ([Handbook 2011](#)). A

rating of 'high' quality evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of 'very low' quality implies that any estimate of effect obtained is very uncertain.

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

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

The 'Summary of findings' tables will 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.

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* Indicates the major publication for the study

ADDITIONAL TABLES**Table 1. Table of Cochrane Reviews**

	Topical antibiotics with steroids	Topical antibiotics	Systemic antibiotics	Topical antiseptics	Aural toileting (ear cleaning)
Topical antibiotics with steroids	Review CSOM-4				
Topical antibiotics	Review CSOM-4	Review CSOM-1			
Systemic antibiotics	Review CSOM-4	Review CSOM-3	Review CSOM-2		
Topical antiseptics	Review CSOM-4	Review CSOM-6	Review CSOM-6	Review CSOM-5	
Aural toileting	Review CSOM-4	Not reviewed	Not reviewed	Not reviewed	Review CSOM-7
Placebo (or no intervention)	Review CSOM-4	Review CSOM-1	Review CSOM-2	Review CSOM-5	Review CSOM-7

CSOM-1: Topical antibiotics for chronic suppurative otitis media ([Brennan-Jones 2018a](#)).

CSOM-2: Systemic antibiotics for chronic suppurative otitis media ([Chong 2018a](#)).

CSOM-3: Topical versus systemic antibiotics for chronic suppurative otitis media ([Chong 2018b](#)).

CSOM-4: Topical antibiotics with steroids for chronic suppurative otitis media ([Brennan-Jones 2018b](#)).

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

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

CSOM-7: Aural toilet (ear cleaning) for chronic suppurative otitis media ([Bhutta 2018](#)).

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

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

APPENDICES

Appendix I. Search strategies

CENTRAL (CRS Web)	MEDLINE (Ovid)	Embase (Ovid)
1 MESH DESCRIPTOR Otitis Media EXPLODE ALL AND CENTRAL:TARGET1061	1 exp Otitis Media/	1 exp otitis media/
2 ("otitis media" or OME):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET2347	2 ("otitis media" or OME).ab,ti.	2 ("otitis media" or OME).ab,ti.
3 MESH DESCRIPTOR Tympanic Membrane Perforation EXPLODE ALL AND CENTRAL:TARGET71	3 exp Tympanic Membrane Perforation/	3 exp eardrum perforation/
4 MESH DESCRIPTOR Tympanic Membrane EXPLODE ALL AND CENTRAL:TARGET257	4 exp Tympanic Membrane/	4 exp eardrum/
5 ("ear drum" or eardrum* or tympanic):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET967	5 ("ear drum" or eardrum* or tympanic).ab,ti.	5 ("ear drum" or eardrum* or tympanic).ab,ti.
6 #4 OR #5 AND CENTRAL:TARGET967	6 4 or 5	6 4 or 5
7 (perforat* or hole or ruptur*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET0	7 (perforat* or hole or ruptur*).ab,ti.	7 (perforat* or hole or ruptur*).ab,ti.
	8 6 and 7	8 6 and 7
	9 1 or 2 or 3 or 4 or 8	9 1 or 2 or 3 or 8
	10 exp Suppuration/ n	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	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	12 10 or 11
	13 exp Chronic Disease/	13 exp chronic disease/
	14 exp Recurrence/	14 exp recurrent disease/
	15 (chronic* or persist* or recurr* or re-	

(Continued)

8 #6 AND #7 AND CENTRAL:TARGET0	peat*).ab,ti.	15 (chronic* or persist* or recurr* or repeat*).ab,ti.
9 #1 OR #2 OR #3 OR #8 AND CENTRAL:TARGET2386	16 13 or 14 or 15	16 13 or 14 or 15
10 MESH DESCRIPTOR Suppuration EXPLODE ALL AND CENTRAL:TARGET891	17 9 and 12 and 16	17 9 and 12 and 16
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	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	18 exp suppurative otitis media/
12 (pain):AB,TI,TO AND CENTRAL:TARGET87639	19 CSOM.ab,ti.	19 CSOM.ab,ti.
13 #10 or #11 or #12 AND CENTRAL:TARGET165103	20 exp Otitis Media, Suppurative/	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
14 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND CENTRAL:TARGET11305	21 (earach* adj6 (chronic or persist* or recurr* or repeat*)).ab,ti	21 (earach* adj3 (chronic or persist* or recurr* or repeat*)).ab,ti
15 MESH DESCRIPTOR Recurrence EXPLODE ALL AND CENTRAL:TARGET10431	22 17 or 18 or 19 or 20 or 21	22 17 or 18 or 19 or 20 or 21
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		

(Continued)

Web of Science (Web of Knowledge)	CINAHL (EBSCO)	Cochrane ENT Register (CRS Web)
<p>#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</p> <p>#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</p> <p>#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</p> <p>#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</p> <p>#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</p> <p>#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</p> <p>#7 TOPIC: ((earach* NEAR/3 (chronic or persist* or recurr* or repeat*))) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S,</p>	<p>S21 S17 OR S18 OR S19 OR S20 S20 TX ((chronic or persist*) N3 (ear or ears or aural) N3 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort)) S19 TX (earach* N3 (chronic or persist* or recurr* or repeat*)) S18 TX csom S17 S9 AND S12 AND S16 S16 S13 OR S14 OR S15 S15 TX chronic* or persist* or recurr* or repeat* S14 (MH "Recurrence") S13 (MH "Chronic Disease") S12 S10 OR S11 S11 TX suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or moist or wet or mucopurulen* or discomfort or pain* or earach*) S10 (MH "Suppuration+") S9 S1 OR S2 OR S3 OR S8 S8 S6 AND S7 S7 TX perforat* or hole or ruptur* S6 S4 OR S5 S5 TX "ear drum*" or eardrum* or tympanic S4 (MH "Tympanic Membrane") S3 (MH "Tympanic Membrane Perforation") S2 TX "otitis media" or OME S1 (MH "Otitis Media+")</p>	<p>1 ("otitis media" or OME):AB,EH,KW, KY,MC,MH,TI,TO AND INREGISTER 2 (("ear drum*" or eardrum* or tympanic):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 3 (perforat* or hole or ruptur*):AB,EH, KW,KY,MC,MH,TI,TO AND INREGISTER 4 #2 AND #3 AND INREGISTER 5 #4 OR #1 AND INREGISTER 6 (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or discomfort or earach* or mucopurulen*):AB,EH,KW,KY, MC,MH,TI,TO AND INREGISTER 7 (pain):AB, TI, TO AND INREGISTER 8 #6 OR #7 AND INREGISTER 9 (chronic* or persist* or recurr* or repeat*):AB,EH,KW, KY,MC,MH,TI,TO AND INREGISTER 10 #5 AND #8 AND #9 AND INREGISTER 11 (csom):AB,EH,KW,KY,MC,MH,TI, TO AND INREGISTER 12 (((chronic* or persist* or recurr* or repeat*) and (ear or ears or aural) and (suppurat* or pus or purulen* or discharg* or mucosal or otorrh* or otorh* or otoliquor* or active or weep* or wet or moist or mucopurulen* or pain* or discomfort or disease*))):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER 13 ((earach* and (chronic or persist* or recurr* or repeat*)):AB,EH,KW,KY,MC, MH,TI,TO AND INREGISTER 14 #10 OR #11 OR #12 OR #13 AND INREGISTER</p>

(Continued)

<p>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</p>		
ClinicalTrials.gov (CRS Web)	ICTRP (WHO Portal)	Other
<p>Search 1: (chronic OR persistent OR recurrence OR recurrent) AND (suppuration OR pus OR discharge OR otorrhea or active OR mucopurulent) AND Condition: "Otitis Media" OR OME AND Study type: interventional Search 2: (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</p>	<p>otitis media AND chronic OR ear discharge OR earache OR wet ear OR weeping ear OR moist ear OR CSOM OR OME AND chronic OR tympanic membrane AND perforation OR eardrum AND hole OR eardrum AND perforation</p>	<p>LILACS TW:"otitis media" OR "TW:"ear discharge" OR TW:earache OR ((TW:eardrum OR TW:tympanic) AND (TW:perforation OR hole)) OR ((TW:wet OR moist OR weeping) AND TW:ear) AND: Filter: Controlled Clinical Trial IndMed 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</p>

Appendix 2. Data extraction form

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

General comments/notes (internal for discussion):

FLOW CHART OF TRIAL:

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

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

²This should be the people who were excluded from all analyses (e.g. because the data could not be interpreted or the outcome was not recorded for some reason). This is the number of people who dropped out, plus the people who were excluded by the authors for some reason (e.g. non-compliant).

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

Methods	X arm, double-/single-/non-blinded, [multicentre] parallel-group/cross-over/cluster RCT, with x duration of treatment and x duration of follow-up
Participants	<p>Location: [country, rural?, no. of sites etc.]</p> <p>Setting of recruitment and treatment: [specialist hospital? general practice? school? state YEAR]</p> <p>Sample size:</p> <ul style="list-style-type: none"> • Number randomised: x in intervention, y in comparison • Number completed: x in intervention, y in comparison <p>Participant (baseline) characteristics:</p> <ul style="list-style-type: none"> • Age: • Gender (F/M): number of females (%)/number of males (%) • Main diagnosis: [as stated in paper - state the diagnostic criteria used]

(Continued)

	<ul style="list-style-type: none"> ● High risk population: Yes/No <ul style="list-style-type: none"> ○ Cleft palate (or other craniofacial malformation): y/N (%) ○ Down syndrome: n/N (%) ○ Indigenous groups (Australian Aboriginals/Greenland natives): n/N (%) ○ Immunocompromised: n/N (%) ● Diagnosis method <i>[if reported]</i>: <ul style="list-style-type: none"> ○ Confirmation of perforated tympanic membrane: Yes/No/NR or unclear <i>[Method]</i> ○ 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: <ul style="list-style-type: none"> ○ 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 (%) <p>Inclusion criteria:</p> <ul style="list-style-type: none"> ● <i>[State diagnostic criteria used for CSOM, if available]</i> <p>Exclusion criteria:</p>
Interventions	<p>Intervention (n = x): drug name, method of administration, dose per day/frequency of administration, duration of treatment</p> <p>For aural toileting: who does it, methods or tools used, frequency, duration</p> <p>Comparator group (n = y):</p> <p>Concurrent treatment:</p> <p>Use of additional interventions (common to both treatment arms):</p>
Outcomes	<p>Outcomes of interest in the review:</p> <p>Primary outcomes:</p> <ul style="list-style-type: none"> ● 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 <p>Secondary outcomes</p> <ul style="list-style-type: none"> ● Hearing, measured as the pure-tone average of air conduction thresholds across 4 frequencies tested (at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz), of the affected ear. If this is not available, the pure-tone average of the thresholds measured. ● Serious complications, including intracranial complications (such as otitic meningitis, lateral sinus thrombosis and cerebellar abscess) and extracranial complications (such as mastoid abscess, postauricular fistula and facial palsy), and death. ● Adverse effects from treatment (this will be dependent on the type of treatment reviewed).
Funding sources	"No information provided"/"None declared"/State source of funding
Declarations of interest	"No information provided"/"None declared"/State conflict
Notes	<p>Clinical trial registry no: (if available)</p> <p>Unit of randomisation: person/ears/other (e.g. cluster-randomised by hospital/school)</p> <p><i>[In the case of randomisation by person]:</i></p> <p>Methods for including patients with bilateral disease, for example:</p>

(Continued)

- Random selection of one ear as the 'study ear'
- Selecting worse/least affected ear as the 'study ear'
- Counting bilateral ears separately
- Reporting 2 sets of results (please specify)
- Other (please state)
- Not stated

RISK OF BIAS TABLE:

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

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

FINDINGS OF STUDY

CONTINUOUS OUTCOMES

Results (continuous data table)							
Outcome	Intervention (name the intervention)			Comparison (name the intervention)			Other summary statistics/Notes
	Mean	SD	N	Mean	SD	N	Mean difference (95% CI), P values etc.

(Continued)

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]							

¹State 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	
Resolution of ear discharge or 'dry ear' at 1 to 2 weeks [Measurement						

(Continued)

<p>method or definition used: not/ unclear if/otoscopically confirmed] 1 Time point: [State actual time point]</p>						
<p>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]</p>						
<p>Resolution of ear discharge or 'dry ear' after 4 weeks [Measurement method or definition used: not/ unclear if/otoscopically confirmed] Time point: [xx]</p>						
<p>Ear pain/ discomfort/ local irritation [Measurement method or definition used e.g. patient-reported] Time point: [xx]</p>						
<p>Suspected ototoxicity [Measurement method or definition used]</p>						

(Continued)

Time point: [xx]						
Sensorineural hearing loss [Measurement method or definition used] Time point: [xx]						
Tinnitus [Measurement method or definition used] Time point: [xx]						
Dizziness/vertigo/balance [Measurement method or definition used] Time point: [xx]						
Serious complications: [State whether the paper had prespecified looking for this event, how it was diagnosed] Time point: state length of follow-up of the trial						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?]						

(Continued)

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						

¹State briefly how this was measured in the study, especially whether there was deviation from what was expected in the protocol. For adverse events, note down how these were collected, e.g. whether the adverse event was one of the prespecified events that the study planned to collect, when it was collected and how/who measured it (e.g. as reported by patients, during examination and whether any scoring system was used).

CONTRIBUTIONS OF AUTHORS

Lee Yee Chong: scoped, designed and wrote the protocol.

Karen Head: helped to scope, design and write the protocol.

Peter Richmond: clinical guidance at all stages of protocol development.

Tom Snelling: clinical guidance at all stages of protocol development.

Anne GM Schilder: clinical guidance at all stages of project scoping and protocol development.

Martin J Burton: clinical guidance at all stages of project scoping and protocol development.

Christopher G Brennan-Jones: helped to scope, design and write the protocol; clinical guidance at all stages of project scoping and protocol development.

DECLARATIONS OF INTEREST

Lee Yee Chong: none known.

Karen Head: none known.

Peter Richmond:

Tom Snelling: none known.

Anne GM Schilder: Professor Anne Schilder is joint Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this review. Her evidENT team at UCL is supported in part by the National Institute of Health Research (NIHR) University College London Hospitals Biomedical Research Centre. The research is funded by the NIHR and EU Horizon2020. She is the national chair of the NIHR Clinical Research Network ENT Specialty. She is the Surgical Specialty Lead for ENT for the Royal College of Surgeons of England's Clinical Trials Initiative. In her role as director of the NIHR UCLH BRC Deafness and Hearing Problems Theme, she acts as an advisor on clinical trial design and delivery to a range of biotech companies, most currently Novus Therapeutics.

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: none known.

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