National Institute for Health and Care Excellence

Final

Otitis media with effusion in under 12s

[K] Evidence reviews for preventing otorrhoea after surgery for hearing loss associated with OME in children

NICE guideline number NG233

Evidence reviews underpinning recommendations 1.6.5 to 1.6.6 and research recommendations in the NICE guideline

August 2023

Final

This evidence review was developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-5341-7

Contents

Preventing otorrhoea after surgery for hearing loss associated with OME in children

Review question

What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for otitis media with effusion (OME)-related hearing loss in children under 12 years?

Introduction

The aim of this review is to assess the effectiveness of intraoperative or postoperative interventions at preventing otorrhoea (ear discharge) after surgery for otitis media with effusion (OME)-related hearing loss in children under 12 years.

At the time of development, the term ventilation tube (VT) was used to refer to tubes inserted during surgery for OME. However, the committee agreed that the term grommet should be used as this is likely to be the term that is more familiar to readers of the guideline and would avoid confusion with tubes used to assist with breathing. Therefore, both terms appear in this evidence review.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	All children under 12 years with confirmed otitis media with effusion (OME) who are undergoing ventilation tube (VT) surgery for OME-related hearing loss.
Intervention	Intraoperative interventions*: • Antiseptic and/or saline washouts • Antibiotic ear drops with or without corticosteroid • Systemic antibiotics • Systemic corticosteroids Postoperative interventions*: • Antibiotic ear drops with or without corticosteroid • Oral antibiotics (either immediately after operation or within 6 months) • Water precautions (actions to ensure ears are kept dry, for example, wearing ear plugs, swimming cap and headband and avoidance of swimming) *Interventions alone or in combination
Comparison	• Head-to-head comparisons between the above intraoperative intervention categories** (alone or in combination) • Head-to-head comparisons between the above postoperative intervention categories** (alone or in combination) • The above intraoperative interventions (alone or in combination) versus placebo • The above postoperative interventions (alone or in combination) versus placebo • The above intraoperative interventions (alone or in combination) versus no intervention for preventing otorrhoea • The above postoperative interventions (alone or in combination) versus no intervention for preventing otorrhoea **Please note, head-to-head comparisons between different interventions within each category (e.g., comparisons between different types of systemic antibiotics) were not included, only head-to-head comparisons of interventions from different categories (e.g., a systemic antibiotic versus a systemic corticosteroid)
Outcome	**Critical** • Otorrhoea (ear discharge) – frequency (either clinically confirmed or parent-reported) • Adverse effects of intervention (including antimicrobial resistance) • Acceptability **Important** • Tube blockage • Tube extrusion • Surgical intervention to remove VTs • Quality of life (measured by OM8-30 questionnaire, Health Utilities Index Mark 3 (HUI3) questionnaire, Otitis Media-6 (OM-6) questionnaire, Quality of Life in Children's Ear Problems (OMQ-14) questionnaire, Evaluation of Children's Listening and Processing Skills (ECLiPS) questionnaire, Auditory Behaviour in Everyday Life (ABEL) questionnaire, Early Listening Function (ELF) questionnaire, Parents' Evaluation of Aural/Oral Performance of Children (PEACH) questionnaire, EuroQol 5 Dimensions (EQ-5D) questionnaire, Infant Toddler Quality of Life Questionnaire, or Child Heath Questionnaire)

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Four randomised controlled trials (RCTs) were included for this review (Mair 2016; Park 2016; Subtil 2019; Wang 2022).

The included studies are summarised in Table 2.

One study compared intraoperative ciprofloxacin ear drops alone, and intraoperative and postoperative ciprofloxacin ear drops to no topical ciprofloxacin (Wang 2022). Two studies compared intraoperative intratympanic ciprofloxacin injection to placebo/sham (Mair 2016, Park 2016). One study compared water precautions to no precautions (Subtil 2019).

One study excluded participants with craniofacial anomalies (Subtil 2019) and 3 studies did not report data on whether any participants had craniofacial anomalies (Mair 2016, Park 2016, Wang 2022). None of the studies reported data on whether any participants had mucociliary conditions.

All studies were conducted in children aged 17 years or under, and included children with a mean age in years of 2.75 (Mair 2016), 2.45 (Park 2016), and 4.4 (Subtil 2019) years. One study (Wang 2022) did not report the mean age, but the median participant age in years was 4.02, with a range of 0.72 to 13.1 years. None of the studies reported the number of previous episodes of otorrhoea or previous episodes of acute otitis media (AOM) participants.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies.

Study	Population	Intervention	Comparison	Outcomes	Comments
Mair 2016 RCT USA	N=83 Children aged 6 months to 12 years with confirmed bilateral middle ear effusion who are undergoing	Intraoperative intratympanic ciprofloxacin injection 4 mg Intraoperative intratympanic ciprofloxacin injection 12 mg	Placebo: Only vehicle administered Sham: Only air administered	• Otorrhoea • Adverse effects of intervention	

Study	Population	Intervention	Comparison	Outcomes	Comments
	tympanostomy tube surgery Age in years, mean (SD): Intraoperative intratympanic ciprofloxacin injection 4 mg: 2.9 (2.6) Intraoperative intratympanic ciprofloxacin injection 12 mg: 2.8 (2.2) Placebo: 2.5 (1.9) Sham: 2.8 (2.3) Sex (male/female): Intraoperative intratympanic ciprofloxacin injection 4 mg: 15/6 Intraoperative intratympanic ciprofloxacin injection 12 mg: 10/9 Placebo: 12/10 Sham: 15/6				
Park 2016 RCT Canada and USA	N=532 Children aged 6 months to 17 years with confirmed middle ear effusion who are undergoing tympanostomy tube surgery Age in years, mean (SD): Intraoperative intratympanic ciprofloxacin injection 6 mg: 2.3 (1.9) Sham: 2.6 (2.3)	Intraoperative intratympanic ciprofloxacin injection 6 mg	Sham: The syringe was empty	• Otorrhoea • Adverse effects of intervention • Tube blockage • Tube extrusion	

Study	Population	Intervention	Comparison	Outcomes	Comments
	Sex (male/female): Intraoperative intratympanic ciprofloxacin injection 6 mg: 200/157 Sham: 104/71				
Subtil 2019 RCT Portugal	N=291 Children aged 2-10 years with chronic OME who are undergoing tympanostomy tube surgery Age in years, mean (SD): 4.4 (1.7)* Sex (male/female): Water precautions: 74/56 No precautions: 64/50 *Not reported split by intervention group	<u>Water precautions:</u> Earplugs and headbands for swimming and earplugs for bathing and showering	<u>No precautions:</u> Showering and swimming with no protections	• Otorrhoea • Quality of life	Quality of life assessed with the PedsQL tool
Wang 2022 RCT Australia	N=296 Children aged 17 years or under with recurrent acute otitis media or chronic OME who are undergoing bilateral VT surgery Age in years, mean (SD): NR, but median (IQR): Intraoperative ciprofloxacin drops: 4.09 (2.81-6.06)	<u>Intraoperative ciprofloxacin drops</u>: 5 drops of ciprofloxacin 0.3% <u>Intraoperative and postoperative ciprofloxacin drops:</u> Ciprofloxacin 0.3% drops during surgery as well as twice a day for 5 days after surgery	<u>No topical ciprofloxacin</u>	• Otorrhoea • Tube blockage	Population is indirect because 34% of population had recurrent acute otitis media. Postoperative ciprofloxacin drops intervention is indirect due to the combination of intraoperative and postoperative ciprofloxacin drops.

Study	Population	Intervention	Comparison	Outcomes	Comments
	Intraoperative and postoperative ciprofloxacin drops: 4.04 (2.46-6.55) No topical ciprofloxacin: 3.63 (2.25-5.91) Sex (male/female): Intraoperative ciprofloxacin drops: 58/29 Intraoperative and postoperative ciprofloxacin drops: 43/37 No topical ciprofloxacin: 52/37				

IQR: interquartile range; NR: not reported; OME: otitis media with effusion; PedsQL: Pediatric Quality of Life Inventory; RCT: randomised controlled trial; SD: standard deviation

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

The evidence was moderate to very low quality due to bias arising from the intervention allocation process, missing outcome data, and measurement of the outcome, seriously imprecise findings, and the inclusion of indirect population, outcome, and intervention.

Intraoperative ciprofloxacin ear drops compared to no topical ciprofloxacin

Intraoperative ciprofloxacin ear drops had an important benefit in terms of reducing otorrhoea compared with no topical ciprofloxacin. In addition, there was a possible important benefit of intraoperative ciprofloxacin ear drops for reducing tube blockage (90% CI: 0.30 to 0.96).

Intraoperative plus postoperative ciprofloxacin ear drops compared to no topical ciprofloxacin

Intraoperative plus postoperative ciprofloxacin ear drops had an important benefit for reducing tube blockage compared with no topical ciprofloxacin; however, there was no important difference between interventions for otorrhoea.

Intraoperative intratympanic ciprofloxacin injection compared to placebo/sham

There was evidence that a 6mg intraoperative intratympanic ciprofloxacin injection had an important benefit in terms of reducing otorrhoea compared with placebo/sham, and very low quality evidence of a possible important benefit for a 12mg intraoperative intratympanic ciprofloxacin injection when compared with placebo/sham (90% CI: 0.09 to 0.96). However, there was no evidence of an important difference at a lower dosage of 4mg when compared to placebo, though this evidence was low quality (90% CI: 0.11 to 1.37). When evidence from intraoperative intratympanic ciprofloxacin injection at 4 mg, 6 mg, and 12 mg was pooled, intraoperative intratympanic ciprofloxacin injection overall had an important benefit for

reducing otorrhoea when compared with placebo/sham (moderate quality). This was also the general pattern within the subgroups although differences often failed to reach clinical importance. One study (Mair 2016) included two groups of no active treatment (placebo and sham), and we arbitrarily assigned each of these groups as the comparison group against intraoperative intratympanic ciprofloxacin injection 4 mg and 12 mg groups. Sensitivity analyses where we swapped the comparison groups over showed that this did not affect the overall or subgroup results for otorrhoea. The pooled effect of intraoperative intratympanic ciprofloxacin injection showed no important difference for adverse effects of the intervention, and this was also the general pattern within the 6 mg and 12 mg subgroups whereas intraoperative intratympanic ciprofloxacin injection of 4 mg had an important benefit for reducing adverse effects of intervention compared with sham. However, adverse effects data from Mair 2016 included otorrhoea as an adverse event, and therefore instances of otorrhoea are double counted within the effect of ciprofloxacin injections at 4 mg and 12 mg for adverse effects outcomes. It is unclear how removing instances of otorrhoea from these data would affect adverse effects outcomes, because otorrhoea was not reported at 29 days follow-up. Although the pooled result of the sensitivity analyses also agreed with the main analysis for adverse events, the results within the subgroups differed in the sensitivity analyses relative to the original analyses, showing no important difference in the 4 mg group and important benefit in the 12 mg group. See appendix L for further details of the sensitivity analysis, included risk ratios and absolute effects.

There was no important difference for tube blockage and tube extrusion.

Water precautions compared to no water precautions

A comparison between water precautions and no precautions showed no important difference and no evidence of important difference (90% CI 1.00 to 2.06) for quality of life and otorrhoea, respectively. The outcomes of acceptability and ‘surgical intervention to remove ventilation tubes’ were not reported by any studies.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation given the low cost of the interventions under consideration in this review.

Unit costs

Resource	Unit costs	Source
Ciprofloxacin ear drops	£0.40	NHS Drugs Tariff December 2022 (Based on £6.01 for a 15-unit pack)

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Otorrhoea is a common complication after grommet surgery, which may both recur and lead to poor quality of life in children with otitis media with effusion. Therefore, otorrhoea was prioritised as a critical outcome. To reduce the risk of otorrhoea following grommet surgery, different types of preventive measures/interventions can be used during (for example, antibiotic ear drops with or without corticosteroids, systemic antibiotics, and systemic corticosteroids) and after surgery (for example, antibiotic ear drops with or without corticosteroids, water precautions and oral antibiotics). However, these preventive measures may have adverse effects in children (for example, local discomfort, rash, headache, gastrointestinal discomfort, and antimicrobial resistance), and the overall ability and willingness of children to use effective preventive measures is important. Therefore, adverse effects and acceptability of preventive measures and interventions were prioritised as critical outcomes.

Tube blockage, tube extrusion and requirement of surgical intervention to remove grommets were selected as important outcomes as they are relatively common in children who undergo grommet placement surgery, and tube blockage and tube extrusion may be related to recurrence of otitis media with effusion. In addition, quality of life was selected as an important outcome as this is a global measure that takes into account both beneficial and adverse effects of the interventions.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence for otorrhoea and adverse effects of the interventions was moderate to very low quality due to risk of bias arising from the intervention allocation, missing outcome data and measurement of outcome, seriously imprecise findings, and the inclusion of indirect populations and interventions. The evidence for tube blockage was low to very low quality because of risk of bias from the intervention allocation, seriously imprecise findings, and the inclusion of indirect populations and interventions. The evidence for tube extrusion and quality of life was low to very low quality due to risk of bias arising from the intervention allocation, missing outcome data and measurement of outcome, seriously imprecise findings, and the inclusion of indirect outcomes.

No evidence was found that reported on the outcomes of acceptability or surgical intervention to remove grommets.

Benefits and harms

There was moderate quality evidence that intraoperative ciprofloxacin drops had an important benefit in terms of presence of otorrhoea at 6 weeks follow-up compared to no drops, and that intraoperative intratympanic ciprofloxacin injection had an important benefit in terms of presence of otorrhoea at 15-29 days follow-up compared to placebo or sham. There was also low quality evidence that intraoperative ciprofloxacin drops had a possible important benefit in terms of tube blockage at 6 weeks follow-up compared to no drops, but there was uncertainty around the estimate and very low quality evidence from another trial showed no evidence of an important difference in terms of tube blockage for an intraoperative intratympanic ciprofloxacin injection compared to sham at 29 days follow-up. The committee agreed there were further inconsistencies in the evidence which raised concerns, such as the fact that Wang 2022 showed no evidence of an important difference in terms of presence of otorrhoea at 6 weeks follow-up when intraoperative and postoperative ciprofloxacin drops were used. The committee agreed it was unusual that the evidence showed a worse result with the addition of postoperative drops than the application of intraoperative drops alone, and there was uncertainty in the importance of the outcome. Additionally, the committee

discussed the indirectness of the population in Wang 2022 and agreed the fact that 34% of the population had acute otitis media (AOM) and not OME was of serious concern because antibiotics would be expected to be more effective for AOM as it is an acute infection, while OME is sterile.

Having considered the reliability and strength of the evidence, the committee agreed it should be interpreted with caution and supplemented with their own expertise. They discussed their knowledge of current practice and agreed there is variation regarding the application of intraoperative ear drops; they tend to only be applied intraoperatively if the ear looks infected when the grommets are put in, or for anticoagulative properties if there is bleeding after insertion of the grommets, to prevent blood clots in the lumen. The committee also discussed whether otorrhoea was a significant issue for people with OME, and whether the resolution of otorrhoea justified the potential for increasing antibiotic resistance. Lay members of the committee observed that some clinicians' experience with incidences of otorrhoea might not reflect the real prevalence of otorrhoea following grommet insertion, because they would usually see patients at 6 weeks follow-up, by which point the otorrhoea might have resolved. They noted that otorrhoea was very painful for the patient and could cause difficulties for families, and therefore attempts to prevent otorrhoea should be made. The committee also agreed that a single dose of ciprofloxacin drops is unlikely to influence antibiotic resistance, and therefore the risk is minimal while the benefits could include prevention of otorrhoea and tube blockage, and increased quality of life in children with OME and their families.

In Mair 2016 and Park 2016, the intraoperative ciprofloxacin was applied using intratympanic injection, which is not standard practice. The committee discussed their expectation that injecting the ciprofloxacin would allow it to be applied more precisely and penetrate the middle ear better but agreed that applying ear drops using the standard method had a lower risk of complications such as dislodging the grommets. Additionally, although there was no important difference between intraoperative intratympanic ciprofloxacin injection and placebo/sham in terms of adverse effects, the committee discussed the fact that this outcome double-counted otorrhoea as an adverse event, and therefore the potential harms of intraoperative intratympanic ciprofloxacin injection when otorrhoea is not included were not known. As a result, the committee recommended that a single application of ciprofloxacin ear drops intraoperatively should be considered to prevent otorrhoea and tube blockage based on the available evidence and their knowledge and experience. However, a stronger recommendation could not be made due to the lack of high quality, reliable evidence. The committee also discussed dosage of ciprofloxacin drops. The committee felt that ciprofloxacin 0.2% ear drops in a 0.25 ml single ampoule dose may be the most appropriate option. However, they were aware that in some areas, ciprofloxacin 0.3% eye drops may also be used in the ear as a single dose of 3-5 drops (equivalent dose as per above). As there was variation in practice regarding the dosage, the committee felt that they could not add details on dosage to the recommendation. There was no evidence of an important difference for water precautions such as earplugs and headbands after grommet insertion in terms of presence of otorrhoea at 6 months follow-up compared to no water precautions, although this evidence was of very low quality and there was uncertainty in the importance of the outcome. The study did not analyse the effectiveness of different precautions, so it was unclear whether some interventions were more effective than others (such as earplugs versus headbands). In addition to the low quality of the evidence, the committee agreed it was difficult to ascertain from the information presented in the study whether and to what extent people in the control group might have avoided water independent of their use of ear plugs or headbands, and therefore whether this would have affected results. Considering the uncertainty of the evidence and the committee's agreement that these interventions also had the potential to dissuade children from swimming at all, no recommendations were made about the use of earplugs and headbands while swimming or bathing. The committee discussed what should happen if a patient has a history of otorrhoea or if otorrhoea repeatedly occurs after surgery and agreed at this point the patient would be considered to

be susceptible to ear infections and should be treated according to the recommendations in Evidence Review L.

The committee agreed that in practice, more involved interventions such as those investigated in Subtil 2019 do not tend to be recommended after grommet insertion. Instead, standard practice is to advise patients to keep the ear dry (that is, avoid swimming and take care when bathing and washing hair) to prevent the risk of water permeating the lumen while the wound is still healing around the grommet, although there is currently variation regarding the number of weeks this is advised for. The committee agreed to make a strong recommendation despite the lack of high quality evidence because water avoidance is sensible to prevent infection at the site of the tube but agreed that 6 to 8 weeks of water avoidance until first follow-up after surgery was excessive as the risk would lower once the wound was healed, which would usually happen long before follow-up. The committee agreed that 2 weeks would usually be enough time for the wound to heal. They agreed that, considering the lack of evidence about this, a shorter timeframe would be more practical as it would have a lower risk of impacting both the child's development (for example, the committee were concerned that water precautions could interfere with children learning to swim) and the quality of life of children and their families.

The committee also considered whether further water precautions after the initial 2 weeks post-surgery should be recommended. They discussed the fact that soapy water (due to soap reducing the surface tension of the water) and diving both increase the potential for permeation of water into the lumen, – and therefore should be avoided for the whole duration that the grommet is in place. However, the available evidence did not provide information regarding these considerations. The committee agreed, based on their experience, that the risk of permeation in these situations after the wound has healed is still very low, and, therefore, that further recommendations were unnecessary.

There was low quality evidence that intraoperative and postoperative ciprofloxacin drops had an important benefit in terms of tube blockage at 6 weeks follow-up compared to no drops, however the committee agreed the evidence for this outcome was unreliable considering intraoperative application only had better outcomes than intraoperative and postoperative application in terms of presence of otorrhoea. The committee agreed that repeat applications of antibiotics would increase the risk for antibiotic resistance and therefore the evidence of effectiveness was not strong enough to recommend postoperative use of ciprofloxacin drops. There was also no evidence available regarding the use of oral antibiotics postoperatively, or for antiseptic or saline washouts, systemic antibiotics, or systemic corticosteroids intraoperatively, and no recommendations were made about these.

There was limited evidence on water precautions for preventing otorrhoea following grommet insertion for children with OME and no evidence on the effectiveness of water avoidance, or on the comparative effectiveness of different water precautions. The committee agreed it would be useful to know which water precautions were the most effective, including the optimal length of time to use water precautions in order to prevent otorrhoea. This would enable the least restrictive recommendations to be made in the future, to promote children's development while also ensuring they are not at risk of developing otorrhoea. Therefore, the committee made a research recommendation.

Cost effectiveness and resource use

This review question was not prioritised for economic analysis and therefore the committee made a qualitative assessment of the likely cost-effectiveness of their recommendations. The committee noted that advice about water precautions would be given in conjunction with other patient information and would have negligible costs. Therefore, the committee concluded that such advice would be cost-effective in minimising the risk of water permeating into the lumen whilst the wound following grommet insertion is still healing. The committee also considered that such advice would be in line with current practice.

The committee considered that the clinical evidence and their own expertise and experience provided some evidence for the likely cost-effectiveness of a single application of intraoperative non-ototoxic antibiotic-containing topical ear drops (such as ciprofloxacin) during grommet insertion to prevent otorrhoea and tube blockage. They reasoned that only a small beneficial effect of treatment would be required for it to be considered cost-effective given the low cost of ear drops. The committee thought it unlikely that a single dose of ciprofloxacin would promote antibiotic resistance and concluded that any risks of intervention were likely to be outweighed by the benefits in the prevention of otorrhoea, tube blockage and improved health related quality of life. Whilst the committee believed that current practice is varied, they recognised that their recommendations could represent a change in practice for some units. However, given the low cost of ear drops and the potential for some savings from reduced rates of otorrhoea the committee did not believe that their recommendation would represent a significant resource impact to the NHS.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.5 to 1.6.6 and the research recommendation on the effectiveness of water precautions in preventing otorrhoea after grommet surgery for OME-associated hearing loss in children under 12 years.

References – included studies

Effectiveness

Mair 2016

Mair, E. A., Moss, J. R., Dohar., Joseph E. et al. (2016). Randomized clinical trial of a sustained-exposure ciprofloxacin for intratympanic injection during tympanostomy tube surgery, The Annals of Otology, Rhinology, and Laryngology 125(2), 105-114

Park 2016

Park, A. H., White, D. R., Moss, J. R. et al. (2016). Phase 3 trials of thermosensitive ciprofloxacin gel for middle ear effusion in children with tubes, Otolaryngology-Head and Neck Surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 155(2), 324-331

Subtil 2019

Subtil, J., Jardim, A., Araujo, J. et al. (2019). Effect of water precautions on otorrhea incidence after pediatric tympanostomy tube: randomized controlled trial evidence, Otolaryngology-Head and Neck Surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 161(3), 514-521

Wang 2022

Wang, L. C., Phyland, D. J., Giddings, C. E. (2022). A randomised clinical trial of single or extended dosing ciprofloxacin versus no intervention for prevention of ventilation tube otorrhoea and obstruction (PreVenTO2), Clinical Otolaryngology: official journal of ENT-UK; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 47(2), 287-294

Appendices

Appendix A Review protocols

Review protocol for review question: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42022334005
Review title	The effectiveness of intraoperative or postoperative interventions at preventing otorrhoea after surgery for hearing loss associated with otitis media with effusion in children
Review question	What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?
Objective	To determine the effectiveness of intraoperative or postoperative interventions at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • International Health Technology Assessment (INAHTA) database • MEDLINE & MEDLINE In-Process Searches will be restricted by: • OECD geographic study filter

Field	Content
	• Date limitations: 2010 onwards (see rationale under “Other exclusion criteria”) • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews • Citation searches of included studies With the agreement of the guideline committee the searches will be re-run between 6-8 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Hearing loss associated with otitis media with effusion
Population	All children under 12 years with confirmed otitis media with effusion (OME) who are undergoing ventilation tube surgery for OME-related hearing loss.
Intervention	Intraoperative interventions*: • Antiseptic and/or saline washouts • Antibiotic ear drops with or without corticosteroid • Systemic antibiotics • Systemic corticosteroids Postoperative interventions*: • Antibiotic ear drops with or without corticosteroid • Oral antibiotics (either immediately after operation or within 6 months) • Water precautions (actions to ensure ears are kept dry, for example, wearing ear plugs, swimming cap and headband and avoidance of swimming) *Interventions alone or in combination

Field	Content
Comparator	• Head-to-head comparisons between the above intraoperative intervention categories** (alone or in combination) • Head-to-head comparisons between the above postoperative intervention categories** (alone or in combination) • The above intraoperative interventions (alone or in combination) versus placebo • The above postoperative interventions (alone or in combination) versus placebo • The above intraoperative interventions (alone or in combination) versus no intervention for preventing otorrhoea • The above postoperative interventions (alone or in combination) versus no intervention for preventing otorrhoea **Please note, we will not include head-to-head comparisons between different interventions within each category (e.g., comparisons between different types of systemic antibiotics), only head-to-head comparisons of interventions from different categories (e.g., a systemic antibiotic versus a systemic corticosteroid)
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs • If insufficient RCTs***: comparative prospective cohort studies with at least 40 participants per arm • If insufficient comparative prospective cohort studies: comparative retrospective cohort studies with at least 40 participants per arm ***Non-randomised studies will be considered for inclusion if insufficient RCT evidence is available for guideline decision making. Sufficiency will be judged taking into account factors including number/quality/sample size of RCTs, outcomes reported and availability of data from subgroups of interest. Non-randomised studies will be downgraded for risk of bias if they do not adequately adjust for the following covariates, but will not be excluded for this reason:

Field	Content
	• Age • Craniofacial anomalies • Socioeconomic status • Additional sensory or learning needs
Other exclusion criteria	• Country limitations: limit studies to OECD high-income countries • Date limitations: 2010 as safety of antibiotics was improved from 2015 (e.g., non-ototoxic antibiotics) and the committee wanted to capture studies leading up to that change. • Language limitations: studies published not in English-language • Conference abstracts will not be considered.
Context	This guidance will fully update the following NICE guideline: Otitis media with effusion in under 12s: surgery (2008; CG60)
Primary outcomes (critical outcomes)	• Otorrhoea (ear discharge) – frequency (either clinically confirmed or parent-reported) • Adverse effects of intervention (including antimicrobial resistance) • Acceptability
Secondary outcomes (important outcomes)	• Tube blockage • Tube extrusion • Surgical intervention to remove VTs • Quality of life (measured by OM8-30 questionnaire, Health Utilities Index Mark 3 (HUI3) questionnaire, Otitis Media-6 (OM-6) questionnaire, Quality of Life in Children's Ear Problems (OMQ-14) questionnaire, Evaluation of Children's Listening and Processing Skills (ECLiPS) questionnaire, Auditory Behaviour in Everyday Life (ABEL) questionnaire, Early Listening Function (ELF) questionnaire, Parents' Evaluation of Aural/Oral Performance of Children (PEACH) questionnaire, EuroQol 5 Dimensions (EQ-5D) questionnaire, Infant Toddler Quality of Life Questionnaire, or Child Heath Questionnaire)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol.

Field	Content
	Dual sifting will be performed on at least 10% of records; 90% agreement is required, if capacity allows it. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer, and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects

Field	Content
	model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences (MIDs):** • Validated scales: Published MIDs where available; if not 0.8 and 1.25 for dichotomous outcomes and 0.5 SD of the control group at baseline for continuous outcomes • All other outcomes: 0.8 and 1.25 for dichotomous outcomes and 0.5 SD of the control group at baseline for continuous outcomes

Analysis of sub-groups	Evidence will be stratified by:
	• Craniofacial anomalies
	• Mucociliary condition such as cystic fibrosis
	
	Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:
	• Previous episode of otorrhoea
	• Previous episode of acute otitis media
	• Age
	  ○ Children <2 years vs ≥2 years
	  ○ Children <4 years vs ≥4 years
	  ○ Children <6 years vs ≥6 years
	
	Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee

Field	Content			
	will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	31/03/2022			
Anticipated completion date	23/12/2022			
Stage of review at time of this submission	Review stage		Started	Completed
	Preliminary searches		☑	☑
	Piloting of the study selection process		☑	☑
	Formal screening of search results against eligibility criteria		☑	☑
	Data extraction		☑	☑
	Risk of bias (quality) assessment		☑	☑
	Data analysis		☑	☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: otitis@nice.org.uk			

Field	Content
	Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
Review team members	National Guideline Alliance
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10193
Other registration details	None
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022334005
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Otitis media with effusion, hearing aids, hearing devices, hearing, quality of life

Field	Content	
Details of existing review of same topic by same authors	None	
Current review status	☐	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; INAHTA: International Health Technology Assessment database; MEDLINE: Medical Literature Analysis and Retrieval System Online; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias in non-randomised studies – of interventions; ROBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

Clinical search

This was a combined search to cover both this review and the evidence review on the effectiveness of interventions for treating otorrhoea after surgery for OME-related hearing loss in children under 12 years.

Database: MEDLINE – OVID interface

Date last searched: 09/11/2022

#	Searches
1	otitis media with effusion/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	Cerebrospinal Fluid Otorrhea/ or Mucus/ or Otitis Media, Suppurative/ or Suppuration/
5	(otor* or discharg* or fluid* or leak* or liquor* or moist* or mucoid* or mucopurulen* or mucus* or otoliquor* or purulen* or pus or secret* or suppurat* or weep* or wet*).ti,ab.
6	4 or 5
7	3 and 6
8	Intraoperative Care/ or exp Intraoperative Period/ or exp Monitoring, Intraoperative/ or Perioperative Care/ or Perioperative Period/ or Postoperative Care/ or exp Postoperative Period/ or Secondary Prevention/ or Adenoidectomy/ or exp Otologic Surgical Procedures/
9	(implant* or intraoperat* or intrasurg* or operat* or otosurg* or perioperat* or postoperat* or postsurg* or surg* or prophyl* or postadenoidectom* or postadenotonsillectom* or postmyringoplast* or postmyringostom* or postmyringotom* or posttubulat* or posttympanoplast or posttympanostom* or adenoidectom* or adenotonsillectom* or grommet* or tube* or tubulat* or tympanoplast* or tympanostom* or tonsillectom* or ventilat*).ti,ab.
10	8 or 9
11	7 and 10
12	exp anti-infective agents/ or Bacterial Infections/ or exp beta-Lactams/ or exp Macrolides/ or exp Trimethoprim/
13	(antibacteri* or anti bacteri* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimyobacteri* or anti myobacteri or bacteriocid*).ti,ab.
14	(penicillin* or aminoglycoside* or amoxicillin* or amix or amoram or amoxident or galenamox or rimoxallin or amoxil or ampicillin* or clavulan* or coamoxiclav or amoxiclav or augmentin or ticarcillin or timentin or flucloxacillin or fluampicil or magnapen or piperacillin or tazocin or cephalosporin* or cefaclor or distaclor or cefadroxil or baxan or cefalexin or ceporex or keflex or cefamandole or kefadol or cefazolin or kefzol or cefixime or suprax or cefotaxime or claforan or cefoxitin or mefoxin or cefpirome or cefrom or cefpodoxime or orelox or cefprozil or cefzil or cefradine or velosel or ceftazidime or fortum or kefadim or ceftriaxone or rocephin or cefuroxime* or zinacef or zinnat or cefonicid or aztreonam or azactam or imipenem or cilastatin or primaxin or meropenem or meronem or tetracycline* or deteclo or demecleocyclin or ledermycin or doxycycline or vibramycin or minocycline or minocine or oxytetracycline or terramycin or macrolide* or erythromycin* or erymax or erythrocin or erythroped or azithromycin* or zithromax or zedbac or clarithromycin or klaricid or mycifor or telithromycin or sulfisoxazole or ketek or trimoxazole or moxifloxacin or avelox or trimethoprim or cotrimoxazole or monotrim or septrin or trimopan or metronidazole or flagyl or metrolyl or quinolone* or ciprofloxacin or ciproxin or phenoxymethylpenicillin or sulfamethoxazole or oxacillin or cephalothin or sulbactam or ofloxacin or clindamycin or gentamycin or vancomycin or sulfisoxazole).ti,ab.
15	Steroids/ or exp Adrenal Cortex Hormones/ or exp Mineralocorticoids/ or exp Prednisolone/ or exp Pregnenediones/
16	(steroid* or adrenal cortex hormone* or corticosteroid* or corticoid* or glucocorticoid* or glucocorticosteroid* or aldosterone or aristocort or baycadron or becloforte or beclomet?a?one or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or betamethasone or budelin or bude?onide or calcort or clobetasol or corlan or cortef or cortisol or cortisone or corticosterone or cortodoxone or cortone acetate or cotolone or decadron or deflazacort or delta?one or desonide or dexametha?one or dexsol or efcortesol or entocort or florinef acetate or flumetha?one or flunisolide or flutica?one or fludrocorti?one or hydrocorti?one or hydrocortone or hydroxycorticosteroid* or hydroxypregnenolone or kenalog or medrone or medrol or solu?medrone or depo?medrone or methylpred or methylpredni?olone or mineralcorticoid*or mometa?one or parametha?one or pediapred or prednicot or predni?olone or predni?one or pregnenedione* or pregnenolone* or prelone or pulmicort or solucortef or symbicort or tetrahydrocortisol or triamcinolone).ti,ab.
17	Saline Solution/ or Saline Solution, Hypertonic/ or Sodium Chloride/ or Therapeutic Irrigation/
18	(antiseptic* or anti septic* or clean* or drop* or eardrop* or hypersaline or hypertonic* or hyper tonic* or irrigat* or lavag* or rins* or saline or salt* or seawater or sodium chloride or solution* or toilet* or wash* or water*).ti,ab.
19	Baths/ or Fresh Water/ or Immersion/ or "Oceans and Seas"/ or Seawater/ or Swimming Pools/ or Swimming/ or Water/
20	(swim* or shower* or bath* or dry or dive or diving or nonswim* or immers* or submers* or submerg* or lake* or pond* or creek* or pool* or river* or freshwater* or sea* or ocean* or ingress*).ti,ab.

#	Searches
21	Ear Protective Devices/
22	(protect* or prevent* or precaution* or barrier* or ear mould* or ear mold* or ear plug* or earplug* or earmold* or earmould* or headband* or head band*).ti,ab.
23	or/12-22
24	11 and 23
25	limit 24 to english language
26	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
27	25 not 26
28	limit 27 to yr="2010 -Current"

Database: Embase – OVID interface

Date last searched: 09/11/2022

#	Searches
1	exp secretory otitis media/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	exp otorrhea/ or mucus/ or suppuration/ or exp suppurative otitis media/
5	(otor* or discharg* or fluid* or leak* or liquor* or moist* or mucoid* or mucopurulen* or mucus* or otoliquor* or purulen* or pus or secret* or suppurat* or weep* or wet*).ti,ab.
6	4 or 5
7	3 and 6
8	exp intraoperative monitoring/ or exp intraoperative period/ or exp perioperative monitoring/ or exp perioperative period/ or exp postoperative period/ or prophylaxis/ or prevention/ or adenoidectomy/ or exp ear surgery/
9	(implant* or intraoperat* or intrasurg* or operat* or otosurg* or perioperat* or postoperat* or postsurg* or surg* or prophyl* or postadenoidectom* or postadenotonsillectom* or postmyringoplast* or postmyringostom* or postmyringotom* or posttubulat* or posttympanoplast or posttympanostom* or adenoidectom* or adenotonsillectom* or grommet* or tube* or tubulat* or tympanoplast* or tympanostom* or tonsillectom* or ventilat*).ti,ab.
10	8 or 9
11	7 and 10
12	exp antiinfective agent/ or bacterial Infection/dt, pc
13	(antibacteri* or anti bacteri* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimyobacteri* or anti myobacteri or bacteriocid*).ti,ab.
14	(penicillin* or aminoglycoside* or amoxicillin* or amix or amoram or amoxident or galenamox or rimoxallin or amoxil or ampicillin* or clavulan* or coamoxiclav or amoxiclav or augmentin or ticarcillin or timentin or flucloxacillin or fluampicil or magnapen or piperacillin or tazocin or cephalosporin* or cefaclor or distaclor or cefadroxil or baxan or cefalexin or ceporex or keflex or cefamandole or kefadol or cefazolin or kefzol or cefixime or suprax or cefotaxime or claforan or cefoxitin or mefoxin or cefpirome or cefrom or cefpodoxime or orelox or cefprozil or cefzil or cefradine or velosel or ceftazidime or fortum or kefadim or ceftriaxone or rocephin or cefuroxime* or zinacef or zinnat or cefonicid or aztreonam or azactam or imipenem or cilastatin or primaxin or meropenem or meronem or tetracycline* or deteclo or demecleocyclin or ledermycin or doxycycline or vibramycin or minocycline or minocine or oxytetracycline or terramycin or macrolide* or erythromycin* or erymax or erythrocin or erythroped or azithromycin* or zithromax or zedbac or clarithromycin or klaricid or mycifor or telithromycin or sulfisoxazole or ketek or trimoxazole or moxifloxacin or avelox or trimethoprim or cotrimoxazole or monotrim or septrin or trimopan or metronidazole or flagyl or metrolyl or quinolone* or ciprofloxacin or ciproxin or phenoxymethylpenicillin or sulfamethoxazole or oxacillin or cephalothin or sulbactam or ofloxacin or clindamycin or gentamycin or vancomycin or sulfisoxazole).ti,ab.
15	steroid/ or exp corticosteroid/ or exp prednisolone/ or pregnane derivative/
16	(steroid* or adrenal cortex hormone* or corticosteroid* or corticoid* or glucocorticoid* or glucocorticosteroid* or aldosterone or aristocort or baycadron or becloforte or beclomet?a?one or aerobec or asmabec or beclazone or becodisks or becotide or clenil modulite or qvar or betamethasone or budelin or bude?onide or calcort or clobetasol or corlan or cortef or cortisol or cortisone or corticosterone or cortodoxone or cortone acetate or cotolone or decadron or deflazacort or delta?one or desonide or dexametha?one or dexsol or efcortesol or entocort or florinef acetate or flumetha?one or flunisolide or flutica?one or fludrocorti?one or hydrocorti?one or hydrocortone or hydroxycorticosteroid* or hydroxypregnenolone or kenalog or medrone or medrol or solu?medrone or depo?medrone or methylpred or methylpredni?olone or mineralcorticoid*or mometa?one or parametha?one or pediapred or prednicot or predni?olone or predni?one or pregnenedione* or pregnenolone* or prelone or pulmicort or solucortef or symbicort or tetrahydrocortisol or triamcinolone).ti,ab.
17	ear drops/ or sodium chloride/ or lavage/
18	(antiseptic* or anti septic* clean* or drop* or eardrop* or hypersaline or hypertonic* or hyper tonic* or irrigat* or lavag* or rins* or saline or salt* or seawater or sodium chloride or solution* or toilet* or wash* or water*).ti,ab.
19	bath/ or fresh water/ or immersion/ or sea water/ or swimming pools/ or swimming/ or water/ or water immersion/
20	(swim* or shower* or bath* or dry or dive or diving or nonswim* or immers* or submers* or submerg* or lake* or pond* or creek* or pool* or river* or freshwater* or sea* or ocean* or ingress*).ti,ab.
21	exp ear protective device/
22	(protect* or prevent* or precaution* or barrier* or ear mould* or ear mold* or ear plug* or earplug* or earmold* or earmould* or headband* or head band*).ti,ab.
23	or/12-22
24	11 and 23
25	limit 24 to english language

#	Searches
26	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.
27	25 not 26
28	limit 27 to (conference abstract or conference paper or conference review or conference proceeding)
29	27 not 28
30	limit 29 to yr="2010 -Current"

Database: Cochrane Database of Systematic Reviews (CDSR); Cochrane Central Register of Controlled Trials (CENTRAL) – Wiley interface

Date last searched: 09/11/2022

ID	Search
#1	MeSH descriptor: [Otitis Media with Effusion] this term only
#2	(("glue ear" or (("middle ear" or "otitis media") near/2 effusion*) or ome or ((secretory or serous) near/2 "otitis media"))):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Cerebrospinal Fluid Otorrhea] this term only
#5	MeSH descriptor: [Mucus] this term only
#6	MeSH descriptor: [Otitis Media, Suppurative] this term only
#7	MeSH descriptor: [Suppuration] this term only
#8	(otor* or discharg* or fluid* or leak* or liquor* or moist* or mucoid* or mucopurulen* or mucus* or otoliquor* or purulen* or pus or secret* or suppurat* or weep* or wet*):ti,ab
#9	{or #4-#8}
#10	#3 and #9
#11	MeSH descriptor: [Intraoperative Care] this term only
#12	MeSH descriptor: [Intraoperative Period] this term only
#13	MeSH descriptor: [Monitoring, Intraoperative] this term only
#14	MeSH descriptor: [Perioperative Care] this term only
#15	MeSH descriptor: [Perioperative Period] this term only
#16	MeSH descriptor: [Postoperative Care] this term only
#17	MeSH descriptor: [Postoperative Period] this term only
#18	MeSH descriptor: [Secondary Prevention] this term only
#19	MeSH descriptor: [Adenoidectomy] this term only
#20	MeSH descriptor: [Otologic Surgical Procedures] explode all trees
#21	(implant* or intraoperat* or intrasurg* or operat* or otosurg* or perioperat* or postoperat* or postsurg* or surg* or prophyl* or postadenoidectom* or postadenotonsillectom* or postmyringoplast* or postmyringostom* or postmyringotom* or posttubulat* or posttympanoplast or posttympanostom* or adenoidectom* or adenotonsillectom* or grommet* or tube* or tubulat* or tympanoplast* or tympanostom* or tonsillectom* or ventilat*):ti,ab
#22	{or #11-#21}
#23	#10 and #22
#24	MeSH descriptor: [Anti-Infective Agents] this term only
#25	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#26	MeSH descriptor: [Anti-Infective Agents, Local] explode all trees
#27	MeSH descriptor: [Bacterial Infections] this term only
#28	MeSH descriptor: [beta-Lactams] explode all trees
#29	MeSH descriptor: [Macrolides] explode all trees
#30	MeSH descriptor: [Trimethoprim] explode all trees
#31	(antibacteri* or "anti bacteri*" or antibiotic* or "anti biotic*" or antiinfect* or "anti infect*" or antimicrob* or "anti microb*" or antimyobacteri* or "anti myobacteri*" or bacteriocid*):ti,ab
#32	(penicillin* or aminoglycoside* or amoxicillin* or amix or amoram or amoxident or galenamox or rimoxallin or amoxil or ampicillin* or clavulan* or coamoxiclav or amoxiclav or augmentin or ticarcillin or timentin or flucloxacillin or fluampicil or magnapen or piperacillin or tazocin or cephalosporin* or cefaclor or distaclor or cefadroxil or baxan or cefalexin or ceporex or keflex or cefamandole or kefadol or cefazolin or kefzol or cefixime or suprax or cefotaxime or claforan or cefoxitin or mefoxin or cefpirome or cefrom or cefpodoxime or orelox or cefprozil or cefzil or cefradine or velosel or ceftazidime or fortum or kefadim or ceftriaxone or rocephin or cefuroxime* or zinacef or zinnat or cefonicid or aztreonam or azactam or imipenem or cilastatin or primaxin or meropenem or meronem or tetracycline* or deteclo or demecleocyclin or ledermycin or doxycycline or vibramycin or minocycline or minocine or oxytetracycline or terramycin or macrolide* or erythromycin* or erymax or erythrocin or erythroped or azithromycin* or zithromax or zedbac or clarithromycin or klaricid or mycifor or telithromycin or sulfisoxazole or ketek or trimoxazole or moxifloxacin or avelox or trimethoprim or cotrimoxazole or monotrim or septrin or trimopan or metronidazole or flagyl or metrolyl or quinolone* or ciprofloxacin or ciproxin or phenoxymethylpenicillin or sulfamethoxazole or oxacillin or cephalothin or sulbactam or ofloxacin or clindamycin or gentamycin or vancomycin or sulfisoxazole):ti,ab
#33	MeSH descriptor: [Steroids] this term only
#34	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
#35	MeSH descriptor: [Mineralocorticoids] explode all trees
#36	MeSH descriptor: [Prednisolone] explode all trees
#37	(steroid* or "adrenal cortex hormone*" or corticosteroid* or corticoid* or glucocorticoid* or glucocorticosteroid* or aldosterone or aristocort or baycadron or becloforte or "beclomet?a?one" or aerobec or asmabec or beclazone or becodisks or becotide or "clenil modulite" or qvar or betamethasone or budelin or bude?onide or calcort or clobetasol

ID	Search
	or corlan or cortef or cortisol or cortisone or corticosterone or cortodoxone or "cortone acetate" or cotolone or decadron or deflazacort or delta?one or desonide or dexametha?one or dexsol or efcortesol or entocort or "florinef acetate" or flumetha?one or flunisolide or flutica?one or fludrocorti?one or hydrocorti?one or hydrocortone or hydroxycorticosteroid* or hydroxypregnenolone or kenalog or medrone or medrol or solu?medrone or depo?medrone or methylpred or methylpredni?olone or mineralcorticoid*or mometa?one or parametha?one or pediapred or prednicot or predni?olone or predni?one or pregnenedione* or pregnenolone* or prelone or pulmicort or solucortef or symbicort or tetrahydrocortisol or triamcinolone):ti,ab
#38	MeSH descriptor: [Saline Solution] this term only
#39	MeSH descriptor: [Saline Solution, Hypertonic] this term only
#40	MeSH descriptor: [Sodium Chloride] this term only
#41	MeSH descriptor: [Therapeutic Irrigation] this term only
#42	(antiseptic* or "anti septic*" or clean* or drop* or eardrop* or hypersaline or hypertonic* or "hyper tonic*" or irrigat* or lavag* or rins* or saline or salt* or seawater or "sodium chloride" or solution* or toilet* or wash* or water*):ti,ab
#43	MeSH descriptor: [Baths] this term only
#44	MeSH descriptor: [Fresh Water] this term only
#45	MeSH descriptor: [Immersion] this term only
#46	MeSH descriptor: [Oceans and Seas] this term only
#47	MeSH descriptor: [Seawater] this term only
#48	MeSH descriptor: [Swimming Pools] this term only
#49	MeSH descriptor: [Swimming] this term only
#50	MeSH descriptor: [Water] this term only
#51	(swim* or shower* or bath* or dry or dive or diving or nonswim* or immers* or submers* or submerg* or lake* or pond* or creek* or pool* or river* or freshwater* or sea* or ocean* or ingress*):ti,ab
#52	MeSH descriptor: [Ear Protective Devices] this term only
#53	(protect* or prevent* or precaution* or barrier* or "ear mould*" or "ear mold*" or "ear plug*" or earplug* or earmold* or earmould* or headband* or "head band*"):ti,ab
#54	{or #24-#53}
#55	#23 and #54
#56	"conference":pt or (clinicaltrials or trialsearch):so
#57	#55 not #56 with Cochrane Library publication date Between Jan 2010 and Nov 2022

Database: Epistemonikos

Date last searched: 09/11/2022

#	Searches
1	(title:(("glue ear" OR (("middle ear" OR "otitis media") AND effusion*) OR ome OR ((secretory OR serous) AND "otitis media"))) OR abstract:(("glue ear" OR (("middle ear" OR "otitis media") AND effusion*) OR ome OR ((secretory OR serous) AND "otitis media")))
2	(title:((otor* OR discharg* OR fluid* OR leak* OR liquor* OR moist* OR mucoid* OR mucopurulen* OR mucus* OR otoliquor* OR purulen* OR pus OR suppurat* OR weep* OR wet*)) OR abstract:((otor* OR discharg* OR fluid* OR leak* OR liquor* OR moist* OR mucoid* OR mucopurulen* OR mucus* OR otoliquor* OR purulen* OR pus OR suppurat* OR weep* OR wet*))
3	1 AND 2
4	date limit: 2010-

Database: International Network of Agencies for Health Technology Assessment (INAHTA)

Date last searched: 09/11/2022

#	Searches
1	"Otitis Media with Effusion"[mhe]
2	((“glue ear” or ((“middle ear” or “otitis media”) and effusion*) or ome or ((secretory or serous) and “otitis media”))
3	1 OR 2
4	(otor* or discharg* or fluid* or leak* or liquor* or moist* or mucoid* or mucopurulen* or mucus* or otoliquor* or purulen* or pus or suppurat* or weep* or wet*)
5	3 AND 4 FROM 2010 TO 2022 AND (English)[Language]

Economic literature search strategy

A global, population-based search was undertaken to find economic evidence covering all parts of the guideline.

Database: MEDLINE – OVID interface

Date last searched: 09/11/2022

#	Searches
1	otitis media with effusion/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	Economics/
5	Value of life/
6	exp "Costs and Cost Analysis"/
7	exp Economics, Hospital/
8	exp Economics, Medical/
9	Economics, Nursing/
10	Economics, Pharmaceutical/
11	exp "Fees and Charges"/
12	exp Budgets/
13	budget*.ti,ab.
14	cost*.ti.
15	(economic* or pharmaco?economic*).ti.
16	(price* or pricing*).ti,ab.
17	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
18	(financ* or fee or fees).ti,ab.
19	(value adj2 (money or monetary)).ti,ab.
20	or/4-19
21	exp models, economic/
22	*Models, Theoretical/
23	*Models, Organizational/
24	markov chains/
25	monte carlo method/
26	exp Decision Theory/
27	(markov* or monte carlo).ti,ab.
28	econom* model*.ti,ab.
29	(decision* adj2 (tree* or analy* or model*)).ti,ab.
30	or/21-29
31	20 or 30
32	3 and 31
33	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
34	32 not 33
35	limit 34 to english language
36	limit 35 to yr="2000 -Current"

Database: Embase – OVID interface

Date last searched: 09/11/2022

#	Searches
1	exp secretory otitis media/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	health economics/
5	exp economic evaluation/
6	exp health care cost/
7	exp fee/
8	budget/
9	funding/
10	budget*.ti,ab.
11	cost*.ti.
12	(economic* or pharmaco?economic*).ti.
13	(price* or pricing*).ti,ab.
14	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15	(financ* or fee or fees).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	or/4-16
18	statistical model/
19	exp economic aspect/
20	18 and 19
21	*theoretical model/
22	*nonbiological model/
23	stochastic model/
24	decision theory/
25	decision tree/
26	monte carlo method/

#	Searches
27	(markov* or monte carlo).ti,ab.
28	econom* model*.ti,ab.
29	(decision* adj2 (tree* or analy* or model*)).ti,ab.
30	or/20-29
31	17 or 30
32	3 and 31
33	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.
34	32 not 33
35	limit 34 to english language
36	limit 35 to yr="2000 -Current"

Database: Cochrane Central Register of Controlled Trials (CENTRAL) – Wiley interface

Date last searched: 09/11/2022

ID	Search
#1	MeSH descriptor: [Otitis Media with Effusion] this term only
#2	(("glue ear" or (("middle ear" or "otitis media") near/2 effusion*) or ome or ((secretory or serious) near/2 "otitis media"))):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Economics] this term only
#5	MeSH descriptor: [Value of Life] this term only
#6	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#7	MeSH descriptor: [Economics, Hospital] explode all trees
#8	MeSH descriptor: [Economics, Medical] explode all trees
#9	MeSH descriptor: [Economics, Nursing] this term only
#10	MeSH descriptor: [Economics, Pharmaceutical] this term only
#11	MeSH descriptor: [Fees and Charges] explode all trees
#12	MeSH descriptor: [Budgets] explode all trees
#13	budget*:ti,ab
#14	cost*:ti
#15	(economic* or pharmaco?economic*):ti
#16	(price* or pricing*):ti,ab
#17	(cost* near/2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)):ab
#18	(financ* or fee or fees):ti,ab
#19	(value near/2 (money or monetary)):ti,ab
#20	{or #4-#19}
#21	MeSH descriptor: [Models, Economic] explode all trees
#22	MeSH descriptor: [Models, Theoretical] this term only
#23	MeSH descriptor: [Models, Organizational] this term only
#24	MeSH descriptor: [Markov Chains] this term only
#25	MeSH descriptor: [Monte Carlo Method] this term only
#26	MeSH descriptor: [Decision Theory] explode all trees
#27	(markov* or "monte carlo"):ti,ab
#28	(econom* next model*):ti,ab
#29	(decision* near/2 (tree* or analy* or model*)):ti,ab
#30	{or #21-#29}
#31	#20 or #30
#32	#3 and #31 with Cochrane Library publication date Between Jan 2000 and Apr 2022

Database: International Network of Agencies for Health Technology Assessment (INAHTA)

Date last searched: 09/11/2022

#	Searches
1	((("Otitis Media with Effusion"[mhe]) OR ((("glue ear" or (("middle ear" or "otitis media") and effusion*) or ome or ((secretory or serous) and "otitis media")))
2	1 and FROM 2000 TO 2022 AND (English)[Language]

Database: NHS Economic Evaluation Database (NHS EED) – CRD interface

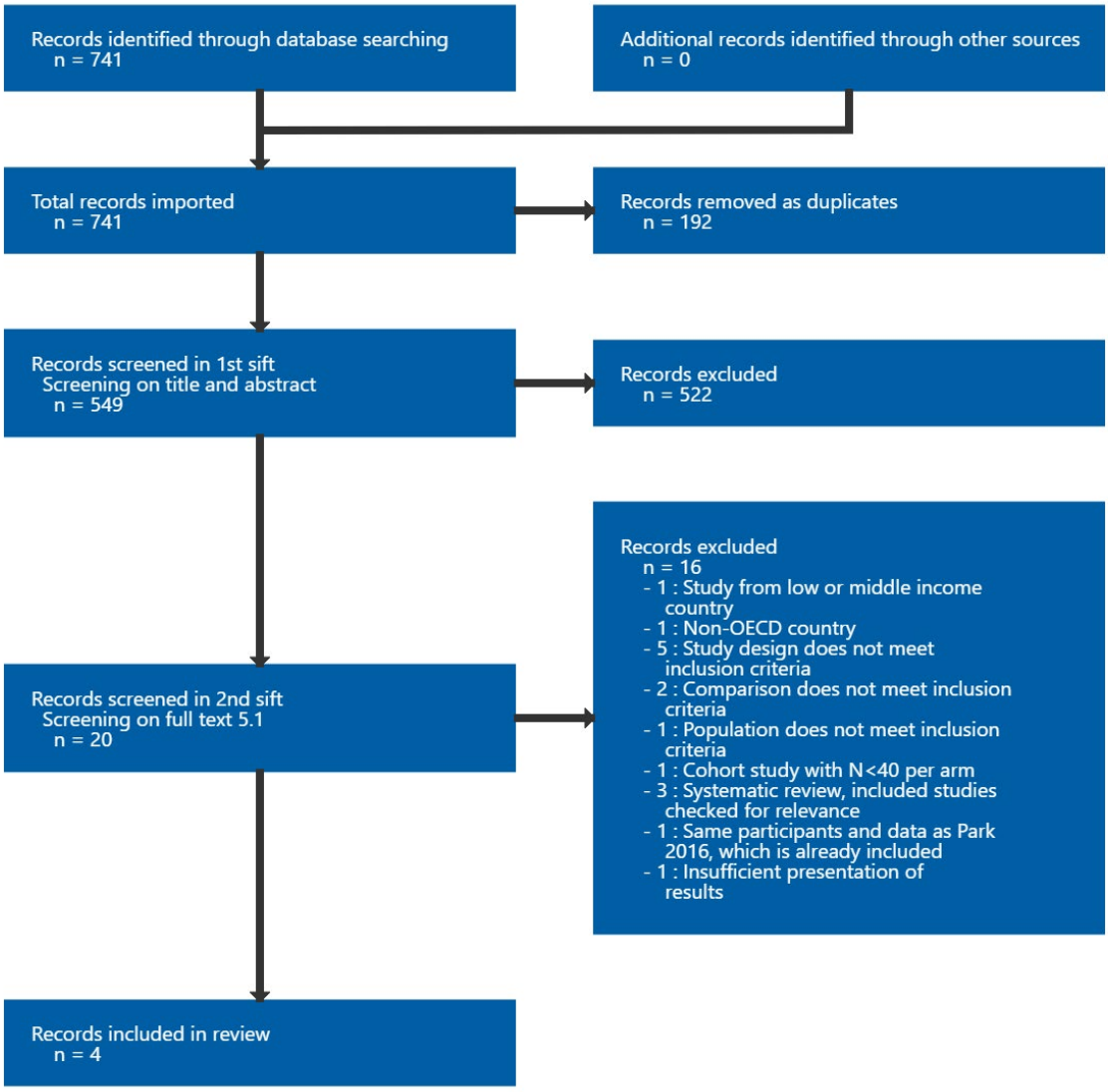
Date last searched: 09/11/2022

Line	Search for
1	MeSH DESCRIPTOR Otitis Media with Effusion EXPLODE ALL TREES
2	((glue ear or ((middle ear or otitis media) and effusion*) or ome or ((secretory or serous) and otitis media))) IN NHS EED
3	#1 OR #2

Appendix C Effectiveness evidence study selection

Study selection for: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

Table 4: Evidence tables

Mair, 2016

Bibliographic Reference	Mair, Eric A; Moss, Jonathan R; Dohar, Joseph E; Antonelli, Patrick J; Bear, Moraye; LeBel, Carl; Randomized Clinical Trial of a Sustained-Exposure Ciprofloxacin for Intratympanic Injection During Tympanostomy Tube Surgery.; The Annals of otology, rhinology, and laryngology; 2016; vol. 125 (no. 2); 105-14

Study details

Country/ies where study was carried out	USA
Study type	Randomised controlled trial (RCT)
Study dates	January 2013 - June 2013
Inclusion criteria	Children aged 6 months to 12 years with confirmed bilateral middle ear effusion with indication of tympanostomy tube placement
Exclusion criteria	History of ear and mastoid surgery, requirement of concurrent surgery, sensorineural hearing loss, history of other chronic or recurrent bacterial infection, history of tympanic membrane perforation, known immunodeficiency, abnormal tympanic membrane or middle ear, use of topical nonsteroid otic medication within 1 day of randomisation, use of topical, inhale or nasal steroid during study, requirement/use of systemic or topical antimicrobial or antifungal medications, concurrent use of oral anti-inflammatory medication, history of allergic reaction to ciprofloxacin or any of the components of OTO-201, serious illness or medical condition, use of an investigational medication or device in the month prior to screening, history of exposure to OTO-201, and menarcheal or post-menarcheal female, and children aged 4 years or younger who did not complete in distortion product otoacoustic emission (DPOAE) test in both ears and visual reinforcement audiometry (VRA) test in 1 ear at 2 frequencies.

Patient characteristics	N=83 (Intraoperative intratympanic ciprofloxacin injection 4 mg: N=21; Intraoperative intratympanic ciprofloxacin injection 12 mg: N=19; Placebo: N=22; Sham: N=21) Mean age in years (SD): Intraoperative intratympanic ciprofloxacin injection 4 mg: 2.9 (2.6) Intraoperative intratympanic ciprofloxacin injection 12 mg: 2.8 (2.2) Placebo: 2.5 (1.9) Sham: 2.8 (2.3) Sex (male/female): Intraoperative intratympanic ciprofloxacin injection 4 mg: 15/6 Intraoperative intratympanic ciprofloxacin injection 12 mg: 10/9 Placebo: 12/10 Sham: 15/6
Intervention(s)/control	Intraoperative intratympanic ciprofloxacin injection (4 mg): intratympanic administration of ciprofloxacin otic suspension 4 mg into both ears following myringotomy Intraoperative intratympanic ciprofloxacin injection (12 mg): intratympanic administration of ciprofloxacin otic suspension 12 mg into both ears following myringotomy Placebo: vehicle administered following myringotomy Sham: air administered following myringotomy
Duration of follow-up	Children were assessed on days 4, 8, 15, and 29.
Sources of funding	Industry funded
Sample size	N=83
Other information	Otorrhoea was assessed by visual external ear examination.

DPOAE: distortion product otoacoustic emission test; RCT: randomised controlled trial; VRA: visual reinforcement audiometry test

Outcomes

Intraoperative intratympanic ciprofloxacin injection (4 mg) versus intraoperative intratympanic ciprofloxacin injection (12 mg) versus placebo versus sham: Otorrhoea and adverse effects of intervention

Outcome	Intraoperative intratympanic ciprofloxacin injection (4 mg), N = 21	Intraoperative intratympanic ciprofloxacin injection (12 mg), N = 19	Placebo, N = 22	Sham, N = 21
Otorrhoea (15 days after surgery) Custom value	2/21	2/19	8/22	5/20
Adverse effects of intervention (treatment-emergent adverse events such as otorrhoea, pyrexia, upper respiratory tract infection, ear infection and diarrhoea) Custom value	13/21	9/19	12/22	18/20

CIP: ciprofloxacin

Critical appraisal - Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment. No significant differences between groups at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(People delivering the intervention were aware of the intervention; however, there is no reason to believe that deviations from the intended intervention arose due to trial context. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(The data were available for 99% of participants for all outcomes.)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Methods of measuring the outcomes were appropriate, and no difference in measurement of the outcomes between intervention groups. Outcome assessors were blinded to intervention status.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that all eligible reported results for the outcome correspond to all intended outcome measurements and analyses.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Park, 2016

Bibliographic Reference	Park, Albert H; White, David R; Moss, Jonathan R; Bear, Moraye; LeBel, Carl; Phase 3 Trials of Thermosensitive Ciprofloxacin Gel for Middle Ear Effusion in Children with Tubes.; Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery; 2016; vol. 155 (no. 2); 324-31

Study details

Country/ies where study was carried out	Canada and USA

Study type	Randomised controlled trial (RCT)
Study dates	November 2013 - June 2014
Inclusion criteria	Children aged 6 months to 17 years who are undergoing tympanostomy tube placement for otoscopically confirmed middle ear effusion on the day of surgery
Exclusion criteria	Requirement of any other surgery concurrently, previous history of mastoid surgery, recurrent or chronic bacterial infections, sensorineural hearing loss, tympanic membrane perforation, immunodeficiency disease, abnormal middle ear or tympanic membrane, use of topical nonsteroid otic medication within 1 day of randomisation, use of otic or topical steroid within 3 days of randomisation, systemic corticosteroid within 7 days of randomisation, use of systemic or topical antimicrobial or antifungal medications, concurrent use of oral anti-inflammatory medication, history of allergic reaction to ciprofloxacin or any of the components of OTO-201, and post-menarcheal or menarcheal female.
Patient characteristics	N=532 (Intraoperative intratympanic ciprofloxacin injection 6 mg: N=357; Sham: N=175) Mean age in years (SD): Intraoperative intratympanic ciprofloxacin injection 6 mg: 2.3 (1.9) Sham: 2.6 (2.3) Sex (male/female): Intraoperative intratympanic ciprofloxacin injection 6 mg: 200/157 Sham: 104/71 Positive microbiology culture (at least one ear): Intraoperative intratympanic ciprofloxacin injection 6 mg: N=70 Sham: N=49
Intervention(s)/control	Intraoperative intratympanic ciprofloxacin injection (6 mg): a single 0.1 ml (6 mg) intratympanic administration of a thermosensitive otic suspension of ciprofloxacin into each ear followed by tympanostomy tube placement Sham: the syringe was empty (tympanostomy tube placement alone)
Duration of follow-up	Children were assessed on days 4, 8, 15, and 29.

Sources of funding	Industry funded
Sample size	N=532
Other information	Otorrhoea was assessed by visual external ear examination

RCT: randomised controlled trial; SD: standard deviation

Outcomes

Intraoperative intratympanic ciprofloxacin injection (6 mg) versus sham: Otorrhoea, adverse effects of intervention, tube blockage and tube extrusion

Outcome	**Intraoperative intratympanic ciprofloxacin injection (6 mg), N = 357**	**Sham, N = 175**
Otorrhoea (29 days after surgery) Custom value	37/352	41/174
Adverse effects of intervention (Treatment-emergent adverse events such as pyrexia, pain, cough, nasopharyngitis, upper respiratory tract infection, irritability, vomiting, nasal congestion and rhinorrhoea; up to 29 days) Custom value	189/357	95/173
Tube blockage (29 days after surgery) Custom value	18/357	7/173
Tube extrusion (29 days after surgery) Custom value	3/357	1/173

Critical appraisal - Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment. No significant differences between groups at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Other than people delivering the intervention, all persons in the trial such as staffs, carers and participants were blinded to the interventions. There is no reason to believe that deviations from the intended intervention arose due to trial context. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(The data were available for nearly all participants (99%) for all outcomes.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Methods of measuring the outcomes were appropriate, and no difference in measurement of the outcomes between intervention groups. Outcome assessors were blinded to intervention status.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that all eligible reported results for the outcome correspond to all intended outcome measurements and analyses.)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable (Although the inclusion criteria extended to children aged up to 17 years old, the mean age and standard deviation of the participants were well within our target age of up to 12 years)

Section	Question	Answer
Overall bias and Directness	Risk of bias variation across outcomes	None

RoB: risk of bias

Subtil, 2019

Bibliographic Reference	Subtil, Joao; Jardim, Ana; Araujo, Joao; Moreira, Carla; Eca, Tiago; McMillan, Merlin; Simoes Dias, Sara; Vera Cruz, Paulo; Voegels, Richard; Paco, Joao; Rosenfeld, Richard; Effect of Water Precautions on Otorrhea Incidence after Pediatric Tympanostomy Tube: Randomized Controlled Trial Evidence.; Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery; 2019; vol. 161 (no. 3); 514-521

Study details

Country/ies where study was carried out	Portugal
Study type	Randomised controlled trial (RCT)
Study dates	February 2015 - August 2017
Inclusion criteria	Children aged 2-10 years with chronic otitis media with effusion (OME) with indication for surgery and concurrent adenoidectomy (either for OME or for a concurrent diagnosis of recurrent acute otitis media, chronic nasal inflammatory symptoms, obstructive sleep apnea, recurrent adenoiditis or sinusitis) and primary caregivers willing to follow the recommendations in either group.
Exclusion criteria	Craniofacial anomalies, history of tympanic surgery and tympanostomy, unilateral surgery, unavailable for follow-up or unable to understand questionnaires in Portuguese, immunodeficiency, poor compliance with prescribed precautions, premature tube extrusion, more than three episodes of otorrhoea and any complication (e.g., acute mastoiditis) during the study.

Patient characteristics	N=291 (Water precautions: N=149; No precautions: N=142) Mean age in years (SD): 4.4 (1.7) *Not reported split by intervention group* Sex (male/female): Water precautions: 74/56 No precautions: 64/50 Children with swimming activities at least once a week: Water precautions: N=82 No precautions: N=64
Intervention(s)/control	Water precautions: wearing moldable silicone earplugs and headbands for swimming and earplugs for bathing and showering No precautions: showering or swimming with no protection
Duration of follow-up	Children were assessed every 2 months for up to 6 months
Sources of funding	None
Sample size	N=291
Other information	N=244 participants included in final analyses Otorrhoea was reported by parents and then confirmed with a specialist. Children underwent tympanostomy tube (ventilation tube) surgery, and the same surgical technique, canal disinfection, and type of tympanostomy tube (fluoroplastic Shepard tube) were used. Children did not receive any other topical treatment.

RCT: randomised controlled trial; SD: standard deviation

Outcomes

Water precautions versus no precautions: Otorrhoea and quality of life

Outcome	Water precautions, N = 149	No precautions, N = 142
Otorrhoea (from 2 weeks after surgery to 6 months) Custom value	41/130	25/114
Quality of life (improvement in quality of life; at 2 months) Custom value	113/130	99/114

Critical appraisal – Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on allocation sequence concealment. No significant differences between groups at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Blinding of participants and personnel may not be possible due to the nature of the intervention; however, there is no reason to believe that deviations from the intended intervention arose due to trial context. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Loss to follow up and discontinued intervention greater in no precautions group compared with water precautions for all outcomes (20% vs 13%); however, intention to treat analysis confirmed that the result was not biased by missing outcome data.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(Methods of measuring the outcomes were appropriate, and no difference in measurement of the outcomes between intervention groups. No information if*

Section	Question	Answer
		outcome assessors were blinded to intervention status. Outcomes reported by patients or parents, such as otorrhoea and quality of life, are somewhat subjective and may be influenced by knowledge of assigned intervention.)
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that all eligible reported results for the outcome correspond to all intended outcome measurements and analyses.)*
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to be at high risk of bias in at least one.)*
Overall bias and Directness	Overall Directness	Directly applicable *(Quality of life was assessed with the PedsQL tool, which is not OME specific)*
Overall bias and Directness	Risk of bias variation across outcomes	None

PedsQL: Pediatric Quality of Life Inventory; RoB: risk of bias

Wang, 2022

Bibliographic Reference	Wang, Luke Chenkan; Phyland, Debra Jean; Giddings, Charles Edward; A randomised clinical trial of single or extended dosing ciprofloxacin versus no intervention for prevention of ventilation tube otorrhoea and obstruction (PreVenTO2).; Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery; 2022; vol. 47 (no. 2); 287-294

Study details

Country/ies where study was carried out	Australia

Study type	Randomised controlled trial (RCT)
Study dates	May 2018 - June 2020
Inclusion criteria	Children aged 17 years or under who are undergoing bilateral VT surgery with or without concurrent upper airway surgery for recurrent acute otitis media or chronic otitis media with effusion
Exclusion criteria	History of allergic reaction to quinolone, purulent middle ear effusion, or significant middle ear condition that needs intervention and insertion of long-term VT
Patient characteristics	N=296 (Intraoperative ciprofloxacin drops: N=102; Intraoperative and postoperative ciprofloxacin drops: N=94; No topical ciprofloxacin: N=100) Median age in years (IQR): Intraoperative ciprofloxacin drops: 4.09 (2.81-6.06) Intraoperative and postoperative ciprofloxacin drops: 4.04 (2.46-6.55) No topical ciprofloxacin: 3.63 (2.25-5.91) Sex (male/female): Intraoperative ciprofloxacin drops: 58/29 Intraoperative and postoperative ciprofloxacin drops: 43/37 No topical ciprofloxacin: 52/37 Children with chronic otitis media with effusion: Intraoperative ciprofloxacin drops: N=56 Intraoperative and postoperative ciprofloxacin drops: N=55 No topical ciprofloxacin: N=58 Children without previous tonsillectomy or adenoidectomy: Intraoperative ciprofloxacin drops: N=78 Intraoperative and postoperative ciprofloxacin drops: N=70 No topical ciprofloxacin: N=78
Intervention(s)/control	Intraoperative ciprofloxacin drops: children received 5 drops of topical ciprofloxacin 0.3% (Ciloxan® ear drops, Novartis AU) into each ear after insertion of VT

	Intraoperative and postoperative ciprofloxacin drops: children received 5 drops of topical ciprofloxacin 0.3% (Ciloxan® ear drops, Novartis AU) into each ear during surgery as well as twice a day for 5 days postoperatively No topical ciprofloxacin: Children did not receive any topical ciprofloxacin
Duration of follow-up	Children were assessed at 6-weeks after surgery
Sources of funding	Not industry funded
Sample size	N=296
Other information	n=512 ears of N=256 participants included in final analyses Analysis was based on a by-ear basis, and each ear was considered as an individual data point. All children received the same type of tympanostomy tube (Reuter-Bobbins VT) using a standardised technique. Otorrhoea was assessed by otoscopy and parent-reported history. Tube blockage was assessed by pneumatic otoscopy and tympanometry.

IQR: interquartile range; RCT: randomised controlled trial

Outcomes

Intraoperative ciprofloxacin drops versus intraoperative and postoperative ciprofloxacin drops versus no topical ciprofloxacin: Otorrhoea and tube blockage

Outcome	Intraoperative ciprofloxacin drops, N = 102	Intraoperative and postoperative ciprofloxacin drops, N = 94	No topical ciprofloxacin, N = 100
Otorrhoea (6 weeks after surgery) Number of ears Custom value	8/174	14/160	24/178

Outcome	Intraoperative ciprofloxacin drops, N = 102	Intraoperative and postoperative ciprofloxacin drops, N = 94	No topical ciprofloxacin, N = 100
Tube blockage (6 weeks after surgery) Number of ears Custom value	11/174	8/160	21/178

Critical appraisal - Cochrane RoB2

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Process of allocation controlled by an external unit, sealed opaque envelopes used for generation of randomisation sequence and allocation concealment. No significant differences between groups at baseline.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(No information on blinding of personnel; however, there is no reason to believe that deviations from the intended intervention arose due to trial context. Appropriate analysis was used.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(The data were available for 95% of participants.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Methods of measuring the outcomes were appropriate, and no difference in measurement of the outcomes between intervention groups. Outcome assessors and data analysts were blinded to intervention status.)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(There is clear evidence that all eligible reported results for the outcome correspond to all intended outcome measurements and analyses.)*
Overall bias and Directness	Risk of bias judgement	Low *(The study is judged to be at low risk of bias for all domains.)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Population is indirect because 34% had recurrent acute otitis media. Although the inclusion criteria extended to children aged up to 17 years old, the mean age and standard deviation of the participants were well within our target age of up to 12 years.)*
Overall bias and Directness	Risk of bias variation across outcomes	None

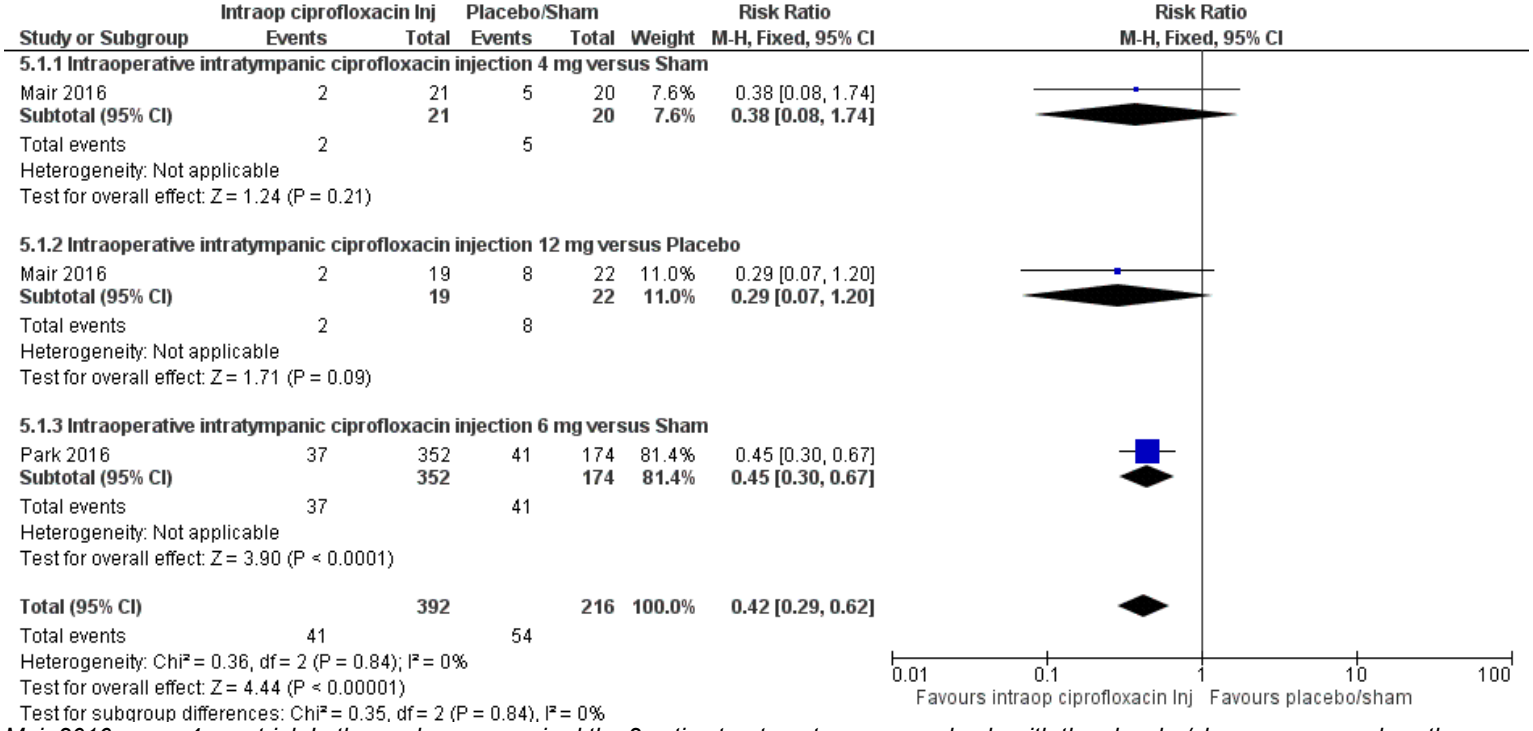
RoB: risk of bias

Appendix E Forest plots

Forest plots for review question: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

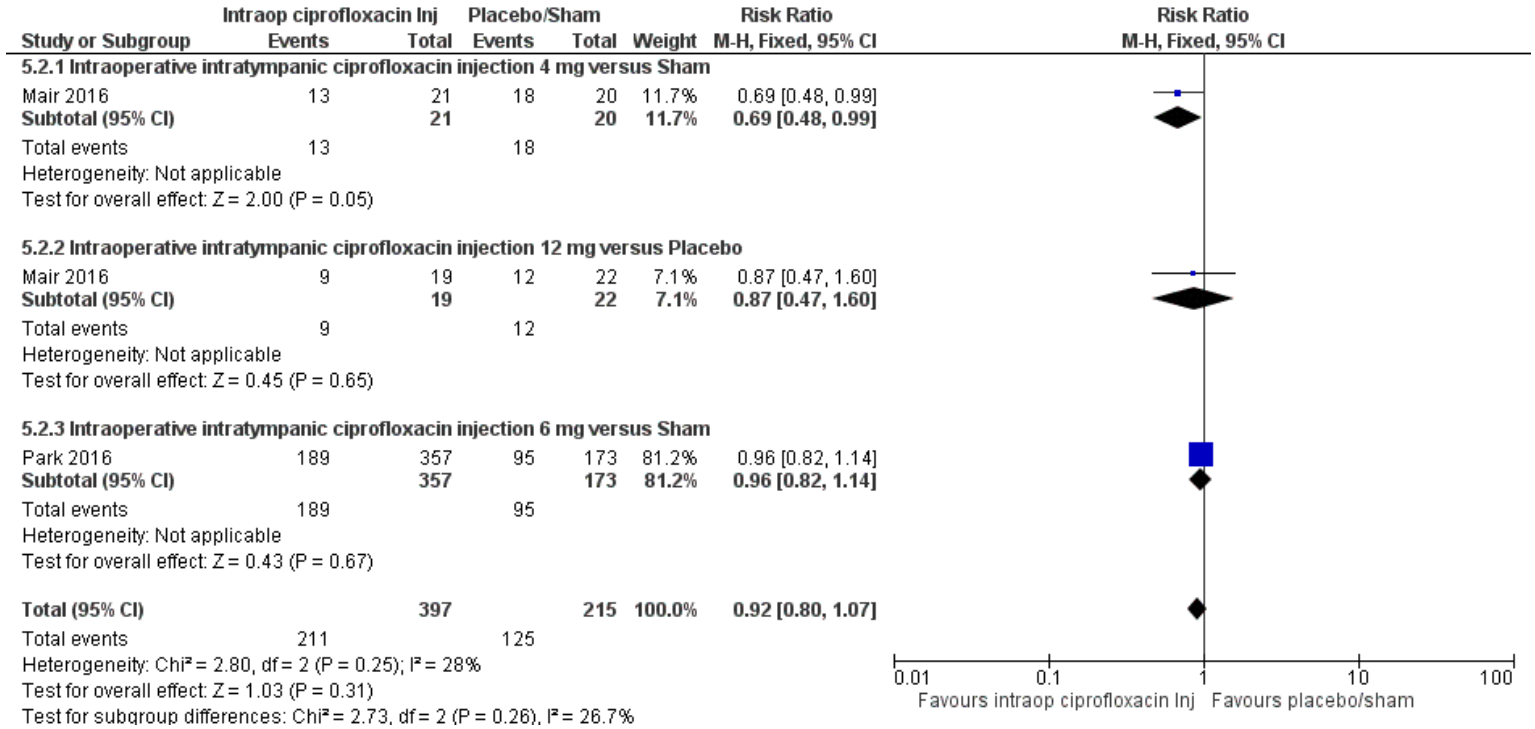
This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Figure 2: Intraoperative intratympanic ciprofloxacin injection versus placebo/sham: Otorrhoea



Mair 2016 was a 4-arm trial. In the analyses we paired the 2 active treatment groups randomly with the placebo/sham groups, and we then conducted sensitivity analyses swapping the Sham/Placebo pairings with the 4 and 12 mg active treatment groups over to assess the impact of the original pairing. These analyses showed for the following comparisons: Intraoperative intratympanic ciprofloxacin injection 4 mg versus Placebo: 0.26 [0.06, 1.09]; Intraoperative intratympanic ciprofloxacin injection 12 mg versus Sham: 0.42 [0.09, 1.92]; Intraoperative intratympanic ciprofloxacin injection 6 mg versus Sham: 0.45 [0.30, 0.67]; Overall effect: 0.42 [0.29, 0.62].
CI: confidence interval; Inj: injection; Intraop: intraoperative; M-H: Mantel-Haenszel

Figure 3: Intraoperative intratympanic ciprofloxacin injection versus placebo/sham: Adverse effects of intervention



Mair 2016 was a 4-arm trial. In the analyses we paired the 2 active treatment groups randomly with the placebo/sham groups, and we then conducted sensitivity analyses swapping the Sham/Placebo pairings with the 4 and 12 mg active treatment groups over to assess the impact of the original pairing. These analyses showed for the following comparisons: Intraoperative intratympanic ciprofloxacin injection 4 mg versus Placebo: 1.13 [0.68, 1.89]; Intraoperative intratympanic ciprofloxacin injection 12 mg versus Sham: 0.53 [0.32, 0.86]; Intraoperative intratympanic ciprofloxacin injection 6 mg versus Sham: 0.96 [0.82, 1.14]; Overall effect: 0.85 [0.59, 1.25].
CI: confidence interval; Inj: injection; Intraop: intraoperative; M-H: Mantel-Haenszel

Appendix F GRADE tables

GRADE tables for review question: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

Table 5: Evidence profile for comparison: intraoperative ciprofloxacin drops versus no topical ciprofloxacin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intraoperative ciprofloxacin drops	No topical ciprofloxacin	Relative (95% CI)	Absolute		
Otorrhoea (follow-up 6 weeks)												
1 (Wang 2022)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	8/174 (4.6%)	24/178 (13.5%)	RR 0.34 (0.16 to 0.74)	89 fewer per 1000 (from 35 fewer to 113 fewer)	MODERATE	CRITICAL
Tube blockage (follow-up 6 weeks)												
1 (Wang 2022)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	11/174 (6.3%)	21/178 (11.8%)	RR 0.54 (0.27 to 1.08)	54 fewer per 1000 (from 86 fewer to 9 more)	LOW	IMPORTANT

CI: confidence interval; RR: risk ratio
[1] Population is indirect because 34% had recurrent acute otitis media.
[2] 95% CI crosses 1 MID

Table 6: Evidence profile for comparison: intraoperative and postoperative ciprofloxacin drops versus no topical ciprofloxacin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intraoperative and postoperative ciprofloxacin drops	No topical ciprofloxacin	Relative (95% CI)	Absolute		

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intraoperative and postoperative ciprofloxacin drops	No topical ciprofloxacin	Relative (95% CI)	Absolute		
Otorrhoea (follow-up 6 weeks)												
1 (Wang 2022)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	14/160 (8.8%)	24/178 (13.5%)	RR 0.65 (0.35 to 1.21)	47 fewer per 1000 (from 88 fewer to 28 more)	LOW	CRITICAL
Tube blockage (follow-up 6 weeks)												
1 (Wang 2022)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[2]	none	8/160 (5%)	21/178 (11.8%)	RR 0.42 (0.19 to 0.93)	68 fewer per 1000 (from 8 fewer to 96 fewer)	LOW	IMPORTANT

CI: confidence interval; RR: risk ratio
[1] Population is indirect due to 34% of population with recurrent acute otitis media, and intervention is indirect due to the combination of intraoperative and postoperative ear drops.
[2] 95% CI crosses 1 MID

Table 7: Evidence profile for comparison: intraoperative intratympanic ciprofloxacin injection versus placebo/sham

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intraoperative intratympanic ciprofloxacin injection	Placebo/Sham	Relative (95% CI)	Absolute		
Otorrhoea (follow-up 15 to 29 days)												
2*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	41/392 (10.5%)	54/216 (25%)	RR 0.42 (0.29 to 0.62)	145 fewer per 1000 (from 95 fewer to 178 fewer)	MODERATE	CRITICAL
Otorrhoea - Intraoperative intratympanic ciprofloxacin injection 4 mg versus Sham (follow-up 15 days)												
1 (Mair 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	2/21 (9.5%)	5/20 (25%)	RR 0.38 (0.08 to 1.74)	155 fewer per 1000 (from 230 fewer to 185 more)	VERY LOW	CRITICAL
Otorrhoea - Intraoperative intratympanic ciprofloxacin injection 12 mg versus Placebo (follow-up 15 days)												
1 (Mair 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	2/19 (10.5%)	8/22 (36.4%)	RR 0.29 (0.07 to 1.2)	258 fewer per 1000 (from 338 fewer to 73 more)	LOW	CRITICAL
Otorrhoea - Intraoperative intratympanic ciprofloxacin injection 6 mg versus Sham (follow-up 29 days)												
1 (Park 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/352 (10.5%)	41/174 (23.6%)	RR 0.45 (0.3 to 0.67)	130 fewer per 1000 (from 78 fewer to 165 fewer)	MODERATE	CRITICAL
Adverse effects of intervention (treatment-emergent events including otorrhoea, pyrexia, upper respiratory tract infection, ear infection and diarrhoea (Mair 2016) or pyrexia, pain, cough, nasopharyngitis, upper respiratory tract infection, irritability, vomiting, nasal congestion and rhinorrhoea (Park 2016)) (follow-up 29 days)												
2*	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	211/397 (53.1%)	125/215 (58.1%)	RR 0.92 (0.8 to 1.07)	47 fewer per 1000 (from 116 fewer to 41 more)	LOW	CRITICAL
Adverse effects of intervention (treatment-emergent events including otorrhoea, pyrexia, upper respiratory tract infection, ear infection and diarrhoea) - Intraoperative intratympanic ciprofloxacin injection 4 mg versus Sham (follow-up 29 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intraoperative intratympanic ciprofloxacin injection	Placebo/Sham	Relative (95% CI)	Absolute		
1 (Mair 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	13/21 (61.9%)	18/20 (90%)	RR 0.69 (0.48 to 0.99)	279 fewer per 1000 (from 9 fewer to 468 fewer)	LOW	CRITICAL
Adverse effects of intervention (treatment-emergent events including otorrhoea, pyrexia, upper respiratory tract infection, ear infection and diarrhoea) - Intraoperative intratympanic ciprofloxacin injection 12 mg versus Placebo (follow-up 29 days)												
1 (Mair 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	9/19 (47.4%)	12/22 (54.5%)	RR 0.87 (0.47 to 1.6)	71 fewer per 1000 (from 289 fewer to 327 more)	VERY LOW	CRITICAL
Adverse effects of intervention (treatment-emergent events including pyrexia, pain, cough, nasopharyngitis, upper respiratory tract infection, irritability, vomiting, nasal congestion and rhinorrhoea) - Intraoperative intratympanic ciprofloxacin injection 6 mg versus Sham (follow-up 29 days)												
1 (Park 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	189/357 (52.9%)	95/173 (54.9%)	RR 0.96 (0.82 to 1.14)	22 fewer per 1000 (from 99 fewer to 77 more)	MODERATE	CRITICAL
Tube blockage (follow-up 29 days)												
1 (Park 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	18/357 (5%)	7/173 (4%)	RR 1.25 (0.53 to 2.93)	10 more per 1000 (from 19 fewer to 78 more)	VERY LOW	IMPORTANT
Tube extrusion (follow-up 29 days)												
1 (Park 2016)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/357 (0.84%)	1/173 (0.58%)	POR 1.42 (0.17 to 11.54)	2 more per 1000 (from 5 fewer to 57 more)	VERY LOW	IMPORTANT

CI: confidence interval; POR: Peto odds ratio; RR: risk ratio
**See corresponding forest plot (Figure 2)*
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[4] 95% CI crosses 2 MIDs
[6] 95% CI crosses 1 MID

Table 8: Evidence profile for comparison: water precautions versus no precautions

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Water precautions	No precautions	Relative (95% CI)	Absolute		
Otorrhoea (follow-up 6 months)												
1 (Subtil 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41/130 (31.5%)	25/114 (21.9%)	RR 1.44 (0.94 to 2.21)	96 more per 1000 (from 13 fewer to 265 more)	VERY LOW	CRITICAL
Quality of life (improvement in quality of life) (follow-up 2 months)												
1 (Subtil 2019)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	113/130 (86.9%)	99/114 (86.8%)	RR 1 (0.91 to 1.1)	0 fewer per 1000 (from 78 fewer to 87 more)	LOW	IMPORTANT

CI: confidence interval; RR: risk ratio

[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2

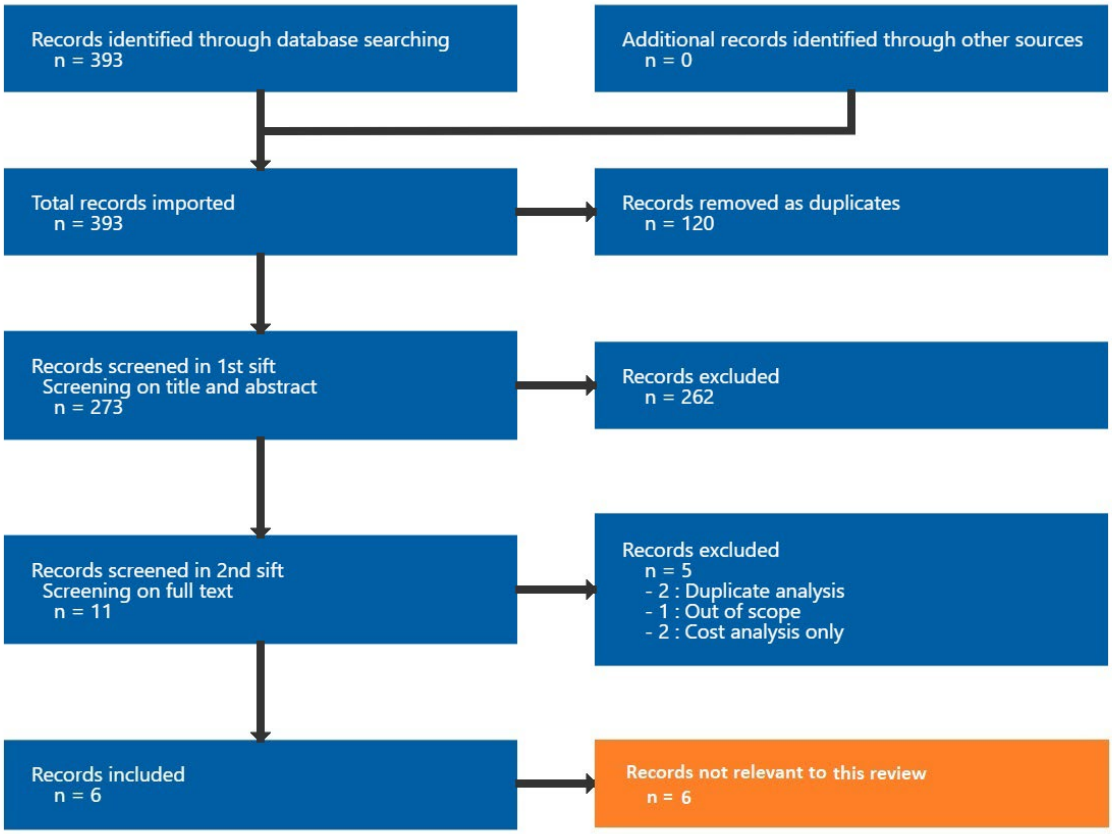
[2] 95% CI crosses 1 MID

Appendix G Economic evidence study selection

Study selection for: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

A global search was undertaken to cover all the review questions considered in this guideline, but no economic evidence was identified which was applicable to this review question (see Figure 4).

Figure 4: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

Excluded effectiveness studies

Table 9: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Alvi, S.A., Jones, J.W., Porter, P. et al. (2018) Steroid Versus Antibiotic Drops in the Prevention of Postoperative Myringotomy Tube Complications. Annals of Otology, Rhinology and Laryngology 127(7): 445-449	- Comparison does not meet inclusion criteria *Head-to-head comparisons between different interventions within each category (ciprofloxacin/dexamethasone drops vs. ofloxacin drops)*
Anonymous (2016) Ciprofloxacin (Otiprio) for tympanostomy tube insertion. The Medical letter on drugs and therapeutics 58(1495): 69-70	- Study design does not meet inclusion criteria *Non-comparative study*
Anonymous. (2016) Ciprofloxacin/fluocinolone (otovel) for otitis media with tympanostomy tubes. Medical Letter on Drugs and Therapeutics 58(1509): 153-155	- Study design does not meet inclusion criteria *Non-comparative study*
Browning, G G (2013) Prophylactic ear drops should not be used routinely to prevent postoperative, ventilation tubes otorrhoea. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 38(4): 324-5	- Study design does not meet inclusion criteria *Editorial comment, no original data*
Dohar, Joseph E, Don, Debra, Koempel, Jeffrey et al. (2018) Safety and efficacy of intratympanic ciprofloxacin otic suspension post-tubes in a real-world pediatric population. American journal of otolaryngology 39(2): 101-106	- Study design does not meet inclusion criteria *No control group, and investigates the safety and efficacy of local antibiotic injection (Intratympanic injection during tympanostomy tube surgery)*
Dohar, Joseph E and Lu, Chung H (2018) Tube patency: Is there a difference following otic drop administration?. American journal of otolaryngology 39(4): 392-395	- Comparison does not meet inclusion criteria *Tympanostomy tube with/without intraoperative local antibiotic injection plus postoperative otic drops (if post-tube otorrhea observed) vs. tympanostomy tube with/without intraoperative local antibiotic injection; tube patency is only outcome reported and only as ranges; analyses not in PICO*
Faramarzi, Mohammad, Roosta, Sareh, Shishegar, Mahmood et al. (2016) The rationale for preventive treatments for early post-tympanostomy tube otorrhea in persistent otitis media with effusion. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated	- Study from low or middle income country

Study	Code [Reason]
with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 273(6): 1405-10	
Gabarain, Gabriel, Baird, Rachel, Morisada, Megan et al. (2019) Early Otorrhea Rates: A Randomized Trial of Ciprofloxacin versus Saline Drops after Tympanostomy Tubes. The Annals of otology, rhinology, and laryngology 128(8): 760-766	- Population does not meet inclusion criteria *Only about 20% of participants had OME and results not presented separately for them*
Ho, Chia-Ying, Chin, Shy-Chyi, Hu, Chih-Yu et al. (2022) The necessity and effect of prophylactic quinolone ear drops after ventilation tube insertion for otitis media with effusion. American journal of otolaryngology 43(1): 103266	- Non-OECD country *Study from Taiwan*
Mair, Eric A, Park, Albert H, Don, Debra et al. (2016) Safety and Efficacy of Intratympanic Ciprofloxacin Otic Suspension in Children With Middle Ear Effusion Undergoing Tympanostomy Tube Placement: Two Randomized Clinical Trials. JAMA otolaryngology-- head & neck surgery 142(5): 444-51	- Same participants and data as Park 2016, which is already included
McManus, Brian, Townsend, William, Stuart, Kinsley et al. (2022) Oxymetazoline vs ofloxacin vs ciprofloxacin/dexamethasone- effects of drops on tympanostomy tube postoperative otorrhea. American journal of otolaryngology 43(6): 103580	- Insufficient presentation of results
Moualed, D., Masterson, L., Kumar, S. et al. (2016) Water precautions for prevention of infection in children with ventilation tubes (grommets). Cochrane Database of Systematic Reviews 2016(1): cd010375	- Systematic review, included studies checked for relevance *All included studies conducted before 2010*
Steele, Dale W, Adam, Gaelen P, Di, Mengyang et al. (2017) Prevention and Treatment of Tympanostomy Tube Otorrhea: A Meta-analysis. Pediatrics 139(6)	- Systematic review, included studies checked for relevance *Included studies conducted before 2010*
Subtil, Joao, Jardim, Ana, Peralta Santos, Andre et al. (2018) Water protection after tympanostomy (Shepard) tubes does not decrease otorrhea incidence - retrospective cohort study. Brazilian journal of otorhinolaryngology 84(4): 500-505	- Cohort study with N<40 per arm
Syed, Mohammed Iqbal, Suller, Sharon, Browning, George G et al. (2013) Interventions for the prevention of postoperative ear discharge after insertion of ventilation tubes (grommets) in children. The Cochrane database of systematic reviews: cd008512	- Systematic review, included studies checked for relevance *Included studies conducted before 2010*

Study	Code [Reason]
van Dongen, Thijs M A (2017) Topical antibiotic-glucocorticoid is superior to oral antibiotics in tympanostomy-tube otorrhea. The Journal of pediatrics 190: 287-290	- Study design does not meet inclusion criteria *Commentary*

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

K.1.1 Research recommendation

What water precautions are effective in preventing otorrhea after ventilation tube (grommet) surgery for hearing loss associated with OME in children under 12 years?

K.1.2 Why this is important

Otorrhoea is a common complication after grommet surgery, which may both recur and lead to poor quality of life in children with otitis media with effusion. Water precautions are preventative measures which reduce the risk of otorrhoea following grommet surgery however there is a lack of high-quality evidence and further research is recommended.

K.1.3 Rationale for research recommendation

Table 10: Research recommendation rationale

Importance to 'patients' or the population	Further research is needed to identify the effectiveness of different water precautions in preventing otorrhea (ear discharge) after ventilation tube surgery for hearing loss associated with OME in children under 12 years. Water precautions are usually recommended as a preventative measure to prevent infection post-surgery.
Relevance to NICE guidance	The lack of evidence regarding this topic currently restricts NICE guidance from making evidence based detailed recommendations about what water precautions are effective in preventing otorrhoea after ventilation tube (grommet) surgery. The research is of interest and will fill this existing evidence gap.
Relevance to the NHS	This research could potentially prevent further complications and reduce the financial impact upon the NHS.
National priorities	The NHS Long Term Plan identifies the role of the NHS and includes secondary prevention, by preventing deterioration in health and reducing symptoms to improve quality of life.
Current evidence base	There is currently variation regarding the number of weeks that water precautions are advised for. The current evidence base does not analyse the effectiveness of different precautions, therefore it is unclear whether some interventions are more effective than others (such as earplugs versus headbands).

Equality considerations	The acceptability of water precautions may vary depending on the individual child and the type of water precaution used e.g. if the child has co-morbidities which affect the shape of the outer ear/pinna then ear buds would not be practicable, or ear buds may not be suitable for younger children or those more at risk of ingesting these.
Feasibility	Given the low cost nature of water precautions, this is considered a feasible research recommendation. Acceptability of the intervention for the child is likely to be the most significant barrier.
Other comments	None

NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OME: otitis media with effusion

K.1.4 Modified PICO table

Table 11: Research recommendation modified PICO table

Population	All children under 12 years who have gromment (ventilation tube) surgery for OME-related hearing loss.
Intervention	• Wearing ear plugs • Wearing a swimming cap or headband • Avoidance of swimming • Length of time using water precautions
Comparator	• No water precautions • Different lengths of time using water precautions to be compared to each other • Head-to-head comparisons between different water precautions
Outcome	Primary Outcomes • Otorrhoea (ear discharge) or infection • Adverse effects of intervention • Surgical intervention to remove ventilation tubes • Acceptability of intervention Secondary Outcomes • Tube blockage • Tube extrusion • Hearing • Need for repeat ventilation tubes • Quality of life (measured by OM8-30 questionnaire, Health Utilities Index Mark 3 (HUI3) questionnaire, Otitis Media-6 (OM-6) questionnaire, Quality of Life in Children's Ear Problems (OMQ-14) questionnaire, Evaluation of Children's Listening and Processing Skills (ECLiPS) questionnaire, Auditory Behaviour in Everyday Life (ABEL) questionnaire, Early Listening Function (ELF) questionnaire, Parents' Evaluation of Aural/Oral Performance

	of Children (PEACH) questionnaire, EuroQol 5 Dimensions (EQ-5D) questionnaire, Infant Toddler Quality of Life Questionnaire, or Child Heath Questionnaire) • Reduced incidents of otorrhea
Study design	RCTs or prospective cohort studies would be preferable, though retrospective cohort studies may be considered. Non-randomised studies should have at least 40 participants per arm and should adequately adjust for the following covariates: • Age • Craniofacial anomalies • Socioeconomic status • Additional sensory or learning needs
Timeframe	1-12 weeks
Additional information	None

OME: otitis media with effusion; RCT: randomised controlled trial

Appendix L Sensitivity analysis

Sensitivity analysis for review question: What intraoperative or postoperative interventions are effective at preventing otorrhoea (ear discharge) after surgery for OME-related hearing loss in children under 12 years?

Sensitivity analyses were conducted for the comparison intraoperative intratympanic ciprofloxacin injection versus placebo/sham because 1 included study (Mair 2016) included two groups of no active treatment (placebo and sham). In the analysis, each of the groups placebo or sham were arbitrarily assigned as the comparison group against intraoperative intratympanic ciprofloxacin injection 4 mg and 12 mg groups. Results are presented below for the relevant outcomes.

Otorrhoea outcomes

Swapping the placebo and sham groups in the comparison did not affect the overall or subgroup results for otorrhoea: the pooled effect of intraoperative intratympanic ciprofloxacin injection showed no important difference for adverse effects of the intervention, and this was also the general pattern within the 6 mg and 12 mg subgroups whereas intraoperative intratympanic ciprofloxacin injection of 4 mg had an important benefit for reducing adverse effects of intervention compared with sham. The risk ratios and absolute risk within the sensitivity analysis for the outcomes were as follows:

- Sensitivity analysis swapping the sham no intervention comparison group with the placebo group for the 4 mg comparison and the placebo group with the sham group for the 12 mg comparison showed the following results: RR 0.42 (0.29 to 0.62); Absolute risk: 145 fewer per 1000 (from 95 fewer to 178 fewer)
- Sensitivity analysis swapping the sham no intervention comparison group with the placebo group showed the following results: RR 0.26 (0.06 to 1.09); Absolute risk: 269 fewer per 1000 (from 342 fewer to 33 more)
- Sensitivity analysis swapping the placebo group with the sham no intervention comparison group showed the following results: RR 0.42 (0.09 to 1.92); Absolute risk: 145 fewer per 1000 (from 227 fewer to 230 more)

Adverse event outcomes

Although the pooled result of the sensitivity analyses also agreed with the main analysis for adverse events, the results within the subgroups differed in the sensitivity analyses relative to the original analyses, showing no important difference in the 4 mg group and important benefit in the 12 mg group.

- Sensitivity analysis swapping the sham no intervention comparison group with the placebo group for the 4 mg comparison and the placebo group with the sham group for the 12 mg comparison showed the following results: RR 0.85 (0.59 to 1.25); Absolute risk: 87 fewer per 1000 (from 238 fewer to 145 more)
- Sensitivity analysis swapping the sham no intervention comparison group with the placebo group showed the following results: RR 1.13 (0.68 to 1.89); Absolute risk: 71 more per 1000 (from 175 fewer to 485 more)
- Sensitivity analysis swapping the placebo group with the sham no intervention comparison group showed the following results: RR 0.53 (0.32 to 0.86); Absolute risk: 423 fewer per 1000 (from 126 fewer to 612 fewer)