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[Intervention Review]

Grommets (ventilation tubes) for recurrent acute otitis media in children

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ABSTRACT

Background

Acute otitis media (AOM) is one of the most common childhood illnesses. While many children experience sporadic AOM episodes, an important group suffer from recurrent AOM (rAOM), defined as three or more episodes in six months, or four or more in one year. In this subset of children AOM poses a true burden through frequent episodes of ear pain, general illness, sleepless nights and time lost from nursery or school. Grommets, also called ventilation or tympanostomy tubes, can be offered for rAOM.

Objectives

To assess the benefits and harms of bilateral grommet insertion with or without concurrent adenoidectomy in children with rAOM.

Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Trials Register; CENTRAL; MEDLINE; EMBASE; CINAHL; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 4 December 2017.

Selection criteria

Randomised controlled trials (RCTs) comparing bilateral grommet insertion with or without concurrent adenoidectomy and no ear surgery in children up to age 16 years with rAOM. We planned to apply two main scenarios: grommets as a single surgical intervention and grommets as concurrent treatment with adenoidectomy (i.e. children in both the intervention and comparator groups underwent adenoidectomy). The comparators included active monitoring, antibiotic prophylaxis and placebo medication.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. Primary outcomes were: proportion of children who have no AOM recurrences at three to six months follow-up (intermediate-term) and persistent tympanic membrane perforation (significant adverse event). Secondary outcomes were: proportion of children who have no AOM recurrences at six to 12 months follow-up (long-term); total number of AOM recurrences, disease-specific and generic health-related quality of life, presence of middle ear effusion and other adverse events at short-term, intermediate-term and long-term follow-up. We used GRADE to assess the quality of the evidence for each outcome; this is indicated in *italics*.

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Main results

Five RCTs (805 children) with unclear or high risk of bias were included. All studies were conducted prior to the introduction of pneumococcal vaccination in the countries' national immunisation programmes. In none of the trials was adenoidectomy performed concurrently in both groups.

Grommets versus active monitoring

Grommets were more effective than active monitoring in terms of:

- proportion of children who had no AOM recurrence at six months (one study, 95 children, 46% versus 5%; risk ratio (RR) 9.49, 95% confidence interval (CI) 2.38 to 37.80, number needed to treat to benefit (NNTB) 3; *low-quality evidence*);

- proportion of children who had no AOM recurrence at 12 months (one study, 200 children, 48% versus 34%; RR 1.41, 95% CI 1.00 to 1.99, NNTB 8; *low-quality evidence*);

- number of AOM recurrences at six months (one study, 95 children, mean number of AOM recurrences per child: 0.67 versus 2.17, mean difference (MD) -1.50, 95% CI -1.99 to -1.01; *low-quality evidence*);

- number of AOM recurrences at 12 months (one study, 200 children, one-year AOM incidence rate: 1.15 versus 1.70, incidence rate difference -0.55, 95% -0.17 to -0.93; *low-quality evidence*).

Children receiving grommets did not have better disease-specific health-related quality of life (Otitis Media-6 questionnaire) at four (one study, 85 children) or 12 months (one study, 81 children) than those managed by active monitoring (*low-quality evidence*).

One study reported no persistent tympanic membrane perforations among 54 children receiving grommets (*low-quality evidence*).

Grommets versus antibiotic prophylaxis

It is uncertain whether or not grommets are more effective than antibiotic prophylaxis in terms of:

- proportion of children who had no AOM recurrence at six months (two studies, 96 children, 60% versus 35%; RR 1.68, 95% CI 1.07 to 2.65, I^2 = 0%, fixed-effect model, NNTB 5; *very low-quality evidence*);

- number of AOM recurrences at six months (one study, 43 children, mean number of AOM recurrences per child: 0.86 versus 1.38, MD -0.52, 95% CI -1.37 to 0.33; *very low-quality evidence*).

Grommets versus placebo medication

Grommets were more effective than placebo medication in terms of:

- proportion of children who had no AOM recurrence at six months (one study, 42 children, 55% versus 15%; RR 3.64, 95% CI 1.20 to 11.04, NNTB 3; *very low-quality evidence*);

- number of AOM recurrences at six months (one study, 42 children, mean number of AOM recurrences per child: 0.86 versus 2.0, MD -1.14, 95% CI -2.06 to -0.22; *very low-quality evidence*).

One study reported persistent tympanic membrane perforations in 3 of 76 children (4%) receiving grommets (*low-quality evidence*).

Subgroup analysis

There were insufficient data to determine whether presence of middle ear effusion at randomisation, type of grommet or age modified the effectiveness of grommets.

Authors' conclusions

Current evidence on the effectiveness of grommets in children with rAOM is limited to five RCTs with unclear or high risk of bias, which were conducted prior to the introduction of pneumococcal vaccination. *Low to very low-quality evidence* suggests that children receiving grommets are less likely to have AOM recurrences compared to those managed by active monitoring and placebo medication, but the magnitude of the effect is modest with around one fewer episode at six months and a less noticeable effect by 12 months. The low to very low quality of the evidence means that these numbers need to be interpreted with caution since the true effects may be substantially different. It is uncertain whether or not grommets are more effective than antibiotic prophylaxis. The risk of persistent tympanic membrane perforation after grommet insertion was low.

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Widespread use of pneumococcal vaccination has changed the bacteriology and epidemiology of AOM, and how this might impact the results of prior trials is unknown. New and high-quality RCTs of grommet insertion in children with rAOM are therefore needed. These trials should not only focus on the frequency of AOM recurrences, but also collect data on the severity of AOM episodes, antibiotic consumption and adverse effects of both surgery and antibiotics. This is particularly important since grommets may reduce the severity of AOM recurrences and allow for topical rather than oral antibiotic treatment.

PLAIN LANGUAGE SUMMARY

Grommets for children with recurring acute middle ear infections

Review question

Do children with recurring acute middle ear infections benefit from placement of grommets in both ears (with or without surgical removal of the adenoids at the same time)?

Background

An acute middle ear infection is one of the most common childhood illnesses. While most children have an occasional episode, some suffer from recurring ear infections (three or more infections over a period of a six months, or four or more in a year). Such recurring infections cause considerable distress through frequent ear pain, fever, general illness, sleepless nights and time lost from nursery or school for the child and from work for their carers. Grommets, also known as ventilation or tympanostomy tubes, can be offered as a treatment. They are tiny plastic tubes put into the eardrum by an ENT surgeon during a short operation.

Study characteristics

This review includes evidence up to 4 December 2017. We included five randomised controlled trials with a total of 805 children with recurring acute middle ear infections. All studies were performed before the introduction of vaccination against pneumococcus, a bacterium that commonly causes ear infections. Surgical removal of the adenoids was not performed in both groups in any of the trials.

Key results

We primarily looked at the difference in the proportion of children who had no further acute middle ear infections at three to six months follow-up (intermediate-term), and who had a persisting perforation (hole) in the ear drum. We also looked at some other outcomes, including the proportion of children who had no further episodes of acute middle ear infection.

Grommets versus active monitoring

We found low-quality evidence that fewer children who were treated with grommets had further episodes of ear infection at six and 12 months follow-up than those managed with active monitoring; three and eight children needed to be treated with grommets to benefit one, respectively. The number of ear infections at six and 12 months follow-up was also lower in the grommets group; the difference was, however, at best modest with around one fewer episode at six months and a less noticeable effect by 12 months (*low to very low-quality evidence*). Children treated with grommets did not have better quality of life at four or 12 months follow-up (*low-quality evidence)*.

Grommets versus antibiotic prophylaxis

It is uncertain whether or not grommets are more effective than antibiotic prophylaxis; we found very low-quality evidence that fewer children who were treated with grommets had further ear infections at six months than those receiving antibiotic prophylaxis (preventative antibiotics); five children needed to be treated with grommets to benefit one. The number of ear infections at six months, however, did not significantly differ between children treated with grommets and those receiving antibiotic prophylaxis (*very-low quality evidence*).

Grommets versus placebo drugs

We found very low-quality evidence that fewer children who were treated with grommets had further ear infections at six months than those receiving placebo drugs; three children needed to be treated with grommets to benefit one. The number of ear infections at six months was also lower in the grommets group; the difference was however at best modest with around one fewer episode (*very low-quality evidence*).

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Negative effects of grommets were not systematically reported in the studies. Two studies reported on the number of children with a persistent perforation of the ear drum; this occurred in 0% (0/54) and 4% (3/76) of children receiving grommets, respectively (*low-quality evidence*).

Quality of evidence

We judged the quality of the evidence on the benefits and harms of placement of grommets in both ears for children with recurring acute middle ear infections to be low to very low due to study limitations (risk of bias) and the small to very small sample sizes of included studies (leading to imprecise effect estimates). This means that the findings of this review should be interpreted with caution since the true effects of grommets in this group of children may be different than the numbers presented.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Grommets versus active monitoring for recurrent acute otitis media in children

Patients: children with recurrent acute otitis media
Setting: secondary and tertiary care
Intervention: grommets
Control: active monitoring

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with active monitoring	Risk with grommets				
Proportion of patients who have no AOM recurrences at 6 months post-randomisation	Study population 49 per 1000	463 per 1000 (116 to 1000)	RR 9.49 (2.38 to 37.80)	95 (1 RCT)	⊕⊕◯◯ **low**[1]	The NNTB based on the study population risk was 1/ (463-49)* 1000 = 2.41
Significant adverse effect: a tympanic membrane perforation persisting for 3 months or longer	-	0 (0/54)	n/a	54 (1 RCT)	⊕⊕◯◯ **low**[1]	-
Proportion of patients who have no AOM recurrences at 12 months post-randomisation	Study population 340 per 1000	479 per 1000 (340 to 677)	RR 1.41 (1.00 to 1.99)	200 (1 RCT)	⊕⊕◯◯ **low**[1]	The NNTB based on the study population risk was 1/ (479-340)* 1000 = 7.19
Total number of AOM recurrences at 6 months post-randomisation	89 AOM recurrences in 41 children; mean number of AOM recurrences per child: 2.17	36 AOM recurrences in 54 children; mean number of AOM recurrences per child: 0.67	MD -1.50, 95% CI -1.99 to -1.01	95 (1 RCT)	⊕⊕◯◯ **low**[1]	-

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Total number of AOM recurrences at 12 months post-randomisation	119 AOM recurrences in 100 children; incidence rate 1.70	92 AOM recurrences in 100 children; incidence rate 1.15	Incidence rate difference -0.55, 95% -0.17 to -0.93	200 (1 RCT)	⊕⊕◯◯ **low**[1]	-
Disease-specific health-related quality of life of the child at 4 and 12 months post-randomisation using the OM-6 questionnaire	"no statistically significant differences between treatment groups were reported at 4 and 12 months for any of the six subdomains of the OM-6 questionnaire"			85 and 81, respectively (1 RCT)	⊕⊕◯◯ **low**[1]	-

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

AOM: acute otitis media; **CI:** confidence interval;**MD**: mean difference; **n/a:** not applicable; **NNTB:** number needed to treat to benefit; **OM-6:** Otitis Media-6; **RCT:** randomised controlled trial; **RR:** risk ratio

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

[1]We downgraded the evidence from high to low quality due to study limitations and imprecise effect estimates (only one study with a small sample size).

BACKGROUND

Description of the condition

Acute otitis media (AOM) is one of the most common childhood illnesses; it is defined as the presence of middle ear fluid together with an acute onset of signs and symptoms of middle ear inflammation (Lieberthal 2013). Bulging of the ear drum or new onset of ear discharge not caused by acute otitis externa are the cardinal signs of AOM, while ear pain, fever, irritability, and problems feeding and sleeping are among the typical AOM symptoms (Lieberthal 2013). AOM is one of the most frequent reasons for primary care visits (Ashworth 1995), and the prime indication for antibiotic prescription in children in more economically developed countries (Finkelstein 2000; Grijalva 2009; Williamson 2006). In addition to high direct healthcare costs (Ahmed 2014; Bondy 2000), AOM causes substantial non-healthcare costs, due to lost days from education or work for parents and the use of over-the-counter medications (Alsarraf 1999; Niemelä 1999).

While many children experience sporadic AOM episodes, an important group suffer from recurrent AOM (rAOM), defined as three or more episodes in six months, or four in one year with one episode in the last six months (Goycoolea 1991; Lieberthal 2013). In this subset of children AOM poses a true burden through frequent episodes of ear pain, general illness, sleepless nights and time lost from nursery or school. The impact of rAOM on quality of life is known to equal that of childhood asthma (Brouwer 2005). This causes families with rAOM to repeatedly seek medical attention to relieve the child's symptoms and prevent future episodes. Importantly, AOM is closely related to otitis media with effusion (OME, 'glue ear'); children with OME are at risk of AOM recurrences (Alho 1995), and following an episode of AOM all children have OME for some time (Tapiainen 2014). This extends the burden of rAOM to OME and hearing loss-related developmental outcomes (Bennett 2001).

The first two years of life represent the period of greatest risk for the first as well as recurrent episodes of AOM (Schilder 2016; Teele 1989). Age-specific incidence of AOM is highest during the second six months of life, which coincides with the lowest level of serum immunoglobulin (antibody) concentrations. Children prone to AOM may have lower age-specific immunoglobulin levels, which may reflect a generalised poorer antibody response (Veenhoven 2004). Breastfeeding protects against AOM, whereas craniofacial malformations like cleft palate and early onset of AOM, a family history of recurrent ear disease, day care attendance, low socioeconomic status and passive smoking are associated with increased risk of AOM (Schilder 2016).

Description of the intervention

The surgical procedures under consideration in children with rAOM are insertion of grommets in both ears (also called ventilation or tympanostomy tubes), adenoidectomy, or a combination of the two.

Grommets are tiny plastic tubes that are inserted in the tympanic membrane (eardrum) by an ENT surgeon; in children this usually happens under general anaesthesia as a day-case procedure. An operating microscope or other magnification is used to visualise the tympanic membrane where a small incision is made (myringotomy), middle ear fluid is aspirated (subject to need and surgical preference) and the grommet is placed in the incision. Grommets facilitate middle ear ventilation and provide a route for drainage of middle ear fluid; they reverse and prevent the formation of middle ear effusions by providing a surrogate to the under-functioning Eustachian tube and so create a less favourable environment for viruses and bacteria to cause recurrent middle ear infections (Rosenfeld 2013; Schilder 2016).

Grommets may also reduce the severity of AOM recurrences, since they allow for drainage of middle ear fluid that builds up during an acute infection; as such they may prevent ear pain caused by pressure against the tympanic membrane. Finally, grommets allow for topical (local) treatment of AOM recurrences with antibiotic eardrops (van Dongen 2014), thereby avoiding the side effects of systemic antibiotics and potentially reducing the risk of antimicrobial resistance (Weber 2004).

It has been suggested that children suffering from rAOM who have unilateral or bilateral middle ear effusion at the time of evaluation for surgery may benefit more from grommets than children who have an aerated middle ear at this time (Rosenfeld 2013).

Grommets are a temporary treatment. After months or years, depending on the type of grommet, they are extruded into the external ear canal and the tympanic membrane closes. There are different types of grommets, which are made out of various materials. Some are so-called short-term grommets that typical stay in place for six to 18 months; others are intermediate/long-term tubes that usually stay in place for a longer period of time.

Complications of grommet insertion include a persisting perforation of the tympanic membrane causing a conductive hearing loss and the risk of infection, misplacement of the grommet in the middle ear, otorrhoea (drainage of middle ear fluid through the tube) and myringosclerosis (calcification or scarring of the tympanic membrane) that may cause (mild) hearing loss.

Why it is important to do this review

Recommendations regarding the use of grommets in children suffering from rAOM vary within and across countries (CBO Richtlijn 2012; Lieberthal 2013; Rosenfeld 2013). Recent US guidelines on the management of AOM (Lieberthal 2013) and on the use of grommets (tympanostomy tubes; Rosenfeld 2013) recommend grommets as an optional treatment in children with rAOM. The latter suggests that grommets should not be offered to

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children with rAOM who have no middle ear effusion at the time of evaluation for surgery. In the UK there is guidance on the use of grommets in children with OME (NICE 2008), but national guidance for those with rAOM is lacking.

The role of adenoidectomy in reducing rAOM is not fully established but adenoidectomy as a standalone operation or as an adjunct to grommets may be most beneficial in children below two years of age (Boonacker 2014; van den Aardweg 2010). Furthermore, it has been suggested that adenoidectomy as an adjunct to primary grommet insertion might reduce the rate of further AOM episodes and the risk of re-insertion of grommets compared to grommet insertion alone (Mikals 2014).

The absence of uniform guidance or consensus on the use of grommets in rAOM contributes to practice variation both within and across countries. For example, a pilot study using UK National Health Service (NHS) Primary Care Trust data showed that in 2012 there was a 40- to 60-fold variation in the rate of grommet insertion for rAOM compared to an eight- to nine-fold variation in grommets for OME (Bohm 2013, personal communication). Moreover, across Western countries the surgical rates for grommets vary from 2 per 1000 children per year in the UK to 20 per 1000 in The Netherlands (Schilder 2004).

An up-to-date, comprehensive systematic review is therefore urgently needed, summarising the available evidence on the effects of grommets with or without concurrent adenoidectomy in children with rAOM.

OBJECTIVES

To assess the benefits and harms of bilateral grommet insertion with or without concurrent adenoidectomy in children with rAOM.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) irrespective of the randomisation method and blinding procedure used. We excluded the second phase of cross-over studies and trials where the patient was not the unit of randomisation, i.e. cluster-randomised trials or trials where 'ears' (right versus left) were randomised.

Types of participants

Children up to age 16 years with rAOM, defined as three or more episodes in the previous six months, or four or more in one year (Goycoolea 1991; Lieberthal 2013).

Types of interventions

Intervention

- Bilateral grommet insertion (of any type).

Comparisons

The overall comparator was no (ear) surgery. This included the following comparators:

- active monitoring (grommets *versus* active monitoring);
- antibiotic prophylaxis for a minimum period of three months (grommets *versus* antibiotic prophylaxis);
- placebo medication (grommets *versus* placebo medication).

We anticipated that both in the intervention and comparator groups AOM recurrences would be managed with analgesics and antibiotics (topical or systemic) either routinely or in selected cases. We planned to apply two main scenarios depending on whether adenoidectomy was performed concurrently:

- grommets as a single surgical intervention: this included studies where children in comparator groups received no other surgical intervention;
- grommets as concurrent treatment with adenoidectomy: this included studies where children in both the intervention and comparator groups underwent adenoidectomy.

Types of outcome measures

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

Primary outcomes

- Treatment success, defined as the proportion of children who have no AOM recurrences at three to six months post-randomisation (intermediate-term follow-up).
- Significant adverse event: tympanic membrane perforation persisting for three months or longer. This has been listed as an important adverse event outcome because a further surgical procedure may ultimately be required to close the perforation if this persists after extrusion of the grommet.

Secondary outcomes

- Treatment success, defined as the proportion of children who have no AOM recurrences at six to 12 months post-randomisation (long-term follow-up).

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In the short- (up to three months), intermediate- (three to six months) and long-term (six to 12 months) post-randomisation:

- Total number of AOM recurrences.
- Disease-specific health-related quality of life of the child and their parents or carers (using any validated instrument; see Brouwer 2007).
- Generic health-related quality of life of the child and parents (using any validated instrument).
- Presence of middle ear effusion.
- Other adverse events: grommet misplaced in middle ear, postoperative otorrhoea (in the first week after grommet insertion), myringosclerosis.

We discussed and included within our outcomes other adverse effects and complications recorded in RCTs but not listed above.

Search methods for identification of studies

The Cochrane ENT Information Specialist conducted systematic searches for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions. The date of the search was 4 December 2017.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Trials Register (searched via the Cochrane Register of Studies to 4 December 2017);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (searched via the Cochrane Register of Studies to 4 December 2017);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 4 December 2017);
- Ovid EMBASE (1974 to 4 December 2017);
- Ovid CAB Abstracts (1910 to 4 December 2017);
- EBSCO CINAHL (1982 to 4 December 2017);
- LILACS, lilacs.bvsalud.org (searched to 4 December 2017);
- KoreaMed (searched via Google Scholar to 4 December 2017);
- IndMed, www.indmed.nic.in (searched to 4 December 2017);
- PakMediNet, www.pakmedinet.com (searched to 4 December 2017);
- Web of Knowledge, Web of Science (1945 to 4 December 2017);
- ClinicalTrials.gov (via the Cochrane Register of Studies and https://clinicaltrials.gov/ to 4 December 2017);
- ICTRP, www.who.int/ictrp (searched to 4 December 2017).

In searches prior to December 2017, we also searched PubMed as a top-up to Ovid MEDLINE (1946 to November 2015).

The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources

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

Data collection and analysis

Selection of studies

Three review authors (LL, PTM and RPV) independently screened titles and abstracts obtained from the database searches and the reference lists of relevant systematic reviews to assess their potential relevance for reviewing the full text. The same review authors independently reviewed the full text of potentially relevant articles against the inclusion and exclusion criteria. We resolved any disagreements by discussion.

Data extraction and management

Three review authors (LL, PTM and RPV) independently extracted data from the included studies using standardised data extraction forms. We extracted the following data from each study:

- Trial characteristics: setting, design, method of data analysis.
- Participants: study population, number of children in each group, participant characteristics such as age and gender.
- Interventions: type of surgery including pre-operative, intra-operative and postoperative treatment.
- Outcomes: primary and secondary outcomes recorded, time points, adverse effects and complications related to the intervention and comparators.
- Aspects of methodology relating to risk of bias (see below).

We also extracted the following summary statistics for each trial and each outcome:

- For continuous data: mean values, standard deviations and number of patients for each treatment group.

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- For binary data: numbers of participants experiencing an event and number of patients assessed at the particular time point.
- For ordinal scale data: if the data appeared to be normally distributed or if the analysis suggested that parametric tests were appropriate, we treated those outcome measures as continuous data. Alternatively, if data were available, we converted them into binary data.

We prespecified the time points of interest for the outcomes in this review. While studies reported data at multiple time points, we only extracted the longest available data within the time points of interest. For example, for 'intermediate-term' follow-up periods, our time point was defined as 'three to six months' post-randomisation. If a study reported data at three, four and six months, we only extracted and analysed the data for the six-month follow-up. Where a study had more than one publication, we retrieved all relevant publications to ensure complete data extraction.

Assessment of risk of bias in included studies

Three review authors (AGMS, RPV and DAN) independently assessed the risk of bias of the included studies and resolved any disagreements by majority opinion. Guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011), we took the following items into consideration:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective reporting (reporting); and
- other sources of bias.

We presented the results of the 'Risk of bias' assessment in a 'Risk of bias' graph and summary figure.

Measures of treatment effect

We expressed pooled measures of treatment effect for dichotomous outcomes as risk ratio (RR) with accompanying 95% confidence intervals (CI). For the key outcomes presented in the 'Summary of findings' table, we also expressed the results as absolute numbers based on the pooled results and compared to the assumed risk. We aimed to calculate the number needed to treat to benefit (NNTB) using the pooled results.

We expressed continuous outcome variables either as a mean difference (MD) with 95% CIs, if reported on the same scale, or as a standardised mean difference (SMD) with 95% CIs, if different continuous scales were used.

Unit of analysis issues

This review did not use data from phase two of cross-over studies or from studies where the patient is not the unit of randomisation, i.e. cluster-randomised trials or studies where 'ears' (right versus left) were randomised.

Dealing with missing data

For continuous outcomes, we aimed to calculate missing statistics, such as standard deviations (SDs), from other available statistics (e.g. P values) according to the methods described in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). Apart from imputations for missing SDs, we did not conduct other imputations. We extracted and analysed all data using the available case analysis method.

Assessment of heterogeneity

First, we assessed the level of clinical diversity between trials by reviewing them for potential differences in the types of participants recruited, interventions used and outcomes measured. We did not pool studies where clinical heterogeneity made it unreasonable to do so. Second, we assessed statistical heterogeneity for each outcome by visually inspecting the forest plots and by using the Chi^2 test, with a significance level set at P value < 0.10, and the I^2 statistic, with I^2 values over 50% suggesting substantial heterogeneity (Higgins 2003).

Assessment of reporting biases

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

Outcome reporting bias

We searched the internet, ClinicalTrials.gov (http://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/trialsearch) for available study protocols to determine whether outcomes reported were pre-defined and whether all outcomes listed in the study protocol were reported in the trial publications. Where there was insufficient information to judge the risk of bias, we classified the risk of bias as unclear (Handbook 2011).

Publication bias

We proposed a more formal method of assessing reporting bias, i.e. by creating funnel plots, if sufficient trials (10 or more) were available for an outcome.

Data synthesis

We conducted all meta-analyses using Review Manager 5.3 (RevMan 2014). We analysed the available data according to the intention-to-treat principle, i.e. by analysing all participants in the groups to which they were originally randomised. As such, we anticipated that some children allocated to the comparator groups

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received surgery before the end of the trial (i.e. crossed over into the surgery group).

We calculated treatment differences with the Mantel-Haenszel method using a fixed-effect model where no substantial statistical heterogeneity was present (I^2 < 50%). If substantial statistical heterogeneity was detected but unresolved by sensitivity analysis and pre-specified subgroup analyses, we calculated treatment differences using a random-effects (DerSimonian and Laird) model to provide a more conservative effect estimate. For dichotomous outcomes, we calculated the number needed to treat to benefit (NNTB) using the results of the meta-analysis (which itself uses risk ratio) based on the average risk of the control groups in the included studies ('study population') (Handbook 2011).

Subgroup analysis and investigation of heterogeneity

We planned to subgroup studies where most participants (80% or more) met the criteria stated below to determine whether the effect of the intervention was different compared to other patients, regardless of whether we observed statistical heterogeneity. We planned to present the main analyses of this review in the form of forest plots based upon our prime subgroup analysis:

- presence of middle ear effusion at randomisation or at the time of grommet insertion - yes versus no.

For this review, effect modifiers included:

- type of grommet (short-term versus intermediate/long-term length of stay);
- age (below two years of age versus two years and older).

We therefore planned to consider these subgroup analyses in the presence of statistical heterogeneity.

Sensitivity analysis

We planned to carry out sensitivity analyses for the following factors to assess the robustness of the review findings:

- risk of bias of included studies: we excluded from analysis studies with high risk of bias defined as high risk of allocation concealment bias and attrition bias (overall loss to follow-up of more than 20% or differential follow-up observed, or both).
- surgical interventions in comparator groups during follow-up as part of protocol: we excluded from analysis studies in which children in the comparator groups underwent surgical interventions if clinical conditions were met (e.g. paracentesis in case of AOM recurrences).
- occurrence of AOM recurrences between the date of randomisation and surgery: we excluded from analysis studies that specifically included AOM recurrences occurring between the date of randomisation and surgery.

If any of these investigations found a difference in the effect size or heterogeneity, we reported this in the Effects of interventions section.

GRADE and 'Summary of findings'

We used the GRADE approach to rate the overall quality of evidence for each outcome. We judged the quality of evidence as high, moderate, low or very low. We judged evidence from RCTs that did not have serious limitations as high quality. However, we downgraded the quality of evidence to moderate, low or very low based on the following factors:

- study limitations (risk of bias);
- indirectness of evidence (directness of evidence);
- imprecision (precision of results);
- inconsistency (consistency of results);
- publication bias (existence of publication bias).

We presented only the top priority outcomes in the 'Summary of findings' tables:

- treatment success, defined as the proportion of children who have no AOM recurrences at three to six months post-randomisation;
- significant adverse effects: a tympanic membrane perforation persisting for three months or longer;
- treatment success, defined as the proportion of children who have no AOM recurrences at six to 12 months post-randomisation;
- total number of AOM recurrences at three to six months post-randomisation;
- total number of AOM recurrences at six to 12 months post-randomisation;
- disease-specific health-related quality of life;
- generic health-related quality of life.

RESULTS

Description of studies

Results of the search

The searches retrieved a total of 1120 records. Removing duplicates left 487 unique articles. After screening titles and abstracts we identified 24 potentially eligible records. We excluded 15 records with reasons (see Characteristics of excluded studies), three studies were classified as ongoing (Aabel 2011; Hoberman 2015; SIUTIT Trial 2015: for details see Characteristics of ongoing studies) and one paper reported additional findings of the Kujala 2012 trial (Kujala 2014) and was therefore included as part of Kujala 2012. This left five studies eligible for inclusion (Casselbrant 1992; El-Sayed 1996; Gebhart 1981; Gonzalez 1986; Kujala 2012). Figure 1 shows the flow chart of study retrieval and selection.

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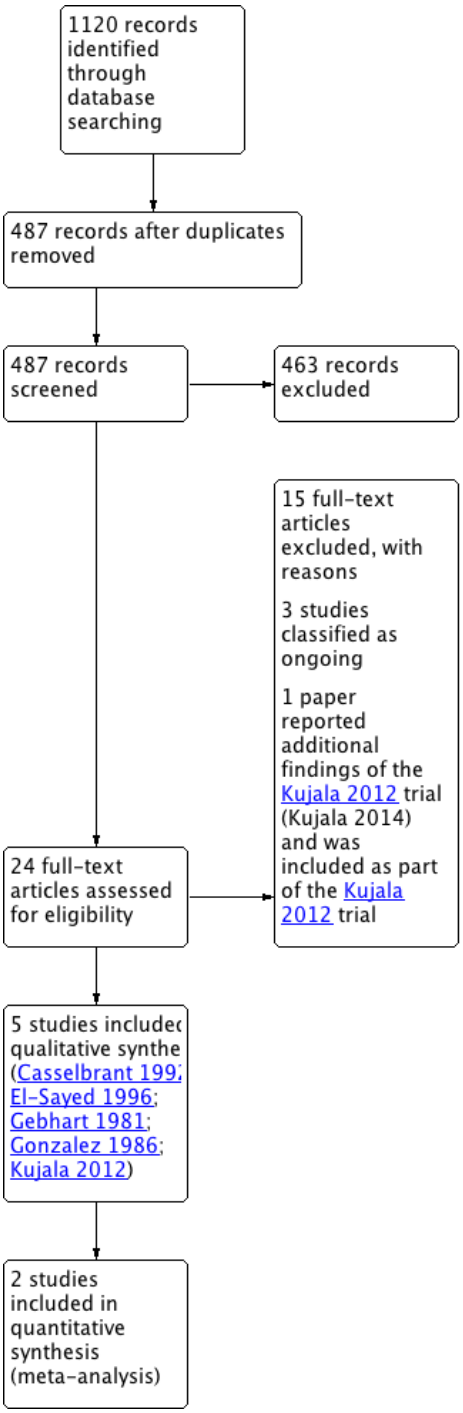
Figure 1. PRISMA flow diagram of search history.



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Included studies

For details of the included studies see the Characteristics of included studies table.

Design

All five studies were RCTs. Two were two-armed trials, whereas three trials had a three-armed parallel design. Due to the nature of the intervention and comparators, all studies were open-label (for the grommets versus no (ear) surgery comparisons).

Setting

Studies were conducted in a secondary and/or tertiary care setting in the USA (three studies), Saudi Arabia (one study) and Finland (one study).

Participants

The number of participants in the included studies ranged from 65 to 300. Participants' ages ranged from 0 to 10 years and 55% to 63% were boys. Children with middle ear effusion at baseline were excluded in two studies. The proportion of children with OME at baseline was not reported in two studies and was 29% (18/63) in one study.

Interventions

In the five included studies insertion of grommets in both ears was compared to active monitoring, antibiotic prophylaxis or placebo medication. None of the studies performed adenoidectomy as background therapy and the effectiveness of grommets as add-on therapy to adenoidectomy could therefore not assessed in this review. Table 1 provides an overview of interventions and comparison pairs included in this review. Further details of the specific interventions can be found in the Characteristics of included studies table.

Outcome measures

Table 2 summarises whether the included studies did (or did not) report on our pre-specified outcomes. All outcomes were reported in at least one study, but adverse events were not systematically assessed in any of the studies.

Funding and conflicts of interest

Two studies received non-commercial (governmental) funding. One study was performed without funding, whereas no details were provided in one study. Pharmaceutical companies provided the study medications in two studies.

Excluded studies

We excluded 15 articles after reviewing the full text. Reasons for exclusion are provided in the Characteristics of excluded studies table.

Risk of bias in included studies

Summaries of the 'Risk of bias' assessments of the included studies are presented in Figure 2 and Figure 3.

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

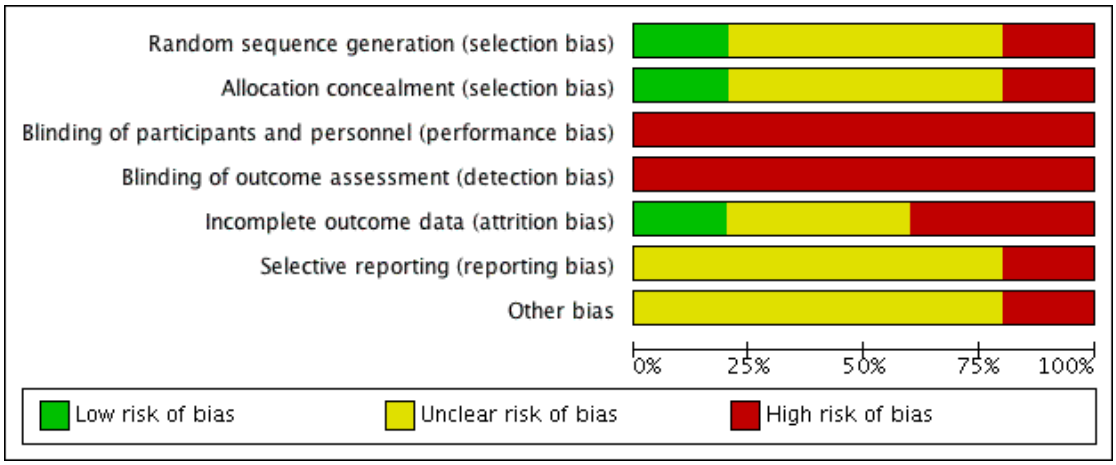

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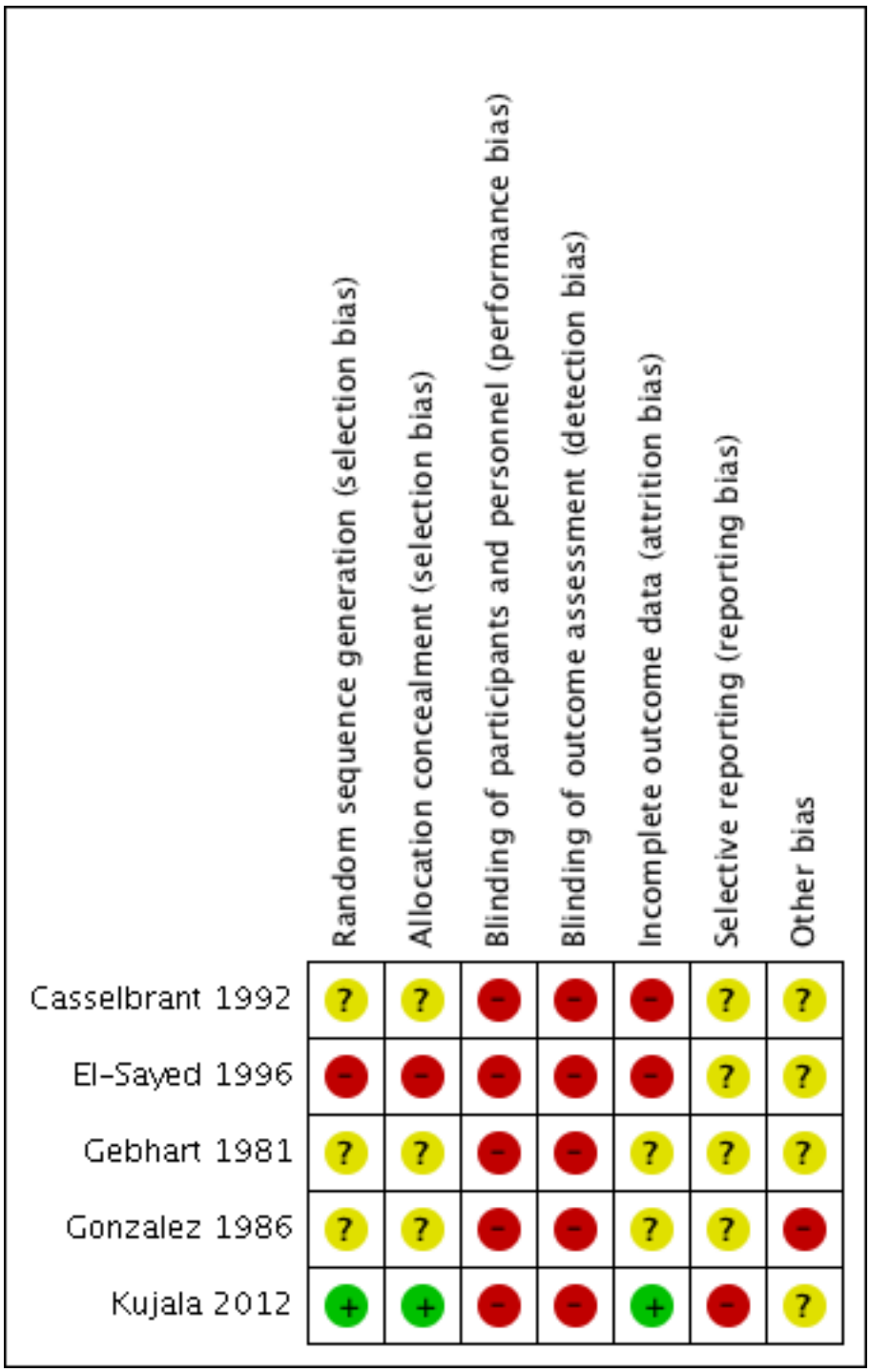
Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



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Allocation

We judged the risk of selection bias due to sequence generation and concealment of allocation to be low in one study (20%), high in one study (20%) and unclear in three studies (60%).

Blinding

Due to the nature of the studies (comparing surgical and non-surgical interventions), blinding of participants and personnel (performance bias) is not possible. Blinding of outcome assessment (detection bias) was not performed in the included studies. As such, we judged both the risk of performance bias and detection bias to be high in all studies.

Incomplete outcome data

We judged the risk of bias for incomplete outcome data to be low in one study (20%), high in two studies (40%) and unclear in two studies (40%).

Selective reporting

We judged the risk of outcome reporting bias to be high for Kujala 2012. We could not retrieve trial protocols for the remaining four studies (80%) and therefore we could not determine the risk of selective outcome reporting bias for these studies.

Other potential sources of bias

We judged the risk of other potential sources of bias to be unclear in four studies (80%) and high in one study (20%).

Effects of interventions

See: **Summary of findings for the main comparison** Grommets versus active monitoring for recurrent acute otitis media in children; **Summary of findings 2** Grommets versus antibiotic prophylaxis for recurrent acute otitis media in children; **Summary of findings 3** Grommets versus placebo medication for recurrent acute otitis media in children

See: Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3. We have reported all available outcome data for all comparison pairs (those not listed were not available).

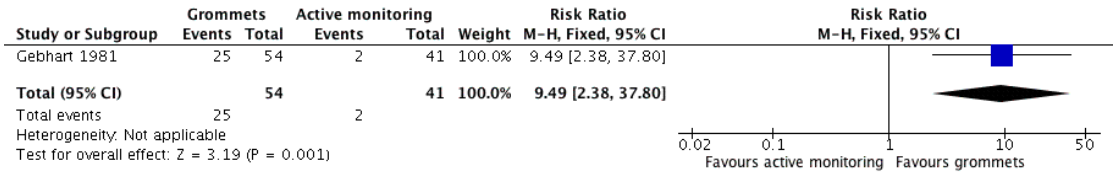
1. Grommets versus active monitoring

Primary outcomes

Treatment success, defined as the proportion of children who have no acute otitis media (AOM) recurrences at six months post-randomisation (intermediate-term follow-up)

For this outcome, we could use data from only one study (108 randomised children; 95 (88%) included in analysis) (Gebhart 1981). Children receiving grommets were more likely to have no AOM recurrences at six months post-randomisation than those managed by active monitoring (46% versus 5%; risk ratio (RR) 9.49, 95% confidence interval (CI) 2.38 to 37.80, number needed to treat to benefit (NNTB) 3) (Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 Grommets versus active monitoring, outcome: 1.1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation.



Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimates (only one study with a small sample size).

Significant adverse event: tympanic membrane perforation

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persisting for three months or longer

For this outcome, we could use data from only one study (Gebhart 1981). In this study, no persistent tympanic membrane perforations were reported among 54 children receiving grommets.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimates (only one study with a small sample size).

Secondary outcomes

Treatment success, defined as the proportion of children who have no AOM recurrences at 12 months post-randomisation (long-term follow-up)

For this outcome, we could use data from only one study (200 randomised children; 200 (100%) included in analysis) (Kujala 2012). Children receiving grommets were more likely to have no AOM recurrences at 12 months post-randomisation than those managed by active monitoring (48% versus 34%; RR 1.41, 95% CI 1.00 to 1.99, NNTB 8) (Analysis 1.2).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimates (only one study with a relatively small sample size).

Total number of AOM recurrences at six months post-randomisation

One study reported on this outcome (108 randomised children; 95 (88%) included in analysis) (Gebhart 1981). At six months post-randomisation, a total of 36 AOM recurrences were observed in the grommets group (54 children) and 89 in the active monitoring group (41 children); the mean number of AOM recurrences per child was 0.67 versus 2.17, respectively (MD -1.50, 95% CI -1.99 to -1.01) (Analysis 1.3).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimates (only one study with a small sample size).

Total number of AOM recurrences at 12 months post-randomisation

One study reported on this outcome (200 randomised children; 200 (100%) included in analysis) (Kujala 2012). At 12 months post-randomisation, a total of 92 AOM recurrences were observed in the grommets group (100 children) and 119 in the active monitoring group (100 children). The one-year AOM incidence rate was estimated at 1.15 versus 1.70, respectively (incidence rate difference -0.55, 95% -0.17 to -0.93).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimates (only one study with a relatively small sample size).

Disease-specific health-related quality of life of the child at four months post-randomisation

One study reported on this outcome for a subset of participating children using the OM-6 questionnaire (105 randomised children; 85 (81%) included in analysis) (Kujala 2012). At four months post-randomisation, "no statistically significant differences" were reported between groups for any of the six sub-domains.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimates (only one study with a small sample size).

Disease-specific health-related quality of life of the child at 12 months post-randomisation

One study reported on this outcome for a subset of participating children using the OM-6 questionnaire (105 randomised children; 81 (77%) included in analysis) (Kujala 2012). At 12 months post-randomisation, "no statistically significant differences" between groups were reported for any of the six sub-domains.

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimates (only one study with a small sample size).

Other secondary outcomes

None of the studies reported on generic health-related quality of life, presence of middle ear effusion or other adverse events.

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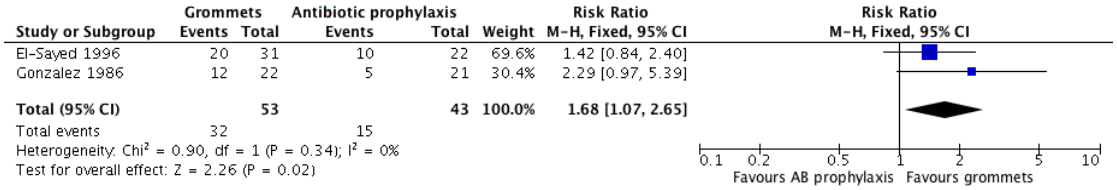
2. Grommets versus antibiotic prophylaxis

Primary outcomes

Treatment success, defined as the proportion of children who have no AOM recurrences at six months post-randomisation

For this outcome, we could combine data from two studies (96 children) (Gonzalez 1986; El-Sayed 1996). Children receiving grommets were more likely to have no AOM recurrences at six months post-randomisation than those receiving antibiotic prophylaxis (60% versus 35%; RR 1.68, 95% CI 1.07 to 2.65, I^2 = 0%, fixed-effect model, NNTB 5) (Analysis 2.1; Figure 5).

Figure 5. Forest plot of comparison: 2 Grommets versus antibiotic prophylaxis, outcome: 2.1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation.



When we excluded the study with high risk of bias (El-Sayed 1996), we observed no statistically significant difference between groups (RR 2.29, 95% CI 0.97 to 5.39). The data did not allow us to perform any of the planned subgroup analyses and remaining sensitivity analyses.

Quality of the evidence

The evidence for this outcome was of very low quality; we downgraded it from high to very low quality due to study limitations (no statistically significant difference between groups was observed after exclusion of the trial with high risk of bias) and imprecise effect estimates (only two studies with small sample sizes).

Significant adverse event: tympanic membrane perforation persisting for three months or longer

For this outcome, we could use data from only one study (Casselbrant 1992). In this study, a persistent tympanic membrane perforation was reported in 3 of 76 children (4%) who were randomised to grommet insertion.

Secondary outcomes

Total number of AOM recurrences at six months post-randomisation

One study reported on this outcome (number of randomised children unknown; 43 included in analysis) (Gonzalez 1986). At six months post-randomisation, a total of 19 AOM recurrences were observed in the grommets group (22 children) and 29 in the antibiotic prophylaxis group (21 children); the mean number of AOM recurrences per child was 0.86 versus 1.38, respectively (MD -0.52, 95% CI -1.37 to 0.33) (Analysis 2.2).

Quality of the evidence

The evidence for this outcome was of very low quality; we downgraded it from high to very low quality due to study limitations and imprecise effect estimates (only one study with a very small sample size).

Other secondary outcomes

None of the studies reported on disease-specific or generic health-related quality of life, presence of middle ear effusion or other adverse events.

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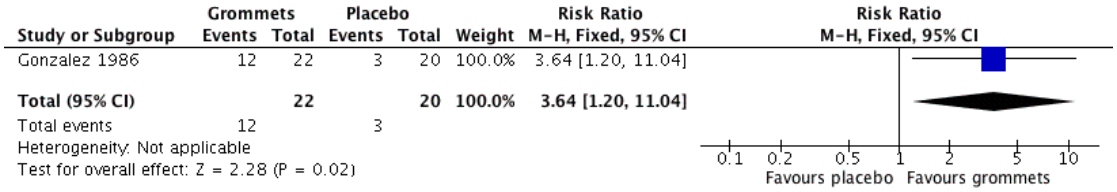
3. Grommets versus placebo medication

Primary outcomes

Treatment success, defined as the proportion of children who have no AOM recurrences at six months post-randomisation

For this outcome, we could use data from only one study (number of randomised children unknown; 42 included in analysis) (Gonzalez 1986). Children receiving grommets were more likely to have no AOM recurrences at six months post-randomisation than those receiving placebo medication (55% versus 15%; RR 3.64, 95% CI 1.20 to 11.04, NNTB 3) (Analysis 3.1; Figure 6).

Figure 6. Forest plot of comparison: 3 Grommets versus placebo medication, outcome: 3.1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation.



Quality of the evidence

The evidence for this outcome was of very low quality; we downgraded it from high to very low quality due to study limitations and imprecise effect estimates (only one study with a very small sample size).

Significant adverse event: tympanic membrane perforation persisting for three months or longer

Only one study reported on the occurrence of persistent tympanic membrane perforation in the grommets group (Casselbrant 1992). The findings are illustrated above (in the grommets versus antibiotic prophylaxis comparison).

Quality of the evidence

The evidence for this outcome was of low quality; we downgraded it from high to low quality due to study limitations and imprecise effect estimates (only one study with a small sample size).

Secondary outcomes

Total number of AOM recurrences at six months post-randomisation

One study reported on this outcome (number of randomised children unknown; 42 included in analysis) (Gonzalez 1986). At six months post-randomisation, a total of 19 AOM recurrences were observed in the grommets group (22 children) and 40 in the placebo medication group (20 children); the mean number of AOM recurrences per child was 0.86 versus 2.0, respectively (MD -1.14, 95% CI -2.06 to -0.22) (Analysis 3.2).

Quality of the evidence

The evidence for this outcome was of very low quality; we downgraded it from high to very low quality due to study limitations and imprecise effect estimates (only one study with a very small sample size).

Other secondary outcomes

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None of the studies reported on disease-specific or generic health-related quality of life, presence of middle ear effusion or other adverse events.

Subgroup analyses

There were insufficient data to determine whether presence of middle ear effusion at randomisation, type of grommet or age modified the effectiveness of grommets.

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ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Grommets versus antibiotic prophylaxis for recurrent acute otitis media in children

Patients: children with recurrent acute otitis media
Setting: secondary and tertiary care
Intervention: grommets
Control: antibiotic prophylaxis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with antibiotic prophylaxis	Risk with grommets				
Proportion of patients who have no AOM recurrences at 6 months post-randomisation	Study population 349 per 1000	586 per 1000 (373 to 924)	RR 1.68 (1.07 to 2.65)	96 (2 RCTs)	⊕◯◯◯ **very low**[1]	The NNTB based on the study population risk was 1/ (586-349)* 1000 = 4.22
Total number of AOM recurrences at 6 months post-randomisation	29 AOM recurrences in 21 children; mean number of AOM recurrences per child: 1.38	19 AOM recurrences in 22 children; mean number of AOM recurrences per child: 0.86	MD -0.52, 95% CI -1.37 to 0.33	43 (1 RCT)	⊕◯◯◯ **very low**[2]	-

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

AOM: acute otitis media; **CI:** confidence interval; **MD**: mean difference; **RCT:** randomised controlled trial; **RR:** risk ratio

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

[1]We downgraded the evidence from high to very low quality due to study limitations (when we excluded the trial with high risk of bias from the analysis, no statistically significant difference was observed between groups) and imprecise effect estimates (only two studies with small sample sizes).

[2]We downgraded the evidence from high to very low quality due to study limitations and imprecise effect estimates (only one study with a very small sample size).

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Grommets versus placebo medication for recurrent acute otitis media in children

Patients: children with recurrent acute otitis media
Setting: secondary and tertiary care
Intervention: grommets
Control: placebo medication

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo medication	Risk with grommets				
Proportion of patients who have no AOM recurrences at 6 months post-randomisation	Study population 150 per 1000	546 per 1000 (180 to 1000)	RR 3.64 (1.20 to 11.04)	42 (1 RCT)	⊕◯◯◯ **very low**[1]	The NNTB based on the study population risk was 1/ (546-150)* 1000 = 2.53
Significant adverse effect: a tympanic membrane perforation persisting for 3 months or longer	-	4% (3/76)	n/a	76 (1 RCT)	⊕⊕◯◯ **low**[2]	-
Total number of AOM recurrences at 6 months post-randomisation	40 AOM recurrences in 20 children; mean number of AOM recurrences per child: 2.0	19 AOM recurrences in 22 children; mean number of AOM recurrences per child: 0.86	MD -1.14, 95% CI -2.06 to -0.22	42 (1 RCT)	⊕◯◯◯ **very low**[1]	-

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

AOM: acute otitis media; **CI:** confidence interval; **MD**: mean difference; **n/a:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

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

[1]We downgraded the evidence from high to very low quality due to study limitations and imprecise effect estimates (only one study with a very small sample size).

[2]We downgraded the evidence from high to low quality due to study limitations and imprecise effect estimates (only one study with a small sample size).

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DISCUSSION

Summary of main results

Current evidence on the effectiveness of bilateral grommet insertion in children with recurrent acute otitis media (rAOM) is limited to five RCTs with unclear or high risk of bias, which were conducted prior to the introduction of pneumococcal vaccination. In none of the studies was adenoidectomy performed concurrently in both groups.

Low to very low-quality evidence suggests that children receiving grommets are less likely to have AOM recurrences at six and 12 months' follow-up compared to those managed by active monitoring and placebo medication, but the magnitude of the effect is modest with around one fewer episode at six months and a less noticeable effect by 12 months.

Low-quality evidence suggests that disease-specific quality of life is similar at four and 12 months in children receiving grommets and those managed by active monitoring.

It is uncertain whether or not grommets are more effective than antibiotic prophylaxis.

The risk of persistent tympanic membrane perforation after grommet insertion is low (0/54 children in one study and 3/76 in another (low-quality evidence)).

Overall completeness and applicability of evidence

The children participating in the five RCTs included in this review represent those most commonly encountered in clinical practice, that is children below six years of age suffering from rAOM. However, we judged the overall completeness and applicability of the evidence to be low.

All trials were conducted at a time when pneumococcal conjugate vaccination had not yet been introduced to national immunisation programmes. Since then pneumococcal vaccination has been introduced in most countries; this may have changed the pathogens causing AOM, its clinical features and the recurrence rate (Coker 2010; Fortanier 2014). How this might impact the results of prior trials is unknown.

None of the studies reported the effect of grommets on the severity of AOM recurrences or antibiotic consumption. This is particularly important since grommets may reduce the severity of AOM recurrences because they allow for drainage of middle ear fluid that builds up during an acute infection; as such they may prevent ear pain caused by pressure against the tympanic membrane. They also allow for topical (local) treatment of AOM recurrences with antibiotic eardrops (van Dongen 2014), and thereby avoid the side effects of systemic antibiotics and potentially reduce the risk of antimicrobial resistance (Weber 2004).

Finally, the included studies did not record adverse events systematically; nor did they compare effects with costs. A thorough evaluation of benefits, harms and cost-effectiveness of grommets versus active monitoring in children with rAOM in the post-pneumococcal conjugate vaccine era is therefore urgently needed.

Quality of the evidence

The quality of the evidence for the outcomes included in the studies comparing grommets versus active monitoring, antibiotic prophylaxis and placebo medication in children with rAOM was very low to low. Our confidence in the effect estimates is therefore (very) limited and the findings of this review should be interpreted with caution since the true effects of grommets in this group of children may be quite different than the effect estimates presented.

Potential biases in the review process

We closely adhered to the methods and analyses presented in our protocol, which was developed and published prior to the conduct of this review (Lau 2015). We used an extensive search strategy without language or publication restrictions and reviewed citation lists of all potentially relevant records; it is therefore unlikely that we have missed relevant studies. The decision, however, to downgrade the quality of evidence according to sample size, i.e. the determination of 'imprecise effect estimate', was not prespecified, but based on a post hoc subjective interpretation by the review authors.

Agreements and disagreements with other studies or reviews

Several systematic reviews of the effects of grommets in children with rAOM have been published in recent years (Cheong 2012; Damoiseaux 2011; Hellstrom 2011; Lous 2011; Steele 2017). Hellstrom concluded in 2011 that "there was insufficient evidence to support an effect of grommet insertion for rAOM" (Hellstrom 2011). Others came to a similar conclusion, i.e. that the "evidence on the effects of grommet insertion for children with rAOM is (severely) limited" (Damoiseaux 2011; Steele 2017).

Despite this limitation, Damoiseaux, Lous and Steele concluded that grommets seem "to have only a short-term benefit" (Damoiseaux 2011), "seems to prevent one attack of AOM or keep one child out of three free from AOM in six months" (Lous 2011) and "may be associated with fewer AOM recurrences" (Steele 2017).

Two important clinical practice guidelines were launched in the USA in 2013: one published by the American Academy of Pediatrics on the management of AOM (Lieberthal 2013), and one by the American Academy of Otolaryngology - Head and Neck Surgery on tympanostomy tubes (Rosenfeld 2013). Both guidelines recommend grommets as an optional treatment in children

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with rAOM. The latter suggests that grommets should not be offered to children with rAOM who have no middle ear effusion at the time of evaluation for surgery (Rosenfeld 2013).

In our review, we planned to present the main analyses of the review in the form of forest plots based on whether middle ear effusion was present at randomisation or at the time of surgery. The data, however, did not allow us to perform such analysis. Children with middle ear effusion at baseline were excluded in two trials and presence of OME was only 29% in one study. In this latter study, results were stratified according to the presence or absence of middle ear effusion at the initial visit (Gonzalez 1986), indicating that the effect of grommets may be larger in children with rAOM and concomitant middle ear effusion (no AOM recurrence at six months in 8/9 of the grommets group, 1/6 of the antibiotic prophylaxis group and 1/3 of the placebo medication group) than in those with no middle ear effusion (no AOM recurrence at six months in 4/12 of the grommets group, 4/15 of the antibiotic prophylaxis group and 2/17 of the placebo medication group). However, we performed this analysis post hoc and it was based upon a very small number of children.

We found that the risk of persistent tympanic membrane perforation after grommet insertion is low. This is in line with a previous meta-analysis of tympanostomy tube sequelae, which indicated that persistent perforation occurred in 2.2% of children receiving short-term grommets (Kay 2001).

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence on the effectiveness of bilateral grommet insertion in children with recurrent acute otitis media (rAOM) is limited in quantity (five randomised controlled trials (RCTs)) and of low to very low quality. The results of the studies included in this review suggest some benefit of grommets in terms of the chance of having no further AOM recurrences and reducing the number of AOM recurrences (around one fewer episode at six months and a less noticeable effect by 12 months) compared to those managed by active monitoring and placebo medication. It is uncertain whether or not grommets are more effective than antibiotic prophylaxis. Our findings suggest that clinicians need to carefully balance the modest potential benefits of grommets in this population against the potential harms and the risks of any surgical intervention in young children.

Implications for research

Widespread use of pneumococcal vaccination has changed the bacteriology and epidemiology of AOM, and how this might impact the results of prior trials is unknown. New and high-quality RCTs comparing grommets with active monitoring in children with rAOM are urgently needed.

Children participating in future trials of grommets for rAOM should be representative of the populations around the world who are receiving grommets either as a single surgical intervention or in combination with adenoidectomy. The type of grommets must be clearly specified and sample sizes need to be sufficient to answer the study question reliably. Preferably, randomisation should be stratified according to the presence of middle ear effusion at the time of evaluation for surgery to assess whether this characteristic modifies the effectiveness of grommets. It is critical that appropriate outcomes are chosen and it would be ideal if the choice was consistent across studies. To ensure future trial results are of maximum value to both professionals and families of children with rAOM, it is key that all stakeholders involved in the care of children with rAOM work together to develop a core set of outcomes to be used clinically and across future research into this condition. These outcomes should likely not only focus on the frequency of AOM recurrences diagnosed by clinicians in both the short term (three to six months) and the long term (up to two years), but also collect outcomes reported by children and their caregivers including validated AOM severity scores such as the AOM Severity of Symptoms Scale (AOM-SOS) (Shaikh 2009) and the AOM Faces Scale (AOM- FS) (Friedman 2006). Furthermore, it is important that adverse effects of grommets, such as the frequency of persistent tympanic membrane perforations, misplaced grommets in the middle ear, postoperative otorrhoea (in the first week after grommet insertion) and myringosclerosis, are consistently monitored and that data on antibiotic use, both topical (eardrops) and systemic, are systematically captured across both treatment groups. Ideally, future trials will also assess the impact of both treatment strategies on antimicrobial resistance by collecting stool samples of participants to detect and quantify the dynamics of the genes in the gut microbiota that confer resistance to the most commonly used antibiotics. Finally, it is important to capture health economic data including direct and indirect healthcare costs to balance the costs of the various treatment strategies against benefits in a health economic analysis.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Casselbrant 1992

Methods	3-arm, non-blinded (for grommets versus no (ear) surgery comparisons), multicentre, parallel-group RCT with 2 years of follow-up
Participants	**Location:** USA, Children's Hospital of Pittsburgh Otitis Media Center and 2 private paediatric practices in Pittsburgh **Setting of recruitment and treatment:** secondary and tertiary care **Sample size:** • **Number randomised:** 86 in intervention, 90 in comparison 1, 88 in comparison 2 • **Number completed:** 57 in intervention, 40 in comparison 1, 37 in comparison 2 **Participant (baseline) characteristics:** • Age: 7 months to 35 months • Gender: 155 boys (59%), 109 girls (41%) **Inclusion criteria:** children aged between 7 months and 35 months with at least 3 AOM episodes in the previous 6 months or more than 4 in the previous 12 months with the most recent episode having occurred in previous 6 months. At time of entry children were required to be free of OME **Exclusion criteria:** OME at time of entry, asthma, chronic sinusitis or previous tonsillectomy or adenoidectomy
Interventions	**Intervention group:** grommets (Teflon® Armstrong type) **Comparator group 1:** antibiotic prophylaxis; amoxicillin suspension 20 mg/kg/day once daily for 2 years **Comparator group 2:** placebo medication; liquid suspension of similar appearance and taste to antibiotic prophylaxis for 2 years In case of AOM episodes, amoxicillin 40 mg/kg/day divided into 3 daily doses for 10 days was prescribed and tympanocentesis was performed in the antibiotic prophylaxis and placebo medication groups. If a participant did not improve and if the culture yielded an amoxicillin-resistant organism, a 10-day course of erythromycin and sulfisoxazole or alternative antimicrobial drug was prescribed. In case of otorrhoea (through a tympanic membrane perforation or grommets), amoxicillin 40 mg/kg/day and neomycin/polymyxin B/hydrocortisone ear drops were prescribed for 10 days **Use of additional interventions:** participants were randomly allocated to antibiotic prophylaxis or placebo medication received a nasopharyngeal and middle ear culture (through tympanocentesis) in case of new AOM or OME episodes
Outcomes	**Primary outcome:** number of AOM episodes in the 2-year postoperative period **Secondary outcomes:** proportion of children without AOM recurrences in the 2-year postoperative period, proportion of children who had ultimate treatment failure (protocol-defined criteria for a fourth tympanocentesis within 6 months or a fifth within 12 months; over 180 days with middle ear effusion in the same ear within 12 months; protocol-defined criteria for a third placement of grommets within 12 months; a suppurative complication; a cholesteatoma; a significant adverse reaction to amoxicillin), persistent tympanic membrane perforation after grommet insertion, bacteriology of middle ear

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Casselbrant 1992 (*Continued*)

	effusions Diagnosis of AOM was based on otoscopic signs (erythema or white opacification, fullness or bulging and decreased mobility of the tympanic membrane), or one or more symptoms (fever, otalgia, irritability) in the presence of middle ear effusions or both
Funding sources	Funded by a grant from the National Institute of Deafness and Communication Disorders, National Institute of Health. Amoxicillin and placebo medication were supplied by Beecham Laboratories, Bristol, TN
Declarations of interest	No details provided
Notes	**Participants lost to follow-up total:** 109/243 (45%) (limited to participants with at least 1 follow-up visit) **Participants lost to follow-up intervention group:** 20/77 (26%); 6 treatment failure, 14 loss to follow-up **Participants lost to follow-up comparator group 1:** 46/86 (53%); 12 treatment failure, 34 loss to follow-up **Participants lost to follow-up comparator group 2:** 43/80 (51%); 11 treatment failure, 32 loss to follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stratified randomisation, but method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The combined attrition rates for the amoxicillin, placebo and tympanostomy tube groups at the 6-, 12-, 18- and 24-month end points were 21.2%, 28.0%, 35.2% and 38.3%, respectively."
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk

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Casselbrant 1992 (*Continued*)

Other bias	Unclear risk	Baseline characteristics: balanced Intention-to-treat analysis: performed Formal sample size calculations were performed Co-interventions: different across groups

El-Sayed 1996

Methods	2-arm, non-blinded, single-centre parallel-group RCT with 6 months of follow-up
Participants	**Location:** Saudi Arabia, ENT unit of King Abdel Azir University Hospital, Riyadh **Setting of recruitment and treatment:** tertiary care **Sample size:** • **Number randomised:** ? in intervention, ? in comparison • **Number completed:** 31 in intervention, 22 in comparison **Participant (baseline) characteristics:** • Age: 3 years and below; mean age 20 months • Gender: 29 boys (55%), 24 girls (45%) **Inclusion criteria:** children aged below 3 years with at least 3 AOM episodes diagnosed, documented and treated by their referring physician in the 6 months prior to referral. Presence or absence of OME did not preclude inclusion in the study **Exclusion criteria:** documented immune deficiency or craniofacial abnormalities such as cleft palate, Down's syndrome
Interventions	**Intervention group:** grommets (type not described) **Comparator group:** antibiotic prophylaxis; sulfamethoxazole-trimethoprim (SMZ-T) 12 mg/kg/day once daily for 6 months Oral antibiotics were administered for individual AOM episodes; cefaclor for 10 days **Use of additional interventions:** none described
Outcomes	**Primary outcome:** proportion of children who have no AOM recurrences in the 6-month postoperative period **Secondary outcomes:** side effects of medication, number of re-insertions of grommets (data provided for the treatment group only) Diagnosis of AOM was based on otoscopy findings and the acute onset of otalgia with or without otorrhoea. For those with grommets in place, diagnosis was based upon the presence of otorrhoea
Funding sources	No details provided
Declarations of interest	No details provided
Notes	**Participants lost to follow-up total:** 15/68 (22%); 7 non-compliance with medication, 8 loss to follow-up. Insufficient information to calculate the number of excluded children for the grommets and control groups

Risk of bias

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El-Sayed 1996 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Methods not described; 8/64 children (13%) were placed on a predetermined treatment regime on the basis of the parent's concern
Allocation concealment (selection bias)	High risk	Methods not described; 8/64 children (13%) were placed on a predetermined treatment regime
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	15/68 children (22%) not included in final analyses; insufficient information to calculate the number of excluded children for the grommets and control groups
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Did not perform intention-to-treat analysis: children who were non-compliant with medication were excluded from analyses Did not perform formal sample size calculations Co-interventions: similar across groups

Gebhart 1981

Methods	2-arm, non-blinded, single-centre, parallel-group RCT with 6 months of follow-up
Participants	**Location:** USA, general ENT practice **Setting of recruitment and treatment:** secondary care **Sample size:** • **Number randomised:** 58 in intervention, 50 in comparison • **Number completed:** 54 in intervention, 41 in comparison **Participant (baseline) characteristics:** • Age: 3 years and below; mean age 20 months • Gender: 60 boys (63%), 35 girls (37%)

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Gebhart 1981 (*Continued*)

	Inclusion criteria: children aged below 3 years with at least 3 AOM episodes diagnosed and treated by their referring physician in the 6 months prior to referral. Presence or absence of OME, by history or physical examination, did not preclude inclusion in the study **Exclusion criteria:** cleft palate, Down's syndrome, recurrent tonsillitis associated with otitis media
Interventions	**Intervention group:** grommets (Shepard Teflon®) **Comparator group:** active monitoring (Topical) antibiotics were administered for individual AOM episodes; ampicillin (or erythromycin plus a sulphonamide in case of ampicillin allergy) for 10 days; if drainage was present, and did not clear with antibiotics, Cortisporin® eardrops were administered **Use of additional interventions:** decongestant for URTI or nasal congestion
Outcomes	**Primary outcome:** number of AOM episodes in the 6-month postoperative period **Secondary outcomes:** proportion of children without AOM recurrences in the 6-month postoperative period, grommets-related adverse effects, number of re-insertions of grommets (data provided for the treatment group only) Diagnosis of AOM was based on otoscopy findings. For those with grommets in place, diagnosis was based upon the presence of ear discharge in the external ear canal
Funding sources	This study was supported in part by a grant from the Medical Research Foundation at Riverside Methodist Hospital and in part by NIH Grant NSO 8854
Declarations of interest	No details provided
Notes	**Participants lost to follow-up total:** 13/108 (12%) **Participants lost to follow-up intervention group:** 4/58 (7%); inadequate follow-up in 3 children and parents of 1 child terminated study **Participants lost to follow-up comparator group:** 9/50 (18%); inadequate follow-up in 7 children and parents or the referring physician of 2 children terminated study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded

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Gebhart 1981 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13/108 (12%) children not included in final analyses; 4/58 (7%) in grommets group and 9/50 (18%) control group; reasons for non-completion are clearly described, but bias due to differential loss to follow-up cannot be excluded
Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	Unclear risk	Baseline characteristics: balanced Intention-to-treat analysis was performed Did not perform formal sample size calculations Co-interventions: similar across groups

Gonzalez 1986

Methods	3-arm, non-blinded (for grommets versus no (ear) surgery comparisons), multicentre, parallel-group RCT with 6 months of follow-up
Participants	**Location:** USA, ENT departments of Army Medical Centres **Setting of recruitment and treatment:** secondary care **Sample size:** • **Number randomised:** ? in intervention, ? in comparison 1, ? in comparison 2 • **Number completed:** 22 in intervention, 21 in comparison 1, 20 in comparison 2 **Participant (baseline) characteristics:** • Age: 6 months to 10 years; mean age 19 months • Gender: 38 boys (60%), 25 girls (40%) **Inclusion criteria:** children aged between 6 months and 10 years with at least 3 AOM episodes in the previous 6 months or more than 4 in the previous 18 months. Presence or absence of OME did not preclude inclusion in the study **Exclusion criteria:** cleft palate, Down's syndrome, previous grommets or sulphonamide sensitivity
Interventions	**Intervention group:** grommets (0.04 mm Paparella design grommet in majority of children) **Comparator group 1:** antibiotic prophylaxis; sulfisoxazole suspension 500 mg twice daily if under 5 years or 1 g twice daily if 5 years and older for 6 months **Comparator group 2:** placebo medication; liquid suspension of similar texture and appearance to antibiotic prophylaxis for 6 months Oral antibiotics for 10 days were administered for individual AOM episodes **Use of additional interventions:** postoperative antibiotic drops were initially used in the grommets group, but were discontinued later in the study Children in the antibiotic prophylaxis or placebo medication groups who had treatment failure (2 or more AOM episodes within 3 months) underwent grommet insertion. Children in the grommets group who had treatment failure were given a course of

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	prophylactic sulfisoxazole. Children with OME that persisted for longer than 3 months underwent grommet insertion (but were not considered treatment failures if rAOM was controlled)
Outcomes	**Primary outcome:** number of AOM episodes in the 6-month postoperative period **Secondary outcomes:** proportion of children without AOM recurrences in the 6-month postoperative period, proportion of children who had treatment failure (2 or more AOM episodes within 3 months), significant complications (no further details provided) Diagnosis of AOM was defined as the rapid and short onset of signs and symptoms of inflammation in the middle ear using the following criteria: otalgia (ear tugging in the infant), fever, tympanic membrane erythema or bulging, decreased tympanic membrane mobility, loss of tympanic membrane landmarks, otorrhoea
Funding sources	Sulfisoxazole and placebo medication were supplied by Hoffman-LaRoche Inc, NJ No further details provided
Declarations of interest	No details provided
Notes	**Participants lost to follow-up total:** unknown; the number of randomised children was not reported 19/41 children (46%) in non-surgical groups underwent grommet insertion during follow-up because of treatment failure 3/22 children (14%) in the grommets group received sulfisoxazole prophylaxis during follow-up because of treatment failure

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "children were then randomized into three groups using a list of random numbers" Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit a judgement of low or high risk since the number of randomised children was not reported

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Gonzalez 1986 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No protocol available; insufficient information to permit a judgement of low or high risk
Other bias	High risk	Baseline characteristics: balanced Intention-to-treat analysis: unknown Did not perform formal sample size calculations Co-interventions: different across groups

Kujala 2012

Methods	3-arm, non-blinded, single-centre, parallel-group RCT with 1 year of follow-up
Participants	**Location:** Finland, ENT department of Oulu University Hospital **Setting of recruitment and treatment:** tertiary care **Sample size:** • **Number randomised:** 100 in intervention, 100 in comparison 1 (and 100 in comparison 2) • **Number completed:** 89 in intervention, 91 in comparison 1 (and 96 in comparison 2) **Participant (baseline) characteristics:** • Age: 10 months to 2 years; mean age 16.0 months • Gender: 110 boys (55%), 90 girls (45%) **Inclusion criteria:** children aged between 10 months and 2 years with at least 3 AOM episodes in the previous 6 months and residence within 25 miles of participating hospital. At time of entry children were required to be free of OME **Exclusion criteria:** chronic OME, previous grommets or adenoidectomy, cranial abnormalities, documented immunological disorders, ongoing prophylaxis for a disease other than AOM
Interventions	**Intervention group:** grommets (Donaldson silicon tubes, TympoVent®, Atos) **Comparator group 1:** active monitoring **Comparator group 2:** grommets plus adenoidectomy; not relevant for this review (since there is no "adenoidectomy alone" group) and therefore no further details related to this comparator reported AOM episodes were treated according to the Finnish guidelines; primary choice of antibiotics: amoxicillin 40 mg/kg/day for 5 days **Use of additional interventions:** not described
Outcomes	**Primary outcomes:** treatment failure (2 AOM episodes in 2 months or 3 in 6 months or middle ear effusion for at least 2 months) and time to intervention failure **Secondary outcomes:** incidence density of AOM episodes and time to first AOM recurrence Diagnosis of AOM was defined as presence of acute upper respiratory symptoms together with middle ear inflammation and effusion (bulging and/or decreased mobility of the ear drum, air-fluid level) detected by pneumatic otoscopy, tympanometry, otomicroscopy or otorrhoea

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Kujala 2012 (*Continued*)

Funding sources	Nothing to declare
Declarations of interest	Nothing to declare
Notes	**Participants lost to follow-up total:** 20/200 (10%); grommets group: 11/100 (11%), control group: 9/100 (9%), but all randomised children were included in analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random allocation sequence using permutated blocks with a block size of 3
Allocation concealment (selection bias)	Low risk	Treatment allocation as indicated in consecutively numbered, sealed, opaque envelopes, which were opened sequentially only after written informed consent had been received
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Total number of dropouts: 20/200 (10%) . Grommets group: 11/100 (11%), control group: 9/100 (9%). All randomised children were included in analyses
Selective reporting (reporting bias)	High risk	Trial protocol available at ClinicalTrials.gov (NCT00162994) Primary outcomes as listed at ClinicalTrials.gov (number of acute otitis media and quality of life issues) differed from those included in manuscript (intervention failure and time to intervention failure) Definition of intervention failure (2 AOM episodes in 2 months or 3 in 6 months, or middle ear effusion for at least 2 months as assessed by one of the team's otolaryngologists) as reported in the manuscript was not prespecified on ClinicalTrials.gov Some of the secondary outcomes as listed on ClinicalTrials.gov (speed of recovery of

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Kujala 2012 (*Continued*)

		each otitis media, number of days with middle ear effusion, number of upper respiratory infections, prevention of otitis media caused by pneumococcus) were not reported
Other bias	Unclear risk	Baseline characteristics: balanced Did perform intention-to-treat analysis Did perform formal sample size calculations, but these were not prespecified on ClinicalTrials.gov Co-interventions: similar across groups

AOM: acute otitis media
ENT: ear, nose and throat
GP: general practitioner
OME: otitis media with effusion
rAOM: recurrent acute otitis media
RCT: randomised controlled trial
URTI: upper respiratory tract infection

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

Study	Reason for exclusion
Bulman 1984	PARTICIPANTS: OME not rAOM
Chow 2007	ALLOCATION AND PARTICIPANTS: Not a RCT; rAOM and OME
de Beer 2005	ALLOCATION: Not a RCT
Gates 1985	PARTICIPANTS: OME not rAOM
Gates 1987	PARTICIPANTS OME not rAOM
Hammaren-Malmi 2005	PARTICIPANTS AND INTERVENTION: rAOM and OME; RCT comparing grommets plus adenoidectomy versus grommets alone
Ingels 2005	PARTICIPANTS: OME not rAOM

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(*Continued*)

Le 1991	PARTICIPANTS AND INTERVENTION: rAOM and OME; RCT with unilateral grommet insertion and in which contralateral ears were randomised to either myringotomy alone or no surgery
Mandel 1989	PARTICIPANTS: OME not rAOM
Mandel 1992	PARTICIPANTS: OME not rAOM
Mattila 2003	INTERVENTION: RCT comparing grommets plus adenoidectomy versus grommets alone
Qvarnberg 1981	PARTICIPANTS AND INTERVENTION: Not rAOM; no grommets
Raol 2017	STUDY TYPE: Not a RCT
Teele 2000	PARTICIPANTS AND INTERVENTION: Infants at risk of rAOM; no grommets
Weigel 1989	COMPARATOR: RCT comparing 4 different types of grommets

AOM: acute otitis media
OME: otitis media with effusion
rAOM: recurrent acute otitis media
RCT: randomised controlled trial

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

Aabel 2011

Trial name or title	"The effect of ventilation tubes on recurrent acute otitis media in children 1-6 years"
Methods	**Allocation:** randomised **Design:** parallel, open-label
Participants	**Number:** 240 **Eligibility criteria:** children aged 1 to 6 years with rAOM defined as the occurrence of 3 AOM episodes in 6 months or 4 episodes in 12 months **Exclusion criteria:** previous grommets, previous adenoidectomy or tonsillectomy, plans to move from district within follow-up time

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Aabel 2011 (*Continued*)

Interventions	**Intervention group:** grommets (type not described) insertion **Comparator group:** active monitoring AOM recurrences will be treated with antibiotics
Outcomes	**Primary outcomes:** number of AOM recurrences during 1-year follow-up, disease-specific health-related quality of life (OM-6 and OMO-22) at 3, 6, 9 and 12 months post-randomisation **Secondary outcomes:** structural changes in tympanic membrane at 3, 6, 9 and 12 months post-randomisation, time grommets stay in place, adverse events (chronic otorrhoea, granulation tissue, persistent tympanic membrane perforation)
Starting date	Ethical approval obtained on 1 November 2011 Status 24 November 2017 - not yet recruiting
Contact information	Peder Aabel, Akershus University Hospital - peder.aabel@ahus.no Magnus von Unge, Akershus University Hospital - magus.von.unge@ahus.no
Notes	ACTRN12611000380998 https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=336693 **Sponsor:** Akershus University Hospital **Principal investigators:** Peder Aabel and Magnus von Unge, Akershus University Hospital, Norway

Hoberman 2015

Trial name or title	Efficacy of tympanostomy tubes for children with recurrent acute otitis media
Methods	**Allocation:** randomised **Design:** parallel, open-label
Participants	**Number:** 240 **Eligibility criteria:** children aged 6 to 35 months with rAOM defined as the occurrence of 3 AOM episodes in 6 months or 4 episodes in 12 months with at least 1 episode in the preceding 6 months, and 2 of these AOM episodes have been documented by trained study personnel **Exclusion criteria:** previous grommets, chronic illness (cystic fibrosis, neoplasm, juvenile diabetes, renal or hepatic insufficiency, immune dysfunction, malabsorption, inflammatory bowel disease, severe asthma requiring at least 4 courses of oral corticosteroids during the last 12 months), allergy to amoxicillin, congenital anomaly (cleft palate, Down's syndrome), OME for at least 3 months in addition to rAOM, sensorineural hearing loss
Interventions	**Intervention group:** grommets (Teflon® Armstrong-type) insertion **Comparator group:** active monitoring AOM recurrences will be treated with antibiotic eardrops in the grommets group and with oral antibiotics in the active monitoring group
Outcomes	**Primary outcome:** average number of AOM recurrences during the 2-year follow-up period **Secondary outcomes:** severity of AOM recurrences, frequency distribution of AOM recurrences during the 2-year follow-up period, time to first AOM recurrence, type of AOM recurrences, antibiotic consumption, adverse events (protocol defined diarrhoea, diaper dermatitis, chronic otorrhoea), antibiotic resistance of nasopharyngeal pathogens, cost-effectiveness

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Hoberman 2015 (*Continued*)

Starting date	November 2015 (estimated completion date February 2021)
Contact information	Diana Kearney, RN, CCRC - diana.kearney@chp.edu Jennifer Nagg, RN - jennifer.nagg@chp.edu
Notes	https://clinicaltrials.gov/ct2/show/NCT02567825 **Sponsor and collaborators:** University of Pittsburgh, George Washington University, National Institute on Deafness and Other Communication Disorders (NIDCD) **Principal investigators:** Alejandro Hoberman, MD - University of Pittsburgh School of Medicine; Children's Hospital of Pittsburgh of UPMC; Diego Preciado, MD, PhD - George Washington University; Childrens National Medical Center

SIUTIT Trial 2015

Trial name or title	SIUTIT Trial
Methods	**Allocation:** randomised **Design:** parallel, single-blind (outcome assessor blinded)
Participants	**Number:** 230 **Eligibility criteria:** children aged 9 to 36 months with at least one Greenland-born parent, B- or C2-type curve tympanogram at 2 visits 3 to 4 months apart or 3 episodes of AOM in 6 months or 4 in 12 months, American Society of Anaesthesiologists physical status classification class 1 and 2 **Exclusion criteria:** orofacial cleft, Down's syndrome or known generalised immune deficiency, American Society of Anaesthesiologists physical status classification class > 2
Interventions	**Intervention group:** grommets (Donaldson-type) insertion **Comparator group:** active monitoring AOM recurrences will be treated according to current practice in Greenland, which includes systemic antibiotic treatment as well as aural toilet and topical antibiotics. Grommet insertion during the study period is not accepted in the control group
Outcomes	**Primary outcome:** number of visits to health clinic during the 2-year follow-up period (assessed by investigating medical records) **Secondary outcomes:** number of AOM episodes during the 2-year follow-up period (assessed by investigating medical records); disease-specific quality of life at baseline, 3 months, 1 year and 2 years follow-up (assessed by OM-6 and Caregiver Impact Questionnaires); number of episodes where oral or intravenous antibiotics have been administered during the 2-year follow-up period (assessed by investigating medical records); proportion of children with uni- or bilateral tympanic membrane perforations at 2 years (based on otoscopic images, which will be anonymised and evaluated by an ENT specialist without knowledge of the intervention), number of ear discharge episodes during the 2-year follow-up period (assessed by investigating medical records); serious adverse events
Starting date	February 2016 (estimated completion date August 2020)
Contact information	Malene N Demant, MD - siutit@peqqik.gl

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SIUTIT Trial 2015 (*Continued*)

Notes	https://clinicaltrials.gov/ct2/show/NCT02490332 **Sponsor and collaborators:** Zealand University Hospital; Government of Greenland, Agency for Health and Prevention; Copenhagen Trial Unit, Center for Clinical Intervention Research **Principal investigator:** Malene N Demant, MD - Køge University Hospital Study director: Preben Homoe, MD PhD - Køge University Hospital

AOM: acute otitis media
OME: otitis media with effusion
OM-6: Otitis Media-6
Otitis Media Outcome-22
rAOM: recurrent acute otitis media

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DATA AND ANALYSES

Comparison 1. Grommets versus active monitoring

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation	1	95	Risk Ratio (M-H, Fixed, 95% CI)	9.49 [2.38, 37.80]
2 Proportion of patients who have no AOM recurrences at 12 months post-randomisation	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.00, 1.99]
3 Total number of AOM recurrences at six months post-randomisation	1	95	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-1.99, -1.01]

Comparison 2. Grommets versus antibiotic prophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation	2	96	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [1.07, 2.65]
2 Total number of AOM recurrences at six months post-randomisation	1	43	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-1.37, 0.33]

Comparison 3. Grommets versus placebo medication

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation	1	42	Risk Ratio (M-H, Fixed, 95% CI)	3.64 [1.20, 11.04]
2 Total number of AOM recurrences at six months post-randomisation	1	42	Mean Difference (IV, Fixed, 95% CI)	-1.14 [-2.06, -0.22]

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Analysis 1.1. Comparison 1 Grommets versus active monitoring, Outcome 1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation.

Review: Grommets (ventilation tubes) for recurrent acute otitis media in children

Comparison: 1 Grommets versus active monitoring

Outcome: 1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation

Study or subgroup	Grommets n/N	Active monitoring n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gebhart 1981	25/54	2/41		100.0 %	9.49 [2.38, 37.80]
Total (95% CI)	**54**	**41**		**100.0 %**	**9.49 [2.38, 37.80]**
Total events: 25 (Grommets), 2 (Active monitoring)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.19 (P = 0.0014)					
Test for subgroup differences: Not applicable					

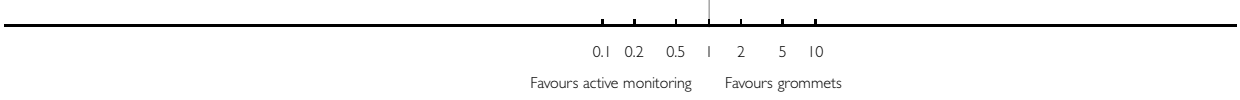
Analysis 1.2. Comparison 1 Grommets versus active monitoring, Outcome 2 Proportion of patients who have no AOM recurrences at 12 months post-randomisation.

Review: Grommets (ventilation tubes) for recurrent acute otitis media in children

Comparison: 1 Grommets versus active monitoring

Outcome: 2 Proportion of patients who have no AOM recurrences at 12 months post-randomisation

Study or subgroup	Grommets n/N	Active monitoring n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kujala 2012	48/100	34/100		100.0 %	1.41 [1.00, 1.99]
Total (95% CI)	**100**	**100**		**100.0 %**	**1.41 [1.00, 1.99]**
Total events: 48 (Grommets), 34 (Active monitoring)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.98 (P = 0.047)					
Test for subgroup differences: Not applicable					



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Analysis 1.3. Comparison 1 Grommets versus active monitoring, Outcome 3 Total number of AOM recurrences at six months post-randomisation.

Review: Grommets (ventilation tubes) for recurrent acute otitis media in children

Comparison: 1 Grommets versus active monitoring

Outcome: 3 Total number of AOM recurrences at six months post-randomisation

Study or subgroup	Grommets N	Mean(SD)	Active monitoring N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gebhart 1981	54	0.67 (0.75)	41	2.17 (1.45)		100.0 %	-1.50 [-1.99, -1.01]
Total (95% CI)	**54**		**41**			**100.0 %**	**-1.50 [-1.99, -1.01]**

Heterogeneity: not applicable

Test for overall effect: Z = 6.04 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Grommets versus antibiotic prophylaxis, Outcome 1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation.

Review: Grommets (ventilation tubes) for recurrent acute otitis media in children

Comparison: 2 Grommets versus antibiotic prophylaxis

Outcome: 1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation

Study or subgroup	Grommets n/N	Antibiotic prophy-laxis n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
El-Sayed 1996	20/31	10/22		69.6 %	1.42 [0.84, 2.40]
Gonzalez 1986	12/22	5/21		30.4 %	2.29 [0.97, 5.39]
Total (95% CI)	**53**	**43**		**100.0 %**	**1.68 [1.07, 2.65]**

Total events: 32 (Grommets), 15 (Antibiotic prophylaxis)

Heterogeneity: Chi^2 = 0.90, df = 1 (P = 0.34); I^2 =0.0%

Test for overall effect: Z = 2.26 (P = 0.024)

Test for subgroup differences: Not applicable

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Analysis 2.2. Comparison 2 Grommets versus antibiotic prophylaxis, Outcome 2 Total number of AOM recurrences at six months post-randomisation.

Review: Grommets (ventilation tubes) for recurrent acute otitis media in children

Comparison: 2 Grommets versus antibiotic prophylaxis

Outcome: 2 Total number of AOM recurrences at six months post-randomisation

Study or subgroup	Grommets		Antibiotic prophy-laxis		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Gonzalez 1986	22	0.86 (1.67)	21	1.38 (1.12)		100.0 %	-0.52 [-1.37, 0.33]
Total (95% CI)	**22**		**21**			**100.0 %**	**-0.52 [-1.37, 0.33]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.20 (P = 0.23)

Test for subgroup differences: Not applicable

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Analysis 3.1. Comparison 3 Grommets versus placebo medication, Outcome 1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation.

Review: Grommets (ventilation tubes) for recurrent acute otitis media in children

Comparison: 3 Grommets versus placebo medication

Outcome: 1 Proportion of patients who have no AOM recurrences at 6 months post-randomisation

Study or subgroup	Grommets n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gonzalez 1986	12/22	3/20		100.0 %	3.64 [1.20, 11.04]
Total (95% CI)	**22**	**20**		**100.0 %**	**3.64 [1.20, 11.04]**
Total events: 12 (Grommets), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.28 (P = 0.023)					
Test for subgroup differences: Not applicable					

Analysis 3.2. Comparison 3 Grommets versus placebo medication, Outcome 2 Total number of AOM recurrences at six months post-randomisation.

Review: Grommets (ventilation tubes) for recurrent acute otitis media in children

Comparison: 3 Grommets versus placebo medication

Outcome: 2 Total number of AOM recurrences at six months post-randomisation

Study or subgroup	Grommets N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Gonzalez 1986	22	0.86 (1.67)	20	2 (1.38)		100.0 %	-1.14 [-2.06, -0.22]
Total (95% CI)	**22**		**20**			**100.0 %**	**-1.14 [-2.06, -0.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.42 (P = 0.016)							
Test for subgroup differences: Not applicable							

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ADDITIONAL TABLES

Table 1. Interventions and comparison pairs included in this review

Study ID	Grommets	Grommets plus adenoidectomy	Active monitoring	Placebo medication	Antibiotic prophylaxis	Adenoidectomy
Casselbrant 1992	x			x	x	
El-Sayed 1996	x				x	
Gebhart 1981	x		x			
Gonzalez 1986	x			x	x	
Kujala 2012	x	x	x			

Comparison pairs for this review

#	Intervention	Comparator	Number of trials	Study ID
1	Grommets	Active monitoring	2	Gebhart 1981; Kujala 2012
2	Grommets	Antibiotic prophylaxis	3	Casselbrant 1992; El-Sayed 1996; Gonzalez 1986
3	Grommets	Placebo medication	2	Casselbrant 1992; Gonzalez 1986

Table 2. Overview of the outcomes reported in the included studies

Outcomes	Casselbrant 1992	El-Sayed 1996	Gebhart 1981	Gonzalez 1986	Kujala 2012
Primary outcomes					
Proportion of children who have no AOM recurrences at 3 to 6 months post-randomisation		x	x	x	
Significant adverse effect: tympanic membrane perforation persisting for 3 months or longer	x		x		
Secondary outcomes					

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Table 2. Overview of the outcomes reported in the included studies (*Continued*)

Proportion of children who have no AOM recurrences at 6 to 12 months post-randomisation					x
Total number of AOM recurrences					
< 3 months					
3 to 6 months			x	x	
6 to 12 months					x
Disease-specific health-related quality of life					
< 3 months					
3 to 6 months					x
6 to 12 months					x
Generic health-related quality of life of the child and parent					
< 3 months					
3 to 6 months					
6 to 12 months					
Presence of middle ear effusion					
< 3 months					
3 to 6 months					
6 to 12 months					
Other adverse effects: ventilation tube misplaced in middle ear, otorrhoea within 1 week			x		

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Table 2. Overview of the outcomes reported in the included studies (*Continued*)

of ventilation tube placement, myringosclerosis					

APPENDICES

Appendix 1. CENTRAL search strategy

CENTRAL (Cochrane Register of Studies)	MEDLINE (Ovid)	Embase (Ovid)	CINAHL (EBSCO)
1 MESH DESCRIPTOR Otitis AND CENTRAL:TARGET 2 (otitis or inflamm* or infect* or disease):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 3 #1 OR #2 4 MESH DESCRIPTOR Ear, Middle AND CENTRAL:TARGET 5 (middle near ear):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 6 #5 OR #4 7 #3 AND #6 8 MESH DESCRIPTOR Otitis Media AND CENTRAL:TARGET 9 MESH DESCRIPTOR Otitis Media with Effusion EXPLODE ALL AND CENTRAL:TARGET 10 (((otitis near media) or OME)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 11 ((middle near ear near effus*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:	1 Otitis/ 2 (otitis or inflamm* or infect* or disease*).ab,ti. 3 1 or 2 4 exp Ear, Middle/ 5 (middle adj3 ear).ab,ti. 6 4 or 5 7 3 and 6 8 otitis media/ or otitis media with effusion/ 9 (middle adj3 ear adj3 effus*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 10 ((otitis adj3 media) or OME).ab,ti. 11 7 or 8 or 9 or 10 12 exp Acute Disease/ 13 (acute or suppurat* or serous or secretory or secretion* or purulent).ab,ti 14 12 or 13 15 11 and 14 16 exp Otitis Media, Suppura-	1 otitis/ 2 (otitis or inflamm* or infect* or disease).ti,ab. 3 1 or 2 4 exp middle ear/ 5 (middle adj3 ear).ti,ab. 6 4 or 5 7 3 and 6 8 otitis media/ 9 secretory otitis media/ 10 ((otitis adj3 media) or OME).ti,ab. 11 (middle adj3 ear adj3 effus*).ti,ab. 12 7 or 8 or 9 or 10 or 11 13 exp acute disease/ 14 (acute or suppurat* or serous or secretory or secretion* or purulent).ti,ab 15 13 or 14 16 12 and 15 17 exp suppurative otitis media/ 18 (AOM or TYMPANITIS).ti,ab. 19 16 or 17 or 18 20 exp recurrent disease/ 21 exp chronic disease/ 22 exp secondary prevention/ 23 (recurrence* or recurrent or	S31 S25 AND S30 S30 S26 OR S27 OR S28 OR S29 S29 TX grommet* S28 TX ((tympanostomy or myringotomy or tympanic) n6 (tube* or tubulation or ventilat*)) S27 TX (middle n3 ear n6 (tube* or ventilat* or tubulation)) S26 (MH "Middle Ear Ventilation") S25 S22 OR S23 OR S24 S24 TX (raom or mastoiditis S23 (MH "Mastoiditis") S22 S17 AND S21 S21 S18 OR S19 OR S20 S20 TX recurrence* or recurrent or chronic or persistent or persistence or prone S19 (MH "Chronic Disease") S18 (MH "Recurrence") S17 S15 OR S16 S16 TX (AOM or TYMPANITIS) S15 S11 AND S14 S14 S12 OR S13 S13 TX (acute or suppurat* or

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(*Continued*)

TARGET
12 #7 OR #8 OR #9 OR #10 OR #11
13 MESH DESCRIPTOR Acute Disease EXPLODE ALL AND CENTRAL:TARGET
14 (acute or suppurat* or serous or secretory or secretion* or purulent):AB,EH,KW,KY,MC, MH,TI,TO AND CENTRAL: TARGET
15 #13 OR #14
16 #12 AND #15
17 MESH DESCRIPTOR Otitis Media, Suppurative EXPLODE ALL AND CENTRAL:TARGET
18 (AOM or TYMPANITIS): AB,EH,KW,KY,MC, MH,TI,TO AND CENTRAL: TARGET
19 #16 OR #17 OR #18
20 MESH DESCRIPTOR Recurrence EXPLODE ALL AND CENTRAL:TARGET
21 MESH DESCRIPTOR Chronic Disease EXPLODE ALL AND CENTRAL:TARGET
22 MESH DESCRIPTOR Secondary Prevention EXPLODE ALL AND CENTRAL:TARGET
23 (recurrence* or recurrent or chronic or persistent or persistence
or prone):AB,EH,KW,KY,MC, MH,TI,TO AND CENTRAL: TARGET
24 #20 OR #21 OR #22 OR # 23
25 #19 AND #24
26
MESH DESCRIPTOR Mastoiditis EXPLODE ALL AND CENTRAL:TARGET
27 (raom or mastoiditis):AB, EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET

tive/
17 (AOM or TYMPANITIS). ab,ti.
18 15 or 16 or 17
19 exp Recurrence/
20 exp Chronic Disease/
21 exp Secondary Prevention/
22 (recurrence* or recurrent or chronic or persistent or persistence or prone).ab,ti
23 19 or 20 or 21 or 22
24 18 and 23
25 Mastoiditis/
26 (raom or mastoiditis).ab,ti.
27 24 or 25 or 26
28 exp Middle Ear Ventilation/
29 (middle adj3 ear adj6 (tube* or ventilat* or tubulation)).ab, ti
30 ((tympanostomy or myringotomy or tympanic) adj6 (tube* or tubulation or ventilat*)).ab,ti
31 "grommet*".ab,ti.
32 28 or 29 or 30 or 31
33 27 and 32
34 randomized controlled trial. pt.
35 controlled clinical trial.pt.
36 randomized.ab.
37 placebo.ab.
38 drug therapy.fs.
39 randomly.ab.
40 trial.ab.
41 groups.ab.
42 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43 exp animals/ not humans.sh.
44 42 not 43
45 33 and 44

chronic or persistent or persistence or prone).ti,ab
24 20 or 21 or 22 or 23
25 19 and 24
26 mastoiditis/
27 (raom or mastoiditis).ti,ab.
28 25 or 26 or 27
29 exp middle ear ventilation/
30 (middle adj3 ear adj6 (tube* or ventilat* or tubulation)).ti,ab
31 ((tympanostomy or myringotomy or tympanic) adj6 (tube* or tubulation or ventilat*)).ti,ab
32 "grommet*".ti,ab.
33 29 or 30 or 31 or 32
34 28 and 33
35 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw
36 (control* adj group*).tw.
37 (trial* and (control* or comparative)).tw.
38 ((blind* or mask*) and (single or double or triple or treble)).tw
39 (treatment adj arm*).tw.
40 (control* adj group*).tw.
41 (phase adj (III or three)).tw.
42 (versus or vs).tw.
43 rct.tw.
44 crossover procedure/
45 double blind procedure/
46 single blind procedure/
47 randomization/
48 placebo/
49 exp clinical trial/
50 parallel design/
51 Latin square design/
52 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/
54 exp human/

serous or secretory or secretion* or purulent)
S12 (MH "Acute Disease")
S11 S7 OR S8 OR S9 OR S10
S10 TX ((otitis n3 media) or OME)
S9 TX middle n3 ear n3 effus*
S8 (MH "Otitis Media with Effusion") OR (MH "Otitis Media")
S7 S3 AND S6
S6 S4 OR S5
S5 TX middle n3 ear
S4 (MH "Ear, Middle")
S3 S1 OR S2
S2 TX otitis or inflamm* or infect* or disease
S1 (MH "Otitis")

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(*Continued*)

28 #25 OR #26 OR #27 29 MESH DESCRIPTOR Middle Ear Ventilation EXPLODE ALL AND CENTRAL:TARGET 30 ((middle near ear near (tube* or ventilat* or tubulation))):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 31 grommet*:AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 32 (((tympanostomy or myringotomy or tympanic) near (tube* or tubulation or ventilat*))):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 33 #29 OR #30 OR #31 OR #32 34 #28 AND #33		55 53 not 54 56 52 not 55 57 34 and 56	
Cochrane ENT Register	**LILACS**	**ClinicalTrials.gov**	**ICTRP**
1 otitis or inflamm* or infect* or disease 2 middle near ear 3 #1 AND #2 4 (otitis near media) or OME 5 middle near ear near effus* 6 #3 or #4 or #5 7 acute or suppurat* or serous or secretory or secretion* or purulent 8 #6 AND #7 9 AOM or TYMPANITIS 10 #8 or #9 11 recurrence* or recurrent or chronic or persistent or persistence or prone 12 #10 and #11 13 raom or mastoiditis 14 #12 or #13 15 middle near ear near (tube* or ventilat* or tubulation) 16 grommet* 17 (tympanostomy or myringotomy or tympanic) near (tube*	((TW:"middle ear" OR TW:"Oído Medio" OR TW:"Orelha Média" OR TW:tympanostomy OR TW:myringotomy OR TW:tympanic) AND (TW:Ventila$ OR TW:tube$ OR TW:tubulation)) OR TW:grommet$ AND Controlled Clinical Trial	**Via the Cochrane Register of Studies** 1 grommet OR grommets OR "tympanostomy tube" OR "tympanostomy tubes" OR "myringotomy tube" OR "myringotomy tubes" OR "middle ear tubulation" OR "tympanic membrane ventilation" OR (middle AND ear AND ventilation) AND INSEGMENT 2 (nct*):AU AND INSEGMENT 3 #1 AND #2 **Via ClinicalTrials.gov** grommet OR grommets OR "tympanostomy tube" OR "tympanostomy tubes" OR "myringotomy tube" OR "myringotomy tubes" OR "middle ear tubulation" OR "tympanic membrane ventilation" OR (middle AND	rAOM OR recurren* AND AOM OR recurren* AND otitis OR recurren* AND tympanitis OR otitis AND prone

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(*Continued*)

or tubulation or ventilat*) 18 #15 or #16 or #17 19 #14 and #18		ear AND ventilation) Study type: Interventional	

CONTRIBUTIONS OF AUTHORS

Drafting and final approval of protocol: all authors

Screening search results: PTM and RPV

Extracting data: PTM and RPV

Assessing risk of bias: AGMS, DAN and RPV

Entering data into RevMan: PTM and RPV

Carrying out analysis: PTM and RPV

Interpreting the analysis: all authors

General advice on the review: all authors

DECLARATIONS OF INTEREST

Roderick P Venekamp: Roderick Venekamp is an Editor for Cochrane Acute Respiratory Infections and Cochrane ENT, but had no role in the editorial process for this review.

Paul Mick (PTM): none known.

Anne GM Schilder: Professor Anne Schilder is joint Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this review. Her evidENT team at UCL is supported by her NIHR Research Professorship award with the remit to develop a UK infrastructure and programme of clinical research in ENT, Hearing and Balance. Her institution has received a grant from GSK for a study on the microbiology of acute tympanostomy tube otorrhoea.

Desmond A Nunez (DAN): none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review has been based on a published protocol (Lau 2015). Any differences between the protocol and the review can be found below.

Types of interventions

The Types of interventions section has been rephrased for clarity. In our protocol, this section had read as follows:

Intervention

- Grommet insertion (of any type).
- Adenoidectomy is only allowed as a co-intervention when used in both treatment arms.

Comparator

The comparator will be no surgical treatment: either AOM episode-specific treatment with analgesia +/- antibiotics or antibiotic prophylaxis for a minimum period of three months. The main comparison pair will be:

- grommet insertion versus AOM episode-specific course of analgesia with or without antibiotics.

Other possible comparison pairs include:

- grommet insertion with concurrent adenoidectomy versus adenoidectomy alone;
- grommet insertion versus antibiotic prophylaxis for a minimum period of three months.

Data collection and analysis

In the protocol, it was stated that two review authors (LL (protocol author) and PTM) would extract data and enter data into RevMan. This has, however, been performed by three review authors (LL, PTM, RPV).

Subgroup analysis and investigation of heterogeneity

The Subgroup analysis and investigation of heterogeneity section has been rephrased for clarity. In our protocol, this section had read as:

If possible, we will perform pre-planned subgroup analyses even if statistical heterogeneity is not observed. We have planned these analyses as the factors indicated are suspected to be potential effect modifiers. They include:

- type of surgery (grommets only versus grommets and concurrent adenoidectomy);
- presence of middle ear effusion at randomisation or at the time of surgery (yes versus no)

In addition to the subgroups above, we will conduct the following subgroup analysis in the presence of statistical heterogeneity:

- age (below two years of age versus two years and older);
- type of grommet (short-term versus intermediate/long-term).

'Summary of findings' tables

In the final review, we presented outcome data for the "total number of AOM recurrences at six to 12 months post-randomisation" in the 'Summary of findings' table for the comparison grommets versus active monitoring. This outcome was, however, initially not listed in the 'Summary of findings' section of our protocol.

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NOTES

This review supersedes the earlier review 'Grommets (ventilation tubes) for recurrent acute otitis media in children' review (McDonald 2008).

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