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Autoinflation for otitis media with effusion (OME) in children (Review)

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[Intervention Review]

Autoinflation for otitis media with effusion (OME) in children

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ABSTRACT

Background

Otitis media with effusion (OME) is an accumulation of fluid in the middle ear cavity, common amongst young children. The fluid may cause hearing loss. When persistent, it may lead to behavioural problems and a delay in expressive language skills. Management of OME includes watchful waiting, medical, surgical and mechanical treatment. Autoinflation is a self-administered technique, which aims to ventilate the middle ear and encourage middle ear fluid clearance by providing a positive pressure of air in the nose and nasopharynx (using a nasal balloon or other handheld device). This positive pressure (sometimes combined with simultaneous swallow) encourages opening of the Eustachian tube and may help ventilate the middle ear.

Objectives

To assess the efficacy (benefits and harms) of autoinflation for the treatment of otitis media with effusion in children.

Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Register; Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE; Ovid Embase; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 20 January 2023.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-randomised trials in children aged 6 months to 12 years with unilateral or bilateral OME. We included studies that compared autoinflation with either watchful waiting (no treatment), non-surgical treatment or ventilation tubes.

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were determined following a multi-stakeholder prioritisation exercise and were: 1) hearing, 2) OME-specific quality of life and 3) pain and distress. Secondary outcomes were: 1) persistence of OME, 2) other adverse effects (including eardrum perforation), 3) compliance or adherence to treatment, 4) receptive language skills, 5) speech development, 6)

cognitive development, 7) psychosocial skills, 8) listening skills, 9) generic health-related quality of life, 10) parental stress, 11) vestibular function and 12) episodes of acute otitis media. We used GRADE to assess the certainty of evidence for each outcome.

Although we included all measures of hearing assessment, the proportion of children who returned to normal hearing was our preferred method to assess hearing, due to challenges in interpreting the results of mean hearing thresholds.

Main results

We identified 11 completed studies that met our inclusion criteria (1036 participants). The majority of studies included children aged between 3 and 11 years. Most were carried out in Europe or North America, and they were conducted in both hospital and community settings. All compared autoinflation (using a variety of different methods and devices) to no treatment. Most studies required children to carry out autoinflation two to three times per day, for between 2 and 12 weeks. The outcomes were predominantly assessed just after the treatment phase had been completed. Here we report the effects at the longest follow-up for our main outcome measures.

Return to normal hearing

The evidence was very uncertain regarding the effect of autoinflation on the return to normal hearing. The longest duration of follow-up was 11 weeks. At this time point, the risk ratio was 2.67 in favour of autoinflation (95% confidence interval (CI) 1.73 to 4.12; 85% versus 32%; number needed to treat to benefit (NNTB) 2; 1 study, 94 participants), but the certainty of the evidence was very low.

Disease-specific quality of life

Autoinflation may result in a moderate improvement in quality of life (related to otitis media) after short-term follow-up. One study assessed quality of life using the Otitis Media Questionnaire-14 (OMQ-14) at three months of follow-up. Results were reported as the number of standard deviations above or below zero difference, with a range from -3 (better) to +3 (worse). The mean difference was -0.42 lower (better) for those who received autoinflation (95% CI -0.62 to -0.22; 1 study, 247 participants; low-certainty evidence; the authors report a change of 0.3 as clinically meaningful).

Pain and distress caused by the procedure

Autoinflation may result in an increased risk of ear pain, but the evidence was very uncertain. One study assessed this outcome, and identified a risk ratio of 3.50 for otalgia in those who received autoinflation, although the overall occurrence of pain was low (95% CI 0.74 to 16.59; 4.4% versus 1.3%; number needed to treat to harm (NNTH) 32; 1 study, 320 participants; very low-certainty evidence).

Persistence of OME

The evidence suggests that autoinflation may slightly reduce the persistence of OME at three months. Four studies were included, and the risk ratio for persistence of OME was 0.88 for those receiving autoinflation (95% CI 0.80 to 0.97; 4 studies, 483 participants; absolute reduction of 89 people per 1000 with persistent OME; NNTB 12; low-certainty evidence).

Authors' conclusions

All the evidence we identified was of low or very low certainty, meaning that we have little confidence in the estimated effects. However, the data suggest that autoinflation may have a beneficial effect on OME-specific quality of life and persistence of OME in the short term, but the effect is uncertain for return to normal hearing and adverse effects. The potential benefits should be weighed against the inconvenience of regularly carrying out autoinflation, and the possible risk of ear pain.

PLAIN LANGUAGE SUMMARY

Autoinflation for otitis media with effusion (OME or 'glue ear') in children

Key messages

Due to a lack of robust evidence, we are uncertain whether autoinflation has any effect on hearing. Using autoinflation two to three times per day may slightly reduce the number of children with OME after three months follow-up. Scores on a questionnaire that looked at quality of life for people with OME were also better for children who carried out autoinflation. However, some children may experience pain when using autoinflation.

What is OME?

Otitis media with effusion (OME, sometimes called 'glue ear') is a common condition affecting young children. Fluid collects in the middle ear, causing hearing impairment. As a result of their poor hearing, children may have behavioural difficulties and delays in their speech development.

How is OME treated?

Most of the time, OME does not need any treatment and the symptoms will get better with time. In children with persistent OME, different treatments have been explored, including medications or surgery. Autoinflation is a technique where children blow air out of their nose against a pressure device (such as a balloon). This forces air back through the Eustachian tube, which connects the back of the nose to the middle ear. Opening of this tube may allow the middle ear fluid to drain away.

What did we want to find out?

We wanted to identify whether autoinflation was better than no treatment, medical treatment or surgical treatment for children with OME.

We also wanted to see if there were any unwanted effects associated with autoinflation.

What did we do?

We searched for studies that compared autoinflation with no treatment or other treatments in children with OME. We compared and summarised the study results, and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 11 studies that involved 1036 children with OME. Most of the studies were in children aged over three years old, and only lasted for up to three months. They compared autoinflation (carried out two to three times per day) with no treatment.

We are uncertain whether autoinflation has any effect on hearing, as there was very little evidence about this.

Autoinflation may slightly reduce the number of children who still have OME after three months of follow-up, and may result in an improvement in quality of life.

Children who use autoinflation may experience more ear pain than those who do not receive any treatment, but only one study assessed this, and the number of children with pain was small (4.4% compared to 1.3% in those who did not have treatment).

What are the limitations of the evidence?

We have very little information about the longer-term effects of autoinflation. A variety of different techniques and devices are available for autoinflation, and we do not know if some of these are more effective than others.

How up-to-date is this evidence?

The evidence is up-to-date to January 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Autoinflation compared to no treatment for otitis media with effusion (OME) in children

Autoinflation compared to no treatment for otitis media with effusion (OME) in children

Patient or population: otitis media with effusion (OME) in children aged 6 months to 12 years
Setting: outpatient
Intervention: autoinflation
Comparison: no treatment

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without autoinflation	With autoinflation	Difference		
Proportion of children whose hearing is normal Follow-up: up to 3 months № of participants: 94 (1 RCT)	RR 2.67 (1.73 to 4.12)	31.9%	85.2% (55.2 to 100)	53.3% more (23.3 more to 68.1more)	⊕⊝⊝⊝ Very low[1,2,3]	The evidence is very uncertain about the effect of autoinflation on return to normal hearing at 3 months.
Disease-specific quality of life Mean difference in standardised OMQ-14 scores (lower score is favourable) Follow-up: 3 months (short-term) № of participants: 247 (1 RCT)	—	—	—	MD 0.42 lower (0.62 lower to 0.22 lower)	⊕⊕⊝⊝ Low[1,4]	The evidence suggests that autoinflation may improve disease-specific quality of life at 3 months. The study authors reported a change of 0.3 as clinically meaningful.
Pain and distress related to the procedure: otalgia Follow-up: 3 months (short-term) № of participants: 320 (1 RCT)	RR 3.50 (0.74 to 16.59)	1.3%	4.4% (1 to 22.6)	3.1% more (0.3% fewer to 19.5% more)	⊕⊝⊝⊝ Very low[1,5]	Autoinflation may slightly increase the risk of ear pain (otalgia), but the evidence is very uncertain.
Persistence of OME Follow-up: 3 months (short-term)	RR 0.88 (0.80 to 0.97)	74.1%	65.2% (59.3 to 71.9)	8.9% fewer (14.8 fewer to 2.2 fewer)	⊕⊕⊝⊝ Low[1,6]	The evidence suggests that autoinflation may slightly reduce persistence of OME at 3 months.

№ of participants: 483 (4 RCTs)				

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

CI: confidence interval; **OME:** otitis media with effusion; **OMQ-14:** Otitis Media Questionnaire-14; **RCT:** randomised controlled trial; **RR:** risk ratio

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

[1]Downgraded by one level for a risk of performance bias.
[2]Downgraded by one level for indirectness, as no description of 'normal hearing' was provided.
[3]Downgraded by one level for imprecision, as the optimal information size (OIS) was not reached (< 300 events).
[4]Downgraded by one level for imprecision, as the OIS was not reached (< 400 participants).
[5]Downgraded by two levels for imprecision, as the OIS was not reached (< 300 events) and the confidence interval crosses two decision thresholds (RR 0.8 and 1.25).
[6]Downgraded by one level for a risk of detection bias.

BACKGROUND

Description of the condition

Otitis media with effusion (OME) is a common condition in early childhood. The condition, also known as 'glue ear' and serous otitis media, is defined as "the presence of fluid in the middle ear without signs or symptoms of acute infection" (Rosenfeld 2016).

A key clinical feature of OME is hearing loss, due to decreased mobility of the tympanic membrane and consequent loss of sound conduction (Rosenfeld 2016). When hearing loss persists, this may affect speech and language development, and lead to behavioural problems in some children (NICE 2008). Other symptoms that may be attributable to OME include balance (vestibular) problems and ear discomfort (Rosenfeld 2016). When symptoms persist, they may lead to poor school performance and affect a child's daily activities, social interactions and emotions, possibly leading to a poorer quality of life for the child (Rosenfeld 2000).

It is thought that up to 80% of children have had OME by the age of four years, but a decline in prevalence is observed for children beyond six years of age (Williamson 2011). Most episodes of OME in children resolve spontaneously within three months, however approximately 35% of children will have more than one episode of OME and, furthermore, 5% to 10% of episodes will last for more than a year (Rosenfeld 2016). Children with OME following an episode of untreated acute otitis media have a 59% rate of resolution by one month rising to 74% by three months, while children with newly diagnosed OME of unknown duration demonstrate a resolution rate of 28% by three months and up to 42% by six months (Rosenfeld 2003). The condition is more prevalent in children with craniofacial syndromes, such as Down syndrome or cleft palate (Flynn 2009 [https://revman.cochrane.org/#/7673210803135753 79/dashboard/htmlView/current?revertEnabled=false&versionWithProductionChanges=false#REF-Flynn-2009]; Maris 2014 [https://revman.cochrane.org/#/7673210803135753 79/dashboard/htmlView/current?revertEnabled=false&versionWithProductionChanges=false#REF-Maris-2014]). Atopy has been considered a potential risk factor for OME in children (Kreiner-Møller 2012; Marseglia 2008; Zernotti 2017), as have parental smoking, attendance at day care and low socioeconomic status (Dewey 2000; Marx 1995; Rovers 2006).

Diagnosis of OME is typically by clinical examination including (pneumatic) otoscopy and/or tympanometry in primary care. Following diagnosis, there will often be a period of active observation for at least three months. During the observation period the care provider may offer a non-surgical intervention such as hearing aids or autoinflation. The National Institute for Health and Care Excellence (NICE) and the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) do not currently recommend the use of antibiotics, antihistamines, decongestants or corticosteroids for OME as there is insufficient evidence to suggest they are effective treatments (NICE 2008; Rosenfeld 2016). If OME has not resolved within the three-month observation period, the child may be referred for further management/active intervention. This may include hearing aid provision or review by an ENT surgeon for consideration for myringotomy, ventilation tubes insertion and/or adenoidectomy. The choice of active intervention varies considerably. Earlier active intervention may be considered for children at increased risk of developmental difficulties (see Rosenfeld 2016 for a list of 'at-risk' factors).

This Cochrane Review focusses on autoinflation as a treatment for OME in children. This review forms part of a suite of five reviews of OME treatment, which will address those interventions identified in a prioritisation exercise as being most important and in need of up-to-date Cochrane Reviews, namely myringotomy and insertion of ventilation tubes, adenoidectomy with or without ventilation tubes, topical and oral steroids, autoinflation and antibiotics (Cochrane ENT 2020).

Description of the intervention

Autoinflation is a technique that forces the Eustachian tube to open by raising intranasal pressure. Its main goal is to aerate the middle ear cavity and equalise pressures in both sides of the tympanic membrane. Autoinflation can be achieved in a number of ways: forced exhalation with mouth and nose closed, for example the Valsalva manoeuvre; blowing up of a balloon through each nostril (demonstrated here); or use of a device that utilises Politzeration, which involves blowing air up the nose while the patient swallows. There are commercial devices available, such as the Otovent nasal balloon device, and the air-pump EarPopper device (RACGP 2016). Given the manipulation required for successful autoinflation, it is considered suitable for children aged four years and over (Williamson 2015). It is a low-cost intervention that can be used during an active observation period post-diagnosis and may avoid the need for a surgical intervention (NICE 2016).

How the intervention might work

The aim of autoinflation is to introduce air into the middle ear, via the Eustachian tube, thus equalising the pressures either side of the tympanic membrane, and promoting drainage of fluid (Perera 2013). Each time the procedure is repeated, it promotes aeration of the middle ear, thereby mitigating any abnormal Eustachian tube function until normal functioning returns (Berkman 2013).

Why it is important to do this review

A Cochrane Review assessing the effects of autoinflation on OME for adults and children was published in 2013 (Perera 2013), updating a review originally published in 2006. Searches were run to 2013 and the review included eight studies. The studies were small and had a short follow-up. The review authors concluded that "it is reasonable to consider autoinflation whilst awaiting natural resolution of otitis media with effusion".

A scoping search undertaken in 2020 identified seven abstracts published since 2013, including five publications assessing the EarPopper device and two publications relating to nasal balloon autoinflation with the Otovent device. Searches also identified two clinical trial registrations relating to a Swedish study of the Otovent device (Ejnell 2015a; Ejnell 2015b). A prioritisation exercise undertaken in 2020 identified a review of autoinflation for OME as a top priority (Cochrane ENT 2020). Given the number of relevant studies published in recent years, it is timely to update the evidence.

This review has been produced as part of a suite of reviews, which also inform a NICE guideline on the management of OME in children (NICE 2023). The population of interest was therefore confined to

children for consistency across the suite of reviews, and to align with the NICE guideline update.

OBJECTIVES

To assess the effects (benefits and harms) of autoinflation for otitis media with effusion (OME) in children.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-randomised trials (where studies were designed as RCTs, but the sequence generation for allocation of treatment used methods such as alternative allocation, birth dates and alphabetical order).

Types of participants

The population of interest was children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME). If a study included children aged younger than 6 months and older than 12 years, we planned to only include the study if the majority of children fit our inclusion criteria, or if the study authors presented outcome data according to age group. We included all children regardless of any comorbidity such as Down syndrome or cleft palate. Clinical diagnosis of OME was confirmed by oto(micro)scopy or tympanometry, or both.

Types of interventions

Intervention

Autoinflation by any method.

Comparator

We planned to assess the following comparisons:

- autoinflation versus watchful waiting;
- autoinflation versus non-surgical treatment;
- autoinflation versus ventilation tubes.

If study participants had received other treatments (for example, intranasal steroids, oral steroids, antibiotics, mucolytics or decongestants), we included the study if both arms received identical treatments.

Types of outcome measures

We analysed the following outcomes in the review, but we did not use them as a basis for including or excluding studies. We assessed all outcomes at very short term (< 6 weeks), short term (> 6 weeks to ≤ 3 months), medium term (> 3 months to ≤ 1 year) and long term > 1 year.

Primary outcomes

- Hearing:
  - Proportion of children whose hearing has returned to normal, with normal hearing defined as 20 dB HL or less (assessed using age-appropriate tests).
  - Hearing threshold.

It was anticipated that study data for these outcomes may be derived from a variety of assessment methods. To avoid loss of important evidence, we extracted all such data for analysis. However, we gave consideration to the appropriateness of pooling different types of data in meta-analysis. Our selection of primary outcomes is based principally upon clinical importance, but also permits applicability across a variety of age-appropriate assessment methods and considers the types of outcome data that are most likely to be available. Accordingly, we regard the proportion of participants whose hearing has returned to normal as the most important measure of hearing impact. We consider medium- and long-term outcome data as the most clinically important.

- Disease-specific quality of life measured using a validated instrument, for example:
  - OM8-30 (Haggard 2003);
  - Otitis Media-6 (Rosenfeld 1997).
- Adverse events - pain and distress caused by the procedure, including otalgia.

Secondary outcomes

- Presence/persistence of OME.
- Adverse events - measured by the number of participants affected:
  - eardrum perforation.
- Compliance.
- Receptive language skills, measured using a validated scale, for example:
  - Peabody Picture Vocabulary Test - Revised (Dunn 2007);
  - Reynell Developmental Language Scales (relevant domains) (Reynell 1985);
  - Preschool Language Scale (PLS) (relevant domains) (Zimmerman 1992);
  - Sequenced Inventory of Communication (SCID) (relevant domains) (Hedrick 1984).
- Speech development, or expressive language skills, measured using a validated scale, for example:
  - Schlichting test (Schlichting 2010);
  - Lexi list (Schlichting 2007);
  - Reynell Developmental Language Scales (relevant domains) (Reynell 1985);
  - PLS (relevant domains) (Zimmerman 1992);
  - SCID (relevant domains) (Hedrick 1984).
- Cognitive development, measured using a validated scale, for example:
  - Griffiths Mental Development Scales (Griffiths 1996);
  - McCarthy General Cognitive Index (McCarthy 1972);
  - Bayley Scales of Infant and Toddler Development (Bayley 2006).
- Psychosocial outcomes, measured using a validated scale, for example:
  - Social Skills Scale of the Social Skills Rating System (Gresham 1990);
  - Child Behaviour Checklist (Achenbach 2011);
  - Strengths and Difficulties Questionnaire (Goodman 1997);
  - Pediatric Symptom Checklist (Jellinek 1988).

- Listening skills, for example listening to stories and instructions effectively. Given that there are few validated scales to assess listening skills in children with OME, we included any methods used by trialists.
- Generic health-related quality of life assessed using a validated instrument, for example:
  - EQ-5D (Rabin 2001);
  - TNO AZL Children's QoL (TACQOL) (Verrips 1998);
  - TNO AZL Pre-school children QoL (TAPQOL) (Fekkes 2000);
  - TNO AZL Infant Quality of Life (TAIQOL) (TNO 1997);
  - Infant Toddler Quality of Life Questionnaire (ITQOL) (Landgraf 1994);
  - Child Health Questionnaire (CHQ) (Landgraf 1996).
- Parental stress, measured using a validated scale, for example: Parenting Stress Index (Abidin 1995).
- Vestibular function:
  - balance;
  - co-ordination.
- Number of doctor-diagnosed acute otitis media (AOM) episodes within a specified time frame.

These outcomes were identified as the most important in two studies that aimed to develop a core outcome set for children with OME (Bruce 2015; Liu 2020). As this review forms part of a suite of reviews of interventions for OME, not all outcomes will be relevant for all reviews.

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. We contacted original authors for clarification and further data if trial reports were unclear, and we arranged translations of papers where necessary. The date of the search was 20 January 2023.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Register (searched via the Cochrane Register of Studies to 20 January 2023);
- the Cochrane Central Register of Controlled Trials (CENTRAL 2023, Issue 1) (searched via the Cochrane Register of Studies to 20 January 2023);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 20 January 2023);
- Ovid EMBASE (1974 to 20 January 2023);
- Web of Science (1945 to 20 January 2023);
- ClinicalTrials.gov, www.clinicaltrials.gov:
  - searched via the Cochrane Register of Studies to 20 January 2023;
  - searched via www.clinicaltrials.gov to 20 January 2023;
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), https://apps.who.int/trialsearch/:
  - searched via the Cochrane Register of Studies to 20 January 2023;
  - searched via https://apps.who.int/trialsearch/ to 20 January 2023.

The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. The search strategies were designed to identify all relevant studies for a suite of reviews on various interventions for OME. 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 Technical Supplement to Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1) (Lefebvre 2020). 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. The Information Specialist also ran non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

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

Data collection and analysis

Selection of studies

The Cochrane ENT Information Specialist used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components:

- Known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as 'a RCT' or as 'not a RCT'.
- The machine learning classifier (RCT model) (Wallace 2017), available in the Cochrane Register of Studies (CRS-Web), which assigns a probability of being a true RCT (from 0 to 100) to each citation. Citations that are assigned a probability score below the cut-point at a recall of 99% are assumed be non-RCTs. For those that scored on or above the cut-point we either manually dual screened these results or sent them to Cochrane Crowd for screening.
- Cochrane Crowd is Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. For more information about Screen4Me and the evaluations that have been done, please go to the Screen4Me website on the Cochrane Information Specialist's portal and see Marshall 2018; McDonald 2017; Noel-Storr 2018; Thomas 2017.

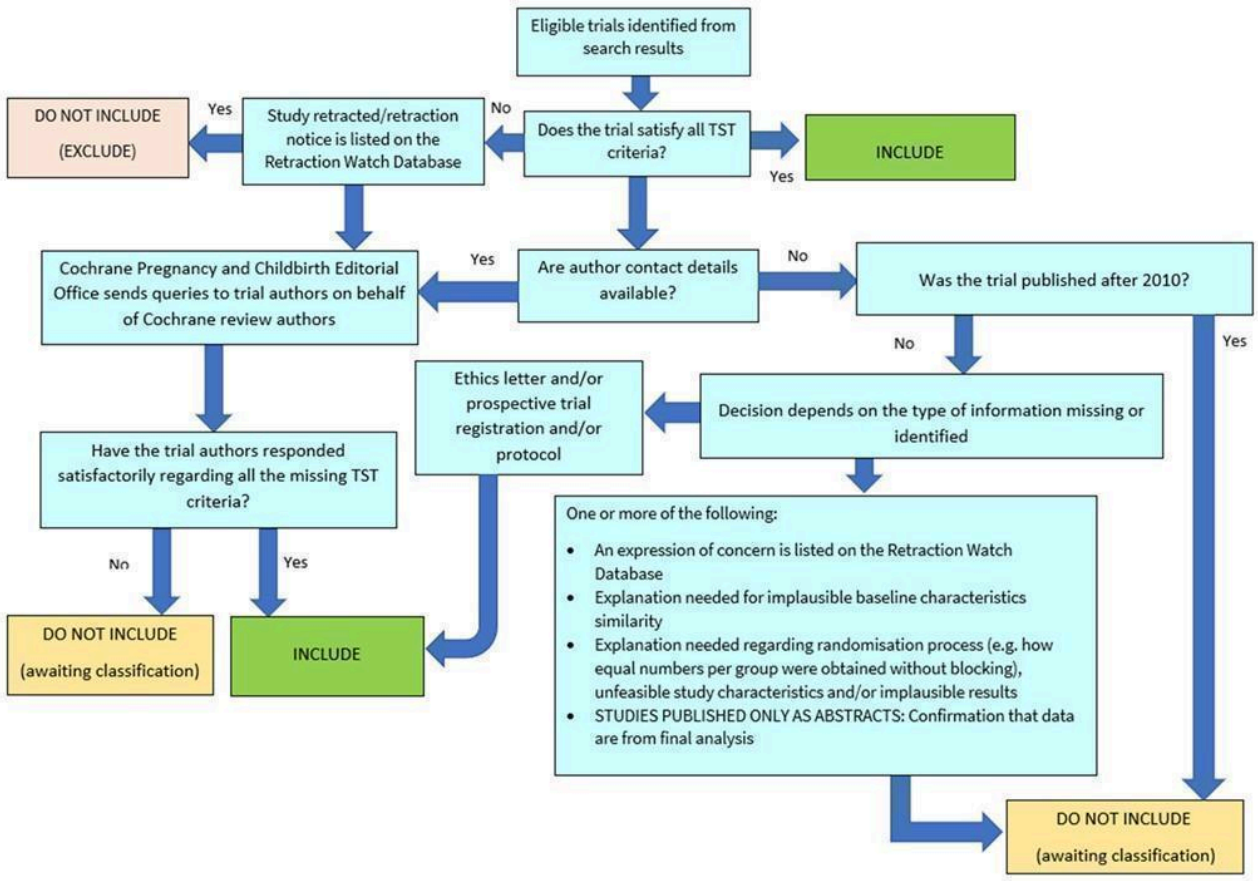
Two review authors (KG, CM) independently screened the remaining titles and abstracts to identify potentially relevant studies. At least two review authors (of KG, SM, CM and KW) then independently evaluated the full text of each potentially relevant study to determine whether it met the inclusion/exclusion criteria for this review. Any differences were resolved by discussion and consensus, with the involvement of a third author where necessary.

Screening eligible studies for trustworthiness

Two review authors (of KG, CM, MR, KW) used the screening tool developed by Cochrane Pregnancy and Childbirth to assess

the trustworthiness of the included studies. This tool includes specified criteria to identify studies that are considered sufficiently trustworthy to be included in the review (see Appendix 2). The process is outlined in Figure 1. We had planned to exclude studies from the main analysis if there were concerns when using this tool.

Figure 1. The Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool



However, for this review we identified some concerns with many of the studies that were assessed as suitable for inclusion. Issues that arose included a lack of prospective trial registration for studies published after 2010 (Banigo 2016; Bidarian-Moniri 2014; Scadding 2014), equal numbers allocated to the control and intervention groups without the use of blocked randomisation (Arick 2005; Banigo 2016; Ercan 2005; Stangerup 1992), and one study where the results on change in hearing were considered implausible (Arick 2005). In addition, some studies failed to describe the baseline characteristics of participants adequately, therefore we were unable to establish whether there was excessive similarity between the groups (Arick 2005; Brooker 1992; Ercan 2005; Stangerup 1992). Only three of the included studies had no concerns when using this tool: Chan 1989, Williamson 2015a and Williamson 2015b.

We attempted to clarify these issues with the authors, where possible, but were not able to obtain additional information. However, we are uncertain whether the concerns highlighted by the trustworthiness tool represent genuine issues with the reliability of the data, or whether the tool may be highly sensitive to trial features that may or may not represent untrustworthy data. We note that this tool, and other tools used for the same purpose, have not yet been validated for use.

We therefore took the decision to include all of these studies in the main analyses for this review. We have undertaken a sensitivity analysis where relevant, to exclude studies that failed to meet the criteria for this tool.

Data extraction and management

At least two review authors (of KG, CM, MR, KW) independently extracted outcome data from each study using a standardised data collection form. Where a study had more than one publication, we retrieved all publications to ensure complete extraction of data. Any discrepancies in the data extracted by the two authors were checked against the original reports, and differences were resolved through discussion and consensus, with recourse to a third author where necessary. If required, we contacted the study authors for clarification. We included key characteristics of the studies, such as the study design, setting, sample size, population and the methods for defining or collecting outcome data in the studies.

We extracted data on study findings according to treatment assignment, irrespective of whether study participants complied with treatment or received the treatment to which they were randomised.

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

- For continuous data: the mean values, standard deviation and number of patients for each treatment group at the different time points for outcome measurement. Where endpoint data were not available, we extracted the values for change-from-baseline data instead. If values for the individual treatment groups were not reported, where possible we extracted summary statistics (e.g. mean difference) from the studies.
- For binary data: we extracted information on the number of participants experiencing an event, and the number of participants assessed at that time point. If values for the individual treatment groups were not reported, where possible we extracted summary statistics (e.g. risk ratio) from the studies.
- For ordinal scale data: we did not include any data from an ordinal scale in this review.

We pre-specified time points of interest for the outcomes in this review. Where studies reported data at multiple time points, we took the longest available follow-up point within each of the specific time frames. For example, if a study reported an outcome at 4 months, 8 months and 12 months of follow-up then we included the 12-month data for the time point > 3 months to ≤ 1 year. For adverse events, it was anticipated that some studies may report frequency data for events and it may not be possible to determine whether these events occurred in one patient on one occasion or more than one occasion. In such circumstances we reported the data narratively.

Assessment of risk of bias in included studies

At least two authors (of KG, CM, MR, KW) undertook assessment of the risk of bias of the included studies independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

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

We used the Cochrane risk of bias tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the study and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

We summarised dichotomous data, such as presence of OME, as risk ratios (RR) and 95% confidence intervals (CI) and we summarised continuous data as a mean difference (MD) and 95% CI. For the outcomes presented in the summary of findings tables, we provide both the relative and absolute measures of effect.

Unit of analysis issues

We planned to include studies that randomised by participant or by cluster, but no cluster-randomised studies were identified as part of this review. We did include cross-over studies, but used data from the first phase of the trial only, prior to cross-over.

For this review we anticipated that the unit of analysis would be the child. However, some studies reported findings by ear and therefore we have used both the child and ear as the unit of analysis.

All studies randomised participants to autoinflation or no treatment (watchful waiting) at the level of the child - as this is an intervention that affects both ears. Some studies in this review included children with bilateral OME - either exclusively (Bidarian-Moniri 2014; Blanshard 1993), or as a proportion of included participants (Arick 2005; Brooker 1992; Chan 1989; Ercan 2005; Stangerup 1992; Williamson 2015a). This gave rise to a number of issues regarding the unit of analysis, as some studies reported outcomes (particularly the persistence of OME) for each ear.

We considered that outcomes for ears within the same individual were likely to be correlated - for example, if a child had resolution of OME in one ear, they may be more likely to experience resolution in the contralateral ear. There is not complete independence between ears of the same individual. Standard meta-analysis techniques assume that all data are independent. Therefore inclusion of the raw data (for the number of ears) is likely to overestimate the precision of any effect, and result in an excessively narrow confidence interval.

To account for this correlation, we used the suggested methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011), which are more commonly employed in the analysis of cluster-randomised trials. We treated individuals who contributed two ears to the analysis (all of those with bilateral disease) as a 'cluster' of two data points. We then attempted to account for the correlation in these clusters, by assuming a certain correlation between ears of the same individual. We could not identify a figure for this correlation in the published literature, so we used an estimated correlation of 0.5 in the main analysis, but conducted sensitivity analyses using correlations of 0 and 1, to test the limits of this assumption. We then reduced the effective size of the trials by the 'design effect' - which accounts for correlation between ears, and the average cluster size (which would be 2 for trials where all children had bilateral disease, and less than 2 if trials included a mixture of children with bilateral and unilateral disease).

Some trials also reported data both as a 'per ear' analysis, and as a 'per child' analysis - where persistence was regarded as the presence of OME in either at least one ear, or all affected ears for children with bilateral disease. Where possible, we included these data as part of a sensitivity analysis, to assess whether the overall results were substantially altered.

Dealing with missing data

We attempted to contact study authors by email where data on an outcome of interest to the review were not reported but the methods described in the paper suggest that the outcome was assessed, or if not all data required for meta-analysis were reported.

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the included studies for potential differences between them in the types of participants recruited, interventions or controls used, and the outcomes measured. We assessed statistical heterogeneity by

considering both the I^2 statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance (with values over 50% suggesting substantial heterogeneity), and the P value from the Chi^2 test (Higgins 2021).

Assessment of reporting biases

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

Outcome reporting bias (within-study reporting bias)

We assessed within-study reporting bias by comparing the outcomes reported in the published report against the study protocol or trial registry, whenever this could be obtained. If the protocol or trial registry entry was not available, we compared the outcomes reported to those listed in the methods section. If results are mentioned but not reported adequately in a way that allows analysis (e.g. the report only mentions whether the results were statistically significant or not), bias in a meta-analysis is likely to occur. We then sought further information from the study authors. If no further information could be found, we noted this as being a 'high' risk of bias when the risk of bias tool was used. If there was insufficient information to judge the risk of bias we noted this as an 'unclear' risk of bias (Handbook 2011).

Publication bias (between-study reporting bias)

If we were able to pool 10 or more studies in a single analysis, we planned to produce a funnel plot to explore possible publication biases. We planned to test for asymmetry using Egger's test (Egger 1997). However, we did not perform this test due to the paucity of data available for meta-analysis.

Data synthesis

Where two or more studies reported the same outcome we performed a meta-analysis using Review Manager 5 (RevMan 2014). We reported pooled effect measures for dichotomous outcomes as a risk ratio (RR) using the Mantel-Haenszel methods. For continuous outcomes measured using the same scales we reported the mean difference (MD). We used a random-effects model.

Where it was not possible to pool the findings from studies in a meta-analysis, we present the results of each study and provide a narrative synthesis of findings.

Subgroup analysis and investigation of heterogeneity

We proposed the following subgroup analyses if sufficient data were available in study reports:

- children with mild hearing loss versus moderate or worse;
- children with allergy versus those without (using the trialists own definition);
- children aged six years and younger versus children older than six years;
- different types of autoinflation device;
- children with previous ventilation tubes versus those without ventilation tubes;
- children with cleft palate versus children without;
- children with Down syndrome versus children without.

However, we did not find any data suitable for conducting these subgroup analyses. No studies provided subgroup data for children with different features (for example, for those with mild hearing loss, compared to those with moderate or worse hearing loss). Many of the trials did not provide sufficient background information (for example, on hearing level) for us to conduct subgroup analysis at the level of the individual study. Where data were provided, trials often recruited a mixed population that encompassed all subgroups (for example, most trials recruited children aged 3 to 10 years, not specifically children aged ≤ 6 years, or older than 6 years).

We did have information on the different types of autoinflation device used in the trials. However, as many studies included custom-made devices, we were unable to group these in a meaningful way to compare devices in a subgroup analysis. Therefore we took the decision to present only the summary effect.

Sensitivity analysis

We planned to carry out the following sensitivity analyses to assess whether our findings were robust to decisions made regarding analyses and inclusion of studies:

- Impact of model chosen: we compared the results using a random-effects versus a fixed-effect model.
- Inclusion of studies at high risk of bias: we planned to compare the results including all studies versus excluding studies at overall high risk of bias, that is four or more of the seven domains of bias are rated as high risk (see Assessment of risk of bias in included studies). However, no study was rated at high risk of bias for four or more domains, therefore we did not conduct this analysis.
- Exclusion of studies with concerns over trustworthiness, as assessed by the Trustworthiness Screening Tool (Figure 1).

Summary of findings and assessment of the certainty of the evidence

At least two authors (KG, CM, KW) independently used the GRADE approach to rate the overall certainty of evidence using GRADEpro GDT (gradepro.org/). The certainty of evidence reflects the extent to which we are confident that an estimate of effect is correct, and we have applied this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high certainty of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low certainty implies that any estimate of effect obtained is very uncertain.

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

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

We include a summary of findings table, constructed according to the recommendations described in Chapter 10 of the *Cochrane*

Handbook for Systematic Reviews of Interventions (Higgins 2021), for the following comparison(s):

- autoinflation versus watchful waiting;
- autoinflation versus non-surgical treatment;
- autoinflation versus ventilation tubes.

We include the following outcomes in the summary of findings table:

- hearing;
- disease-specific quality of life;
- adverse events - pain and distress caused by the procedure (otalgia);
- presence/persistence of OME.

We prioritised data from the longest available time point for presentation in the summary of findings tables.

RESULTS

Description of studies

Results of the search

The searches (September 2021 and January 2023) retrieved a total of 7441 records. This reduced to 4157 after the removal of duplicates. The Cochrane ENT Information Specialist sent all 4157 records to the Screen4Me workflow. The Screen4Me workflow identified 84 records as having previously been assessed: 50 had been rejected as not RCTs and 34 had been assessed as possible RCTs. The remaining 4073 references were sent to the RCT classifier, which rejected an additional 1514 records as not RCTs (with 99% sensitivity). The Cochrane Crowd assessed 2443 of the remaining references, rejecting 1313 as not RCTs and identifying 1130 as possible RCTs. Following this process, the Screen4Me workflow had rejected 2877 records and identified 1280 possible RCTs for title and abstract screening (see Table 1).

We identified 76 additional duplicates. We screened the titles and abstracts of the remaining 1204 records. We discarded 886 records and assessed 318 full-text records. We subsequently discarded an additional 266 records and identified an additional five duplicates.

We excluded 25 records with reasons recorded in the review (see Excluded studies and Characteristics of excluded studies).

We included 11 studies (15 records) where results were available (Arick 2005; Banigo 2016; Bidarian-Moniri 2014; Blanshard 1993; Brooker 1992; Chan 1989; Ercan 2005; Scadding 2014; Stangerup 1992; Williamson 2015a; Williamson 2015b). See Characteristics of included studies.

We identified five ongoing studies (six records). See Characteristics of ongoing studies for further details of these studies.

One study is awaiting classification as we were unable to obtain the full text for assessment (Tawfik 2002).

A flow chart of study retrieval and selection is provided in Figure 2.

Figure 2.

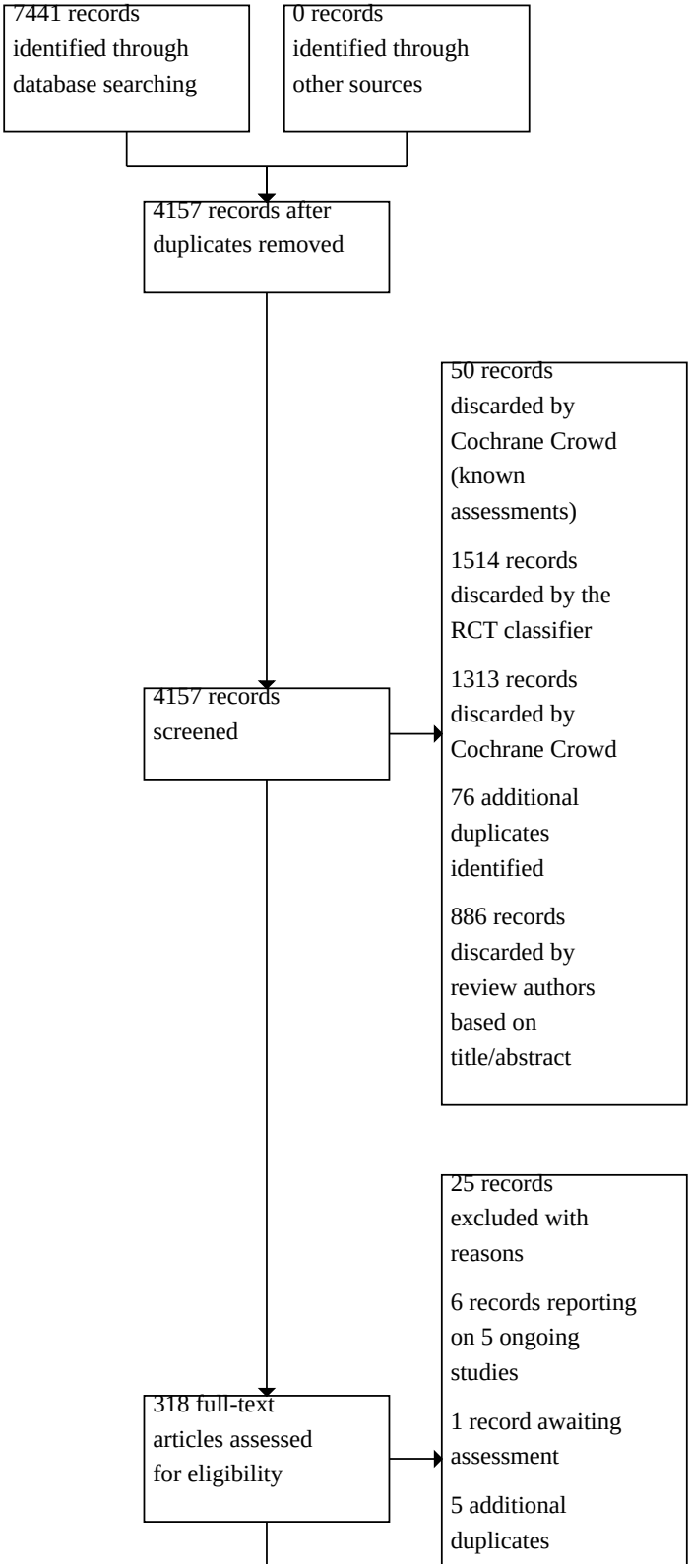
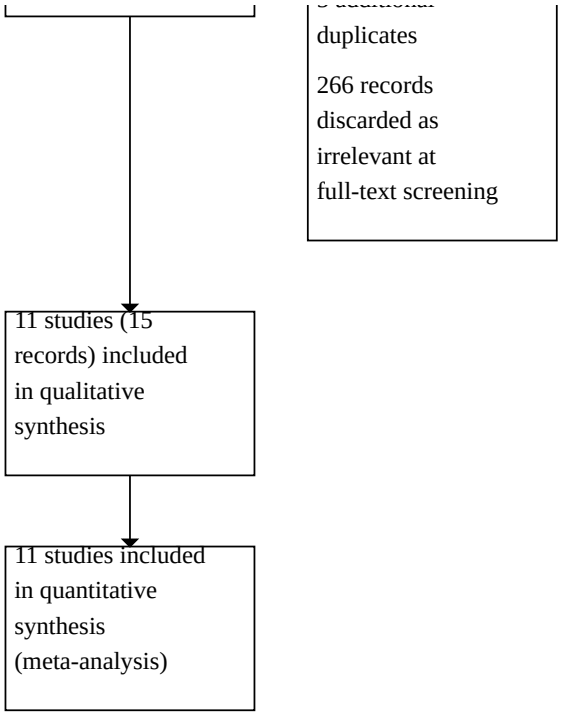


Figure 2. (Continued)



Included studies

We included 11 completed RCTs (Arick 2005; Banigo 2016; Bidarian-Moniri 2014; Blanshard 1993; Brooker 1992; Chan 1989; Ercan 2005; Scadding 2014; Stangerup 1992; Williamson 2015a; Williamson 2015b). One RCT, Williamson 2015b, was a pilot trial for another included RCT (Williamson 2015a).

A summary of key participant characteristics, interventions, outcomes measured and follow-up time is provided in Table 2.

Study design

All included trials were RCTs; one was a cross-over trial so we only used data from the first stage of the trial, prior to cross-over (Bidarian-Moniri 2014). While all studies recruited children, eight presented some findings by ear (Arick 2005; Bidarian-Moniri 2014; Blanshard 1993; Brooker 1992; Chan 1989; Ercan 2005; Stangerup 1992; Williamson 2015a). The majority of studies followed participants for three months. The shortest follow-up time was two weeks (Chan 1989) and the longest was two years (Scadding 2014).

Participants

A total of 1036 participants were included. The majority of studies aimed to recruit children aged approximately 3 to 11 years old. Chan 1989 recruited children up to the age of 18 years, although most were aged three to six years. Most studies recruited children with at least a three-month history of OME (Banigo 2016; Bidarian-Moniri 2014; Blanshard 1993; Chan 1989; Scadding 2014; Stangerup 1992; Williamson 2015a; Williamson 2015b). Ercan 2005 recruited children with a four-week history of OME, Arick 2005 recruited children with a two-month history of OME, and Brooker 1992 did not report the duration of OME. Some studies included children with bilateral disease, whilst others recruited participants with either bilateral or unilateral OME.

Interventions and comparisons

We identified studies that assessed two of our three comparisons of interest.

Comparison 1: autoinflation versus no treatment (watchful waiting)

Eleven completed RCTs assessed this comparison:

- Arick 2005 (94 participants, 174 ears)
- Banigo 2016 (30 participants)
- Bidarian-Moniri 2014 (45 participants)
- Blanshard 1993 (85 participants)
- Brooker 1992 (40 participants, 78 ears)
- Chan 1989 (41 participants)
- Ercan 2005 (60 participants, 93 ears)
- Scadding 2014 (200 participants)
- Stangerup 1992 (100 participants)
- Williamson 2015a (320 participants)
- Williamson 2015b (21 participants)

All provided data we could use in this review except for Scadding 2014, which did not provide data for any of our outcomes of interest.

Of these 11 trials, five used an Otovent as the autoinflation intervention (Blanshard 1993; Ercan 2005; Scadding 2014; Williamson 2015a; Williamson 2015b), one used an EarPopper (Banigo 2016), and one used a modified Politzer device (Arick

2005). Three trials used devices designed by the trial authors (Bidarian-Moniri 2014; Brooker 1992; Stangerup 1992) and one used a modified Valsalva technique (Chan 1989).

In nine trials, the comparison group received no treatment (Arick 2005; Banigo 2016; Bidarian-Moniri 2014; Blanshard 1993; Brooker 1992; Chan 1989; Stangerup 1992; Williamson 2015a; Williamson 2015b). In one trial, both the intervention and control group were treated with nasal saline irrigation three times a day for six weeks (Ercan 2005), and in the trial Scadding 2014 there were four treatment arms including autoinflation, autoinflation and nasal steroids, nasal steroids and placebo.

Three ongoing studies are investigating this comparison but provide no usable data for this current review (INFLATE (ACTRN12617001652369); NCT00393159; NCT05324696). INFLATE (ACTRN12617001652369) uses Otovent as the intervention and the comparison is usual care, while NCT02038400 uses EarPopper and the comparison is no treatment. NCT05324696 uses a custom-made device (based on the one used by Bidarian-Moniri 2014), and will compare this to the use of a sham device.

Comparison 2: autoinflation versus ventilation tubes

Two ongoing studies will assess this comparison but do not provide any data we could use (NCT02038400; NCT02546518). For one trial, autoinflation is achieved using a Kinetube, and the other will use a custom-made device, similar to that used by Bidarian-Moniri 2014.

Outcomes

Hearing

Assessment of hearing varied across the studies. Two studies considered the proportion of children whose hearing returned to normal. Normal hearing was defined in one study as a hearing threshold of < 20 dB HL (Bidarian-Moniri 2014), and simply stated as 'normal hearing' with no definition by Arick 2005. Three other studies measured the mean hearing level using pure tone audiometry and reported this as a pure tone average, or as separate values for the different frequencies.

Three studies provided some data related to hearing, which we could not use in our analyses. Banigo 2016 reported on the number of children who were no longer listed for ventilation tube insertion, as their hearing had improved, and they failed to meet the criteria for ventilation tube insertion. However, the threshold used for this appeared to be a hearing threshold of < 25 dB HL, which may not be regarded as 'normal hearing'. In addition, other factors were taken into account when assessing whether ventilation tubes should be fitted. Therefore we considered that these data could not be used as a surrogate measure for 'children with normal hearing'. Brooker 1992 reported on the number of children with improvement in hearing (10 dB HL in the pure tone audiogram frequencies from 250 Hz to 2000 Hz) and who developed a peak in a previously flat tympanogram. As this only considers 'improvement', these data will not include all children with normal hearing at the end of follow-up, therefore they were not included. Scadding 2014 reported a composite outcome of the proportion of children who had persistent hearing loss ≥ 30 dB HL, or grommet insertion, by the time of follow-up.

Disease-specific health-related quality of life

This was reported by only one of the included studies, using the Otitis Media Questionnaire-14 (OMQ-14) (Williamson 2015a).

Pain and distress at the time of the procedure

This broad outcome measure was not reported by any of the included studies. However, we considered that 'otalgia' should be viewed as part of this outcome measure. One study did report on the presence of otalgia in both groups (Williamson 2015a).

Presence/persistence of OME

Trial authors often described "resolution" of OME (rather than persistence), and this was frequently assessed by tympanometry. For example, Williamson 2015a defined resolution of OME as "a change from at least one type B (fluid) to A/C1 (clear) tympanogram". Where studies reported resolution we took the inverse data to assess presence or persistence of OME.

Adverse events

Five studies reported some information regarding adverse events (Banigo 2016; Bidarian-Moniri 2014; Chan 1989; Scadding 2014; Williamson 2015a).

Compliance

A number of studies gave a narrative report of the levels of compliance with the intervention.

Receptive language skills

Williamson 2015a was the only included study to assess developmental outcomes, in this case receptive language skills. However, due to problems with the website-based assessment and late ethics permission, insufficient numbers of children completed this follow-up test, and the data were not reported.

Number of doctor-diagnosed episodes of acute otitis media

Four studies provided some information for this outcome, over different durations of follow-up.

Our other outcomes of interest were not reported by any of the included studies. This included speech development, cognitive development, psychosocial outcomes, listening skills, generic health-related quality of life, parental stress and vestibular function.

Excluded studies

We excluded 25 studies from this review for the following reasons:

- Eleven studies were not randomised controlled trials (Bidarian-Moniri 2016; Gibson 1996; Head 1992; Iino 1989; Li 2021; Paradise 1997; Parlea 2012; Shubich 1996; Silman 2005; Stenstrom 2005; Tham 2018).
- Two studies included an incorrect population - one included adult participants and one included children with recurrent acute otitis media, not OME (Ferrara 2005; Li 2020).
- Ten studies considered an intervention that was not relevant for this review (Ardehali 2008; ChiCTR2000035008; Choung 2008; De Nobili 2008; El Hachem 2012; Endo 1997; Heaf 1991; Marchisio 1998; Rohail 2006; Starcevic 2011). Some of these studies are included in other reviews in this suite.

- One study included an incorrect comparison. Autoinflation was used before and after adenoidectomy, and compared to adenoidectomy alone (Leunig 1995).
- Finally, one study was withdrawn before any data were available (NCT03534219).

Risk of bias in included studies

The risk of bias in the included studies shows a mixed picture of low, unclear and high-risk ratings. See Figure 3 for the risk of bias graph (our judgements about each risk of bias item presented as percentages across all included studies) and Figure 4 for the risk of bias summary (our judgements about each risk of bias item for each included study).

Figure 3. Risk of bias graph (our judgements about each risk of bias item presented as percentages across all included studies).

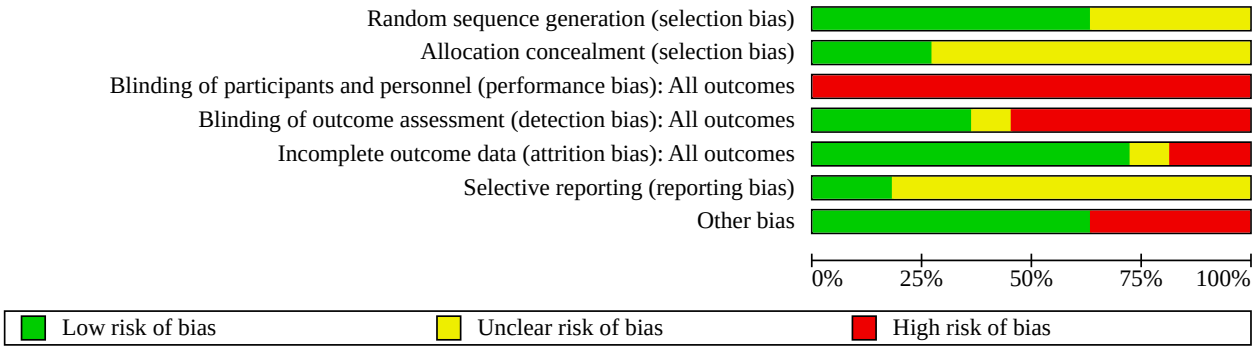
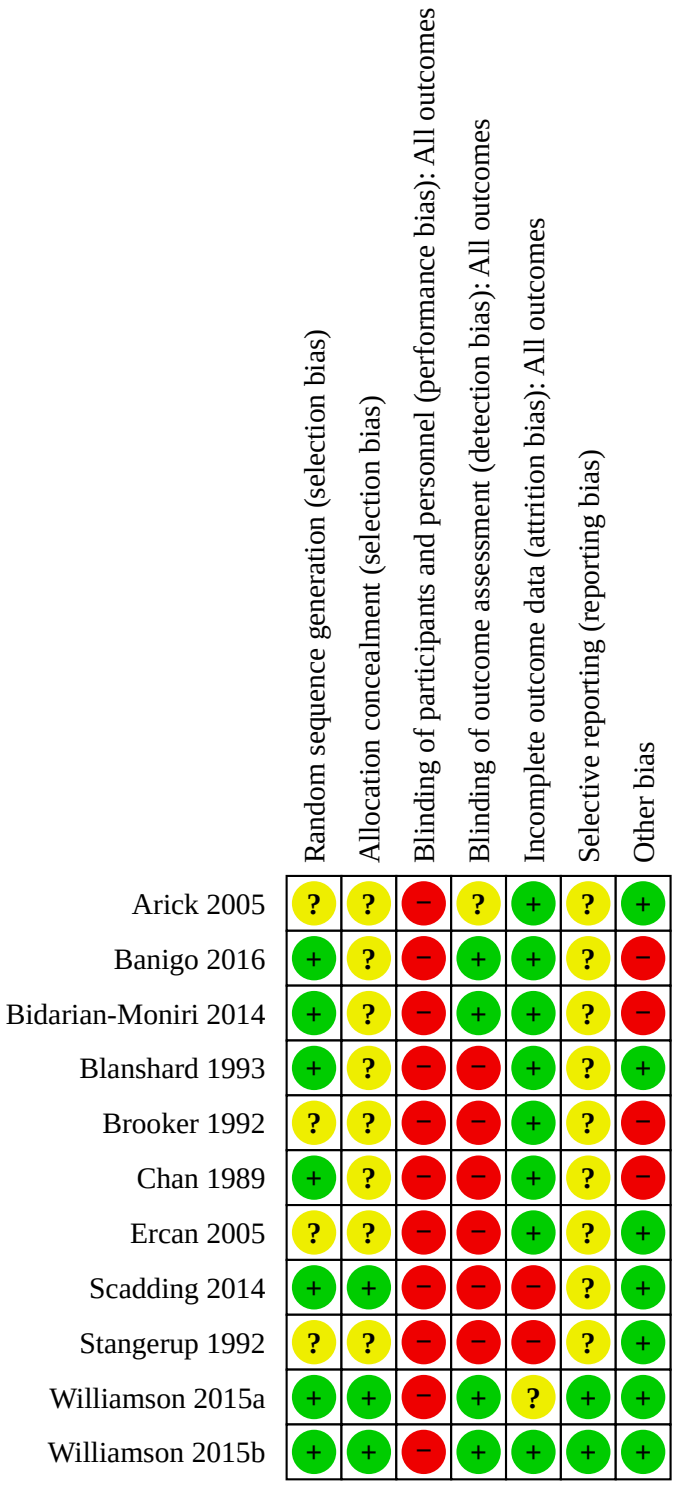


Figure 4. Risk of bias summary (our judgements about each risk of bias item for each included study).



Allocation

We rated seven of the studies at low risk of bias when assessing random sequence generation (Banigo 2016; Bidarian-Moniri 2014; Blanshard 1993; Chan 1989; Scadding 2014; Williamson 2015a; Williamson 2015b), but we rated the risk as unclear for the remaining five studies. We rated only three studies at low risk of bias for allocation concealment (Scadding 2014; Williamson 2015a; Williamson 2015b); we rated the remaining six at unclear risk, due to insufficient information.

Blinding

We rated all 11 studies to be at high risk of performance bias as it was not possible to blind study participants and personnel to treatment group.

We rated six studies at high risk of detection bias (Blanshard 1993; Brooker 1992; Chan 1989; Ercan 2005; Scadding 2014; Stangerup 1992). These studies did not state that outcome assessors were blinded, therefore we considered that it is unlikely that they were. We rated Arick 2005 as unclear and the remaining studies as at low risk of detection bias.

Incomplete outcome data

We rated eight studies at low risk of attrition bias. We rated Scadding 2014 and Stangerup 1992 as high risk. Scadding 2014 reported an attrition rate of 38% and Stangerup 1992 reported many results as a 'per protocol' analysis - only for those who successfully carried out autoinflation. We rated Williamson 2015a at unclear risk of attrition bias: although loss to follow-up was similar across the groups, sensitivity analyses from the main publication indicated that imputation for missing data resulted in a loss of the significant difference between the two groups for some outcome measures.

Selective reporting

We rated two studies at low risk of reporting bias as we found a published protocol for the trials (Williamson 2015a; Williamson 2015b). We rated the remaining nine trials at unclear risk of reporting bias as we could not locate protocols for these trials.

Other potential sources of bias

We rated seven trials at low risk of other bias. We rated Banigo 2016, Bidarian-Moniri 2014, Brooker 1992 and Chan 1989 at unclear risk of other bias due to a short follow-up period that did not allow sufficient time for changes in the control (no treatment) groups.

Effects of interventions

See: **Summary of findings 1** Autoinflation compared to no treatment for otitis media with effusion (OME) in children

Comparison 1: Autoinflation versus no treatment

See Summary of findings 1 for details of the primary outcome measures.

Hearing

Proportion of children whose hearing is normal

Very short-term follow-up (< 6 weeks)

One study provided data for this outcome (Bidarian-Moniri 2014). As Bidarian-Moniri 2014 reported this outcome by ear, we adjusted the data using a correlation coefficient of 0.5, to account for correlation between ears of the same participant. The mean difference in the likelihood of achieving a hearing threshold of < 20 dB HL using autoinflation was 4.45 (95% confidence interval (CI) 2.14 to 9.27; 86% versus 19%; 1 study, 45 participants; Analysis 1.1; very low-certainty evidence). Sensitivity analyses using different correlation coefficients of either 1 (Analysis 1.10) or 0 (Analysis 1.11) produced little change in the findings.

Short-term follow-up (6 weeks to 3 months)

Arick 2005 provided data for this outcome (Analysis 1.2). Arick 2005 used a modified Politzer method for autoinflation and reported a risk ratio of 2.67 for the return to normal hearing (in at least one ear) in those who received autoinflation (95% CI 1.73 to 4.12; 85% versus 32%; 1 study, 94 participants; Analysis 1.2; very low-certainty evidence).

Medium-term follow-up (> 3 months to ≤ 1 year)

This outcome was not assessed at this time point by any of the included studies.

Hearing threshold

Very short-term follow-up (< 6 weeks)

A single study reported this outcome at this time point. The change from baseline in average pure-tone air conduction threshold was estimated to be -5.00 dB HL lower in those who received autoinflation compared to those who received no intervention (95% CI -10.1 to 0.1; 1 study, 45 participants; Analysis 1.3; very low-certainty evidence). These data were reported in the original text with a mean value, median value and full range, therefore we used the reported mean values, and estimated the standard deviation using the methods given by Wan 2014.

Short-term follow-up (6 weeks to 3 months)

Two studies reported this outcome. Data in both studies were reported separately for four different frequencies. We were unable to pool these data (and estimate the pure tone average) due to insufficient information regarding the correlation between hearing at different frequencies. Therefore, we have presented the data separately for the four frequencies assessed. At each frequency the direction of effect was in favour of autoinflation (mean differences between groups ranging from -9.04 to -12.88 dB HL, 95% CI ranging from -2.83 to -17.85; 2 studies, 113 participants; I^2 from 0% to 57%; Analysis 1.4; low-certainty evidence). One study reported data separately for the left and right ear. We used data from the right ears for the main analysis, but sensitivity analysis showed little difference when using data from the left ears (Analysis 1.13).

Additional data were reported by Blanshard 1993. After three months of follow-up, the mean change in hearing threshold (as assessed with pure tone audiometry) was reported for those who had high adherence with the use of Otovent, those with low adherence and those in the control group. The mean change overall for the Otovent group (38 ears) was an increase (worsening) of

hearing threshold by 0.98 dB HL, although outcomes were better for those with high adherence (an improvement of -2.13 dB HL in 19 ears) than those with low adherence (a worsening of 4.08 dB HL in 19 ears). This compared to a worsening of 0.52 dB HL in the control group (34 ears). As no standard deviations were reported, we were unable to include these data in the meta-analysis, although they are suggestive of a trivial difference between the groups.

Disease-specific quality of life

Short-term follow-up

A single study reported this outcome (Williamson 2015a). The authors used a standardised version of the OMQ-14, measured with a 14-item scale. Total raw scores are then converted using a weighted scoring system into a standardised score. The range of this score is not explicit, but appears to be between approximately -3 and +3, with lower scores reflecting better quality of life. The mean difference was adjusted for potential confounders, including sex, age, centre (primary care trust), baseline values and baseline severity of disease. The adjusted mean difference was -0.42 for those who received autoinflation (95% CI -0.62 to -0.22; 1 study, 247 participants; Analysis 1.5; low-certainty evidence). The authors report that a change of 0.3 on this scale would be regarded as clinically meaningful, indicating that this would represent a moderate improvement in quality of life.

Pain and distress at the time of the procedure

This broad outcome measure was not reported by any of the included studies. However, one study did report specifically on otalgia, and the results of this analysis are presented here.

Otalgia

A single study reported on otalgia as a complication of treatment. No definition of otalgia was given. The risk ratio was 3.50 for those who carried out autoinflation (95% CI 0.74 to 16.59; absolute risk 7/160 participants in the autoinflation group, compared to 2/160 in the no treatment group; 1 study, 320 participants; Analysis 1.6; very low-certainty evidence).

Persistence of OME

Please see Unit of analysis issues for further details on how these analyses were conducted.

Very short-term follow-up (< 6 weeks)

Seven studies reported this outcome at between two weeks and six weeks of follow-up.

Overall, a risk ratio of 0.86 was found for the persistence of OME at < 6 weeks in children who received autoinflation (95% CI 0.72 to 1.04; 67% versus 78%; 7 studies, 688 participants; I^2 = 74%; Analysis 1.7; very low-certainty evidence). It should be noted that there is considerable inconsistency in this analysis, with one study appearing to favour no intervention, and two studies showing little difference between the two groups. As described above, most data were reported 'per ear', therefore to account for correlation between ears of the same individual we have carried out some adjustment of the data. Imputing different correlation coefficients, and the use of 'per child' rather than 'per ear' data where reported, made little difference to the overall result (Analysis 1.14; Analysis 1.15; Analysis 1.16).

Short-term follow-up (> 6 weeks to ≤ 3 months)

Four studies also reported at this time point. The risk ratio of 0.88 was similar to that seen at earlier time points (95% CI 0.80 to 0.97; 65% versus 74%; 4 studies, 483 participants; I^2 = 0%; Analysis 1.8; low-certainty evidence). Again, adjustment using different correlation coefficients, or assessing 'per child' data made very little difference to the overall effect estimate (Analysis 1.17; Analysis 1.18; Analysis 1.19).

The study Banigo 2016 also reported the number of children who "still had hearing loss and met the criteria set by NICE (including history, otoscopic examination, tympanometry and audiometry findings) so they had ventilation tubes inserted" after seven weeks of follow-up. However, we considered that some children with a persistent effusion may not meet the criteria required for surgery, and would not be included, therefore this could not be used as a proxy for 'persistence of OME'.

Adverse events

Perforation of the tympanic membrane

This was not described in any of the studies. As described below, for some studies we are unsure if this is because no tympanic membrane perforations occurred, or because this outcome was not fully assessed or reported.

Other adverse events

Five studies provided very limited information on adverse events:

- Banigo 2016 reported, "The most common complaint from the children in treatment group was ear discomfort and a blocked sensation in the ears immediately following its use, which was short-lived and did not affect compliance".
- Bidarian-Moniri 2014 reported, "No adverse effects were observed".
- Chan 1989 reported, "Of the 40 subjects who returned for the two-week visit, none reported any untoward side effects related to performing autoinflation during the study period". It is not clear whether the side effects prioritised in this review were specifically assessed.
- Scadding 2014 reported that no adverse events were seen in their trial. The authors state that "Minor adverse events were recorded, but none was of sufficient severity to cause cessation of the treatment or withdrawal from the trial. The commonest was minor epistaxis which occurred in fewer than 10% of subjects."
- Williamson 2015b reported that one child experienced nosebleeds while using autoinflation. The parent reported that the child had suffered from previous recurrent nosebleeds, but chose to continue with the study anyway.

Six studies did not report any information on adverse events. It is not clear whether this was because no events occurred, or because they were not assessed or reported (Arick 2005; Blanshard 1993; Brooker 1992; Ercan 2005; Stangerup 1992; Williamson 2015a).

Compliance

Details on compliance of study participants with autoinflation are provided in Table 3. Overall, most trials that reported compliance seemed to rate this as satisfactory or good.

Episodes of acute otitis media

Two studies assessed the occurrence of acute otitis media during short-term follow-up. The risk ratio was 0.82 for those who carried out autoinflation, although the confidence intervals were wide (95% CI 0.49 to 1.36; 2 studies, 403 participants; I^2 = 0%; Analysis 1.9; very low-certainty evidence).

Two further studies reported this outcome. However, we were not able to include the data in the meta-analysis:

- Stangerup 1992 used a 'per protocol' analysis - data were only reported for participants who regularly underwent autoinflation, not for the whole group of individuals who were allocated to autoinflation. Therefore, these data were not included in the review.
- Banigo 2016 provided a narrative report, stating "There was no report of an acute otitis media during EarPopper use". No details are provided regarding whether any episodes occurred in the control group, therefore we were unable to provide an accurate comparison of the two groups.

See Table 4 for the results of the sensitivity analyses conducted as part of this review.

DISCUSSION

It should be noted that most of the studies included in this review lasted up to three months, and required children to perform autoinflation two to three times per day. Furthermore, outcomes were reported just after treatment had been completed. Therefore, we are uncertain whether any effects of autoinflation persist into the longer term. As we did not assess the proportion of children who went on to receive medical or surgical treatment for OME, we do not know whether the use of autoinflation has any impact on this. It may simply hasten recovery for children in whom OME would have resolved anyway.

Summary of main results

Short-term effects (up to three months)

Overall, autoinflation may slightly increase the proportion of children whose hearing returns to normal at up to three months follow-up, but the evidence was very uncertain. We are uncertain whether mean hearing threshold is an appropriate method of assessing hearing in this condition (see below). Nonetheless, at less than six weeks there appeared to be little difference in the mean hearing threshold between those who received autoinflation and no treatment, but the evidence was very uncertain. After six weeks to three months of follow-up, autoinflation may result in a small improvement in hearing threshold. It may also result in an improvement in quality of life.

Autoinflation may also result in a reduction in the proportion of children with persistent OME at six weeks to three months of follow-up, although the evidence at the earlier time point (less than six weeks) was very uncertain. After three months of follow-up, there may be a very slight reduction in the proportion of children who experience acute otitis media, but the evidence was very uncertain. The evidence about ear pain was also very uncertain, but the occurrence of pain may increase with the use of autoinflation.

We did not identify any evidence on generic quality of life, expressive or receptive language skills, cognitive development, psychosocial outcomes, listening skills, parental stress or vestibular function.

Longer-term effects (over three months)

We did not identify evidence for any outcomes over this time frame.

Overall completeness and applicability of evidence

Most of the studies included recruited children aged over three years. Autoinflation may be difficult for children in younger age groups to perform, therefore we considered that this was an appropriate population. However, it should be noted that few studies provide any evidence regarding the use of autoinflation in children aged less than three years.

We intended to include studies where children had craniofacial anomalies, or conditions such as Down syndrome. However, a number of studies specifically excluded children with these conditions (Bidarian-Moniri 2014; Blanshard 1993; Chan 1989; Ercan 2005; Scadding 2014; Williamson 2015a; Williamson 2015b). The remaining studies did not state that children with these conditions were excluded, but none specifically recruited children with these high-risk conditions. Therefore, we do not know whether the efficacy of autoinflation may differ for these children.

Many of the studies included in this review enrolled children who had OME for at least three months, however children with a shorter duration of disease were also included. It is not clear whether the efficacy of the intervention may vary depending on the duration of the disease, or perhaps according to prior treatment. Further information is required to identify whether this intervention may be more suitable for use in a primary care setting, as an early intervention for OME, or whether it is better suited to use in secondary care, for children with persistent or treatment-resistant disease.

A variety of devices and techniques were used to carry out autoinflation, ranging from custom-made devices to commercially available products such as Otovent. We did not have enough data to consider this as part of a subgroup analysis, so cannot say if one method works better than another.

The data obtained as part of this review on adherence to treatment were encouraging, showing moderate or good adherence when using autoinflation devices. However, we note that a substantial proportion of studies did not assess compliance. In addition, the studies that did provide an assessment of compliance used different measures to assess this. We are aware that compliance may differ in routine clinical practice, as compared to a trial setting. As highlighted in the review, autoinflation may be associated with an increase in ear pain, and the willingness of children to engage with the procedure may wane over time, which may impact on efficacy.

We have concerns that assessment of hearing using the mean difference in final hearing threshold (or mean change in hearing threshold) may not be the most appropriate way to assess hearing. OME has a high spontaneous resolution rate. Consequently, we would anticipate that the change in hearing threshold for most children will be similar across the groups – as many children will improve with or without treatment. Therefore, even if a subset

of children had substantial benefit from the intervention, the overall mean difference between the two groups would appear to be small. When assessed using the mean difference, the marked benefit seen in a subgroup of participants is 'diluted' by the children who get better regardless of treatment. Therefore, an apparently small mean difference between the two groups may actually be consistent with a substantial change in the number of children in whom hearing returns to normal. It should be noted that persistence (or resolution) of OME is always expressed as a proportion. Most children included in these studies would be expected to have a return to normal hearing alongside resolution of OME. In the absence of our preferred outcome measure of proportion of children with return to normal hearing it may be that presence (and resolution) of OME provides a better or more useful estimate of effect on hearing in these studies.

Finally, we did not assess the number of children who received further treatment for OME (including medical or surgical interventions) as part of this review. Therefore, we do not have data to show whether this intervention prevents children from ultimately receiving surgery and ventilation tube insertion as a treatment for OME. However, this is likely to be an important consideration when deciding on a treatment strategy for OME.

Quality of the evidence

We rated the evidence included in this review as low- or very low-certainty. This was due to a number of issues. Firstly, many of the outcomes were affected by the potential for bias in the individual studies. We rated all the studies at high risk of performance bias, as participants and study personnel were aware of the group allocation. Some studies also had additional problems, including detection bias (where outcome assessors were also aware of the group allocation for participants), loss to follow-up or extremely short follow-up times.

As well as the potential for bias, the effect estimates for many of the outcomes had confidence intervals that crossed from a threshold of potential benefit or harm to a trivial effect, leading to uncertainty in the overall effect estimates. For some analyses very few participants were included, which resulted in extremely wide confidence intervals and more uncertainty in the overall result.

Potential biases in the review process

As part of the development of this review we conducted comprehensive searches, and made significant efforts to locate and include all relevant studies on this topic. Not all of our outcomes of interest were reported by every study. If these outcome data were assessed but not reported, then there is a risk of bias in the meta-analysis results.

We acknowledge that there is little consensus on the definition of 'normal hearing'. Consequently, our selection of a hearing threshold of ≤ 20 dB HL as 'normal' was based on discussion between the author team, review of earlier studies and a pragmatic choice of outcome measure. However, we were as inclusive as possible with this outcome measure, and have included data where authors provided an alternative definition of normal hearing. If we had rigidly used a definition of ≤ 20 dB HL then the data included in this review would have been even more sparse.

During the preparation of this review, we had to consider the definition of autoinflation. We originally included one study that utilised nose-blowing as an autoinflation technique (Heaf 1991). However, in response to comments from our peer reviewers, we subsequently excluded this study from the review. Different definitions of 'autoinflation' could therefore lead to inclusion of different studies, and potentially impact on the findings of the review.

Agreements and disagreements with other studies or reviews

The previous Cochrane Review on this topic included eight studies, with a total of 702 participants (Perera 2013). The review authors concluded that autoinflation has a beneficial effect on resolution of OME. However, the authors noted that none of the included studies were rated as high quality, and many of the effect estimates had wide confidence intervals and failed to reach conventional statistical significance. This review differs slightly, as we have used the GRADE approach to formally assess the certainty of the evidence for each outcome. Given some concerns over the potential for bias in the included studies, and the imprecision in some effect estimates, the overall certainty of the evidence is therefore rated as low or very low. In addition, the outcome measures used for the original review and this updated review differ slightly. However, despite these differences, the summary of both reviews is similar - that there may be some small benefit from autoinflation for some outcomes, but that longer follow-up is required, including an assessment of quality of life and developmental outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

There may be some small benefit from the use of autoinflation for otitis media with effusion (OME) with regard to persistence of OME and quality of life, although whether this benefit persists in the long term is unclear. The evidence is uncertain regarding return to normal hearing and adverse events. We are also unable to identify whether one type of autoinflation device is more effective than another.

We did not look for evidence regarding the need for additional treatment in children with OME, and the data on longer-term follow-up were sparse. Therefore, we do not know whether the use of autoinflation has any impact on the requirement for medical treatment (such as antibiotics or steroids), or any effect on the number of children who require surgery for OME.

Implications for research

We identified a number of trials in this area, including a total of 1036 participants. Nonetheless, the evidence available for this intervention remains low- or very low-certainty. Further consideration should be given to which children may be most likely to benefit from this intervention before embarking on large-scale trials. This review forms part of a suite of five reviews, which consider interventions for OME (Galbraith 2022; MacKeith 2022a; MacKeith 2022b; Mulvaney 2022a; Mulvaney 2022b). Here we present implications for research in this field, which are shared across the suite of reviews:

- As OME is a fluctuating condition with high rates of resolution and recurrence, and a highly variable impact on children, clinical trials (and, in particular, randomised controlled trials) may not be the research design of choice. Instead, evidence

may be better obtained from surgical or clinical registries (for example, see Schmalbach 2021) or prospective cohort studies, with the use of 'big data'. These data sets may also be used to help identify subgroups of children who are at greater risk of persistent disease or long-term consequences of OME. A clearer understanding of possible subgroups of children is needed to better target interventions to those who need them most, whilst avoiding over-treatment for those in whom spontaneous resolution is anticipated.

- Adverse effects of interventions are important, and should always be assessed. However, randomised controlled trials are also not the best method to consider these - especially when events are rare. Observational studies with longer follow-up and larger numbers of participants are needed to provide more robust evidence on the frequency of side effects. It is important to note that the protocol, inclusion criteria and search strategy used for this review would have excluded these types of studies. It is therefore possible that evidence of this type may exist. With this in mind, we would advocate a review of observational data, to assess whether evidence regarding longer-term outcomes and adverse events is already available. This may be particularly important when assessing harms from serious but rare adverse events.
- It is encouraging that a core outcome set has been developed in this field (Bruce 2015; Liu 2020). Guidance on *how* to measure the different outcomes would also be helpful for future research.
- Comparison of mean hearing thresholds is widely used in research to assess the impact of different interventions on hearing. However, this outcome measure risks underestimating the potential impact of interventions on hearing. Small changes in mean hearing thresholds may be consistent with a substantial improvement in the number of children whose hearing returns to normal - particularly in a condition with a high spontaneous resolution rate. We would encourage researchers to assess hearing with the proportion of children in whom hearing returns to normal, in preference to mean hearing thresholds.

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Editorial and peer reviewer contributions

Cochrane ENT supported the authors in the development of this review.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Adrian James, Department of Otolaryngology - Head and Neck Surgery, Hospital for Sick Children, Toronto, Canada
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Liz Bickerdike, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer reviewer comments and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Jenny Bellorini, Cochrane Central Production Service
- Peer reviewers: Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods); Jo Platt, Central Executive Information Specialist (search); Hannah E Cooper, UCL Ear Institute (clinical); Jonathan Walsh, Johns Hopkins School of Medicine Department of Otolaryngology - Head and Neck Surgery (clinical); Carolyn M Jenks, MD, Johns Hopkins University School of Medicine Department of Otolaryngology - Head and Neck Surgery (clinical); Dr Jessica Scaife, Surgical Intervention Trials Unit, Nuffield Department of Surgical Sciences, University of Oxford (consumer)

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arick 2005

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial with 7 weeks treatment and 11 weeks follow-up

Participants	**Setting:**
	
	Single-centre, conducted in ENT outpatients setting in the USA. Study dates are not reported.
	
	Sample size:
	
	• **Number randomised:** 94 participants (174 ears)
	• **Number completed:** 94 participants (174 ears)
	
	Participant (baseline) characteristics:
	
	• **Age:**
	  ○ Not reported
	• **Gender:**
	  ○ Not reported
	• **Hearing thresholds**
	  ○ Autoinflation group: right ear (n = 43)
	  ■ 500 Hz: mean 33.0 (SD 10.9)
	  ■ 1000 Hz: mean 32.1 (SD 10.1)
	  ■ 2000 Hz: mean 23.8 (SD 11.0)
	  ■ 4000 Hz: mean 29.4 (SD 12.1)
	  ○ Autoinflation group: left ear (n = 45)
	  ■ 500 Hz: mean 35.3 (SD 11.4)
	  ■ 1000 Hz: mean 37.7 (SD 10.8)
	  ■ 2000 Hz: mean 26.0 (SD 12.2)
	  ■ 4000 Hz: mean 31.4 (SD 11.7)
	  ○ Control group: right ear (n = 45)
	  ■ 500 Hz: mean 32.7 (SD 7.8)
	  ■ 1000 Hz: mean 32.4 (SD 9.3)
	  ■ 2000 Hz: mean 21.2 (SD 10.7)
	  ■ 4000 Hz: mean 30.8 (SD 11.2)
	  ○ Control group: left ear (n = 41)
	  ■ 500 Hz: mean 32.3 (SD 8.3)
	  ■ 1000 Hz: mean 32.6 (SD 12.0)
	  ■ 2000 Hz: mean 21.8 (SD 11.5)
	  ■ 4000 Hz: mean 30.4 (SD 12.8)
	
	Inclusion criteria:
	
	Aged 4 to 11 years
	
	Minimum of a 2-month history of middle ear effusion and associated hearing loss as documented by a physician
	
	Pure tone air conduction thresholds of 20 dB HL or more at 3 frequencies between 500 Hz and 4000 Hz with air-bone gaps of 15 dB or more at these frequencies *or* pure tone air conduction thresholds of 25 dB HL or more at 2 frequencies between 500 Hz and 4000 Hz with air-bone gaps of 15 dB or more at these frequencies at the final pretest
	
	A tympanometric peak pressure of -100 daPa or less at the final pretest

Arick 2005 *(Continued)*

	Otologic diagnosis of middle ear effusion at the final pretest **Exclusion criteria:** Enlarged adenoids, acute otitis media and other ear abnormalities at the final pretest otologic examination
Interventions	**Autoinflation group (n = 47 (88 ears) randomised)** Modified Politzer device. Hand-held, battery-operated. A probe tip is inserted into the nostril, while compressing the other nostril with a finger. Child holds a small amount of water in the mouth without swallowing. The device is turned on to introduce air flow into the nostril. After 1 to 2 seconds of air flow the child swallows the water. Air pressure was initially 5.2 psi. This was reduced to 2.5 over the course of the study due to some discomfort. The protocol was then changed to 2.5 psi for children ≤ 7 years and increased if tolerated. Pressure could be lowered if needed due to discomfort. Used twice a day for 7 weeks **Control group (n = 47 (86 ears) randomised)** No treatment

Outcomes	**Primary outcomes relevant to this review:**
	
	• **Hearing**
	  ◦ Proportion of children with hearing returned to normal, assessed by audiometry at 11 weeks
	  ◦ Mean (SD) final hearing thresholds (dB) per ear, assessed by audiometry at 11 weeks
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse events**
	  ◦ Not reported
	
	Secondary outcomes relevant to this review:
	
	None
	
	Other outcomes reported in the study:
	
	Tympanic membrane motility, only for those ears that had achieved normal hearing
	
	Tympanometric peak pressure

Funding sources	This research was supported by a grant (No. 5R44DC0036 I3-03) from the Small Business Innovation Research Program, National Institute on Deafness and Other Communication Disorders, National Institutes of Health to Arisil Instruments
Declarations of interest	No declaration made, but note that the principal investigators appear to own a business to develop this instrument (Arisil Instruments)
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • This study was published prior to 2010, therefore prospective trial registration is not applicable • Limited baseline characteristics were described, therefore we are unable to assess whether there are excessive similarities between the 2 groups • No loss to follow-up was reported (although some data on hearing sensitivity were missing) • Results for hearing for the active intervention were noted to be very considerable (an improvement of between -14.8 and -18.3 dB HL at different frequencies, compared to -0.9 to -4.3 for the control group), which may be implausible • Equal numbers of participants were randomised to each group, without any description of block randomisation

Arick 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Of this group, 47 patients (88 ears) were randomly assigned to the experimental group and 47 patients (86 ears) were assigned to the control group". Comment: no further information.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Audiologists were blinded to each patient's otologic findings, and otolaryngologists were blinded to each patient's audiometric findings. At the posttest, audiologists and otolaryngologists were blinded to each patient's disease status. The statistician was blinded as to whether test results were obtained before or after therapy and to the disease status of each patient." (page 57) Comment: blinding of outcome assessors is not described, although outcome assessors (audiologists and ENT surgeons) were independent of each other. It is not clear if outcomes assessors were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data are available for almost all randomised participants.
Selective reporting (reporting bias)	Unclear risk	No protocol has been found to enable assessment of selective reporting.
Other bias	Low risk	No other concerns identified.

Banigo 2016

Study characteristics

Methods	Two-arm, single-blind, parallel-group, randomised controlled trial with 7 weeks of treatment and follow-up
Participants	**Setting:** Single-centre, conducted in an outpatient hospital clinic in the UK between September 2008 and March 2013 **Sample size:** • **Number randomised**: 30 participants • **Number completed:** 29 participants **Participant (baseline) characteristics:** • **Age:**

Banigo 2016 *(Continued)*

- Autoinflation group:
  - Mean 5.94 years
  - Range 4.36 to 8.19 years
- Control group
  - Mean 5.55 years
  - Range 3.96 to 7.79 years

- **Hearing thresholds**
  - Autoinflation group:
    - 0.5 kHz = mean 40.5 mean
    - 1.0 kHz = mean 37.5
    - 2.0 kHz = mean 35
    - 4.0 kHz = mean 38.6
  - Control group:
    - 0.5 kHz = mean 38.6
    - 1.0 kHz = mean 36.5
    - 2.0 kHz = mean 32.1
    - 4.0 kHz = mean 37.3

Inclusion criteria:

Aged 4 to 11 years with hearing loss from persistent OME over a 3-month period and an average air conduction of 25 dB HL or worse in the better ear across 0.5, 1.0, 2.0 and 4.0 kHz were considered eligible for the trial

Children who were placed on a waiting list for VT insertion and had a wait of > 7 weeks

Exclusion criteria:

- Suppurative otitis media
- Tympanic membrane perforation
- Adenoid hypertrophy
- Tumour
- Severe systemic diseases
- Allergy or intolerance to macrolides

Interventions	**Autoinflation group (n = 15 randomised, n = 15 completed)** Use of EarPopper® device. Used twice a day, twice in each nostril. Device used on low-pressure settings (level I) for 7 weeks. **Control group (n = 15 randomised, n = 14 completed)** No details given but presumably nothing done/no placebo

Outcomes	**Primary outcomes relevant to this review:**
	
	• **Hearing**
	  ◦ Mean (SD) final hearing thresholds (dB), air conduction at 7 weeks
	  ◦ Mean (SD) change in hearing thresholds (dB) from baseline, air conduction thresholds at 7 weeks
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse events**
	  ◦ Not reported
	
	Secondary outcomes relevant to this review:
	
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ◦ History, otoscopic examination, tympanometry and audiometry at 7 weeks
	• **Other adverse effects**

Banigo 2016 *(Continued)*

	○ No data, a narrative summary provided **Other outcomes reported in the study:** Number of patients requiring ventilation tubes at longer-term follow-up
Funding sources	Not reported
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • No prospective trial registration was identified • Baseline characteristics in the groups were not excessively similar • Only 1 participant was lost to follow-up, but as all participants were awaiting surgery this is not an implausible result • No implausible results were reported • Equal numbers of participants were randomised to each group, without any description of block randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "children were allocated to treatment or control groups using a randomly allocated computer-generated code". Comment: computer-generated randomisation.
Allocation concealment (selection bias)	Unclear risk	No information on concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The audiologists performing the final audiogram at 7 weeks were blinded to which group each child belonged to". Comment: outcomes assessed by blinded personnel.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one dropout in the trial and this is unlikely to influence results.
Selective reporting (reporting bias)	Unclear risk	No protocol was identified.
Other bias	High risk	Follow-up is 7 weeks and therefore this is insufficient time for follow-up of no treatment.

Bidarian-Moniri 2014

Study characteristics

Bidarian-Moniri 2014 *(Continued)*

Methods	Two-arm, randomised, controlled, cross-over, with follow-up at 4 weeks and 1 year Data from the first phase of the study were used in this review

Participants	**Setting:**
	
	Multicentre study, conducted in hospitals in Sweden and Portugal between May 2010 and June 2012
	
	Sample size:
	
	• **Number randomised:** 45 participants
	• **Number completed:**
	  ◦ 45 participants at 4 weeks
	  ◦ 40 participants at 12 months
	
	Participant (baseline) characteristics:
	
	• **Age:**
	  ◦ Autoinflation group: mean 68 months
	  ◦ Control group: mean 53 months
	• **Gender:**
	  ◦ Autoinflation group:
	  ■ 13/22 (59%) male
	  ■ 9/22 (41%) female
	  ◦ Control group:
	  ■ 12/23 (52%) male
	  ■ 11/23 (48%) female
	• **Number with bilateral disease**
	  ◦ All participants
	• **Hearing thresholds in best ear**
	  ◦ Autoinflation group: mean 20 dB
	  ◦ Control group: mean 25 dB
	• **Other measure of hearing status: hearing thresholds > 20 dB**
	  ◦ Autoinflation group: 25 ears (66%)
	  ◦ Control group: 35 ears (88%)
	
	Inclusion criteria:
	
	Aged 2 to 8 years with history of persistent bilateral otitis media with effusion with a duration of disease of at least 3 months and history of subjective hearing loss, waiting for grommet surgery
	
	Children underwent otomicroscopy, tympanometry and audiometry. Those with bilateral OME with type C2 or B tympanogram.
	
	Exclusion criteria:
	
	• Children with uncontrolled asthma
	• Craniofacial anomaly
	• Active otological disease such as otorrhoea
	• Deep retraction pockets
	• Perforations of the tympanic membrane

Interventions	**Autoinflation group (n = 22 randomised first)** A new autoinflation device consisting of an inflatable facemask, a T-shaped junction tube connecting at one end to the facemask, another end to a balloon and the third end to a handheld pump. The pump was covered by a teddy bear in order to improve compliance in young children. Three different balloons with the respective opening pressures of 20 ± 3, 40 ± 2 and 60 ± 5 cm H_2O were used.

Bidarian-Moniri 2014 *(Continued)*

	Children used the device twice a day to perform 20 inflations at each session (approximately 5 to 10 minutes) during a period of 4 weeks **Control group (n = 23 randomised first)** No treatment

Outcomes	**Primary outcomes relevant to this review:**
	
	• **Hearing**
	  ○ Proportion of ears with hearing returned to normal: hearing thresholds < 20 dB
	  ○ Mean (SD) change in hearing thresholds (dB) from baseline (the better hearing ear was assessed): pure tone air conduction thresholds at 4 weeks
	• **Disease-specific quality of life**
	  ○ Not reported
	• **Adverse events**
	  ○ Not reported
	
	Secondary outcomes relevant to this review:
	
	• **Presence/persistence of OME:** proportion of ears with persistence of OME
	  ○ Type B or C1 on tympanometry at 4 weeks
	• **Other adverse effects**
	  ○ No data, a narrative summary was presented
	
	Other outcomes reported in the study:
	
	• Middle ear pressure
	• Compliance
	• Some long-term follow-up, but not relevant as both groups had then received the treatment

Funding sources	This work was partially financed by grants from the Rune and Ulla Amlöv Foundation for Neurological, Rheumatological and Audiological Research, Sweden
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • No prospective trial registration was identified • Baseline characteristics of the groups were not excessively similar • Some loss to follow-up was reported over longer follow-up (12 months) • No implausible results were reported • Block randomisation was used to allocate equal numbers to the groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Computer-generated, independent allocation sequences were used for randomisation. To avoid disproportionate numbers of patients in each group, randomisation was performed in blocks of six subjects (three allocated to the treatment and three to the control group).” Comment: computer-generated.
Allocation concealment (selection bias)	Unclear risk	Quote: “Computer-generated, independent allocation sequences were used for randomisation. To avoid disproportionate numbers of patients in each group, randomisation was performed in blocks of six subjects (three allocated

Bidarian-Moniri 2014 *(Continued)*

		to the treatment and three to the control group). The children were enrolled by a secretary and assigned to group A or B by one of the authors." Comment: with a relatively small block size in this unblinded study, it may be possible to predict the next allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Pure tone air conduction thresholds for each ear or sound field audiometry for both ears were performed by an experienced audiologist who was blinded to the group allocation of the child."
Incomplete outcome data (attrition bias) All outcomes	Low risk	There do not appear to be any missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration was found.
Other bias	High risk	Follow-up is at 1 month - this is insufficient time for follow-up of no treatment.

Blanshard 1993

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial, with 3 months of treatment and follow-up

Participants	**Setting:**
	
	Single-centre, conducted in an ENT clinic in the UK from July to December 1991
	
	Sample size:
	
	• **Number randomised:** 85 participants
	• **Number completed:** 83 participants
	
	Participant (baseline) characteristics:
	
	• **Age:**
	  ◦ Autoinflation group: mean 57.3 months (SD 14.2)
	  ◦ Control group: mean 59.9 months (SD 18.3)
	• **Gender:**
	  ◦ Autoinflation group:
	  ■ 25 males
	  ■ 17 females
	  ◦ Control group:
	  ■ 27 males
	  ■ 14 females
	• **Duration of disease**
	  ◦ Autoinflation group: mean 27.8 (SD 16.2)
	  ◦ Control group: mean 27.2 (SD 15.2)
	
	Inclusion criteria:

Blanshard 1993 *(Continued)*

	Aged 3 to 10 years with confirmation of bilateral type B or C2 tympanograms on 2 occasions separated by at least 3 months and on the waiting list for grommets **Exclusion criteria:** • Children treated previously by adenoidectomy or tonsillectomy • Chromosomal abnormalities • Cranio-facial abnormalities
Interventions	**Autoinflation group (n = 42 completed)** The Otovent device is a rounded plastic nose piece with a balloon attached. Used once through each nostril 3 times a day. Balloon changed every 3 days. Not to be used during the first few days of an URTI, or an episode of otalgia **Control group (n = 41 completed)** No intervention

Outcomes	**Primary outcomes relevant to this review:**
	
	• **Hearing**
	  ◦ Mean (SD) change in hearing thresholds (dB) from baseline: pure tone audiometry
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse events**
	  ◦ Not reported
	
	Secondary outcomes relevant to this review:
	
	• **Presence/persistence of OME: proportion of ears with persistence:**
	  ◦ Type B or C2 tympanogram at 3 months
	• **Episodes of acute otitis media: mean (SD) number of episodes**
	  ◦ At least 1 episode of AOM at 3 months

Funding sources	Not reported
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • Prospective trial registration was not applicable as this study was published before 2010 • Baseline characteristics of the groups were not excessively similar, although limited information was provided • Some loss to follow-up was reported • No implausible results were reported • The number randomised to each group is not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “They were allocated to either the treatment or to the control group by computer generated random numbers”. Comment: computer-generated method of randomisation.

Blanshard 1993 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No information is provided regarding whether outcome assessors were blinded. It is likely they were unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was minimal dropout.
Selective reporting (reporting bias)	Unclear risk	No protocol available. Most analyses are conducted according to a per protocol analysis of those with high compliance versus control, rather than the entire treatment group.
Other bias	Low risk	No other concerns.

Brooker 1992

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial of 3 weeks treatment and follow-up

Participants	**Setting:**
	
	Single-centre, conducted in a hospital audiology clinic in the UK. Study dates were not reported.
	
	Sample size:
	
	• **Number randomised:** 40 participants (78 ears)
	• **Number completed:** 40 participants (78 ears)
	
	Participant (baseline) characteristics:
	
	• **Age:**
	  ◦ 3 to 10 years
	  ◦ Average age 5.7 years
	• **Gender:**
	  ◦ Not reported
	
	Inclusion criteria:
	
	Children aged less than 10 years referred to audiology clinic with unilateral or bilateral glue ears diagnosed by otoscopy, audiogram and tympanogram. The children had to be able to inflate a carnival blower nasally.
	
	Exclusion criteria:
	
	Not reported

Interventions	**Autoinflation group (n = 21 (41 ears) randomised)**

Brooker 1992 *(Continued)*

	Three times daily for 3 weeks. Device comprised of a toy balloon attached to a carnival blower mouthpiece. Pressure required to inflate was in the range 35 to 40 mmHg then settled to 20 to 23 mmHg once the balloon had started to inflate. Children were taught how to do it initially. **Control group (n = 19 (37 ears) randomised)** No treatment

Outcomes	**Primary outcomes relevant to this review:**
	
	• **Hearing**
	  ○ Not reported
	• **Disease-specific quality of life**
	  ○ Not reported
	• **Adverse events**
	  ○ Not reported
	
	Secondary outcomes relevant to this review:
	
	• **Presence/persistence of OME: proportion of ears with persistence of OME**
	  ○ Number of ears with persistent flat tympanogram at 3 weeks

Funding sources	Not reported
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • The trial was published prior to 2010, therefore prospective registration is not applicable • Very few baseline characteristics were reported, therefore we cannot assess whether the groups were excessively similar • No loss to follow-up was reported, but the groups were extremely small, therefore this may be plausible • No implausible results were reported • Different numbers of participants were allocated to each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The children so selected were, with the informed consent of their parents, allocated at random into two groups." Comment: insufficient information to judge random sequence generation.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	There is no statement to indicate that outcome assessors were blinded.

Brooker 1992 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No protocol was identified.
Other bias	High risk	Follow-up was for 3 weeks - this is insufficient time for as assessment of the 'no treatment' group, as they would not be expected to have improved during this time frame.

Chan 1989

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial with 2 weeks of treatment and follow-up

Participants	**Setting:**
	
	Single-centre, conducted in the USA between February 1986 and February 1987
	
	Sample size:
	
	• **Number randomised:** 41 participants
	• **Number completed:** 40 participants
	
	Participant (baseline) characteristics:
	
	• **Age:**
	  ◦ Autoinflation group:
	  ▪ 3 to 6 years: 14 (93.6%)
	  ▪ 7 to 11 years: 4 (21.1%)
	  ▪ > 12 years: 1 (5.3%)
	  ◦ Control group
	  ▪ 3 to 6 years: 13 (59.1%)
	  ▪ 7 to 11 years: 7 (31.8%)
	  ▪ > 12 years: 2 (9.2%)
	• **Gender:**
	  ◦ Autoinflation group:
	  ▪ 13 males
	  ▪ 6 females
	  ◦ Control group:
	  ▪ 14 males
	  ▪ 8 females
	• **Duration of disease**
	  ◦ Autoinflation group:
	  ▪ < 3 months: 5 (25.3%)
	  ▪ > 3 months: 13 (68.4%)
	  ▪ Unknown: 1 (5.3%)
	  ◦ Control group:
	  ▪ < 3 months: 3 (16.3%)
	  ▪ > 3 months: 18 (81.8%)
	  ▪ Unknown: 1 (4.5%)
	• **Number with bilateral disease**
	  ◦ Autoinflation group: 14 (73.6%)

Chan 1989 *(Continued)*

	○ Control group: 13 (59.1%) **Inclusion criteria:** Aged 3 to 18 years with chronic otitis media with effusion. The aim was to include those that had persistence for at least 3 months (although this was not everyone). Failed to respond to conventional antimicrobial treatment. **Exclusion criteria:** • Acute otitis media symptoms, e.g. fever or otalgia • Craniofacial anomaly • Underlying systemic disease • Active symptoms of URTI or inhalant allergy • Active otologic findings, such as otorrhoea, deep retraction pocket, cholesteatoma or sensorineural hearing loss • Antimicrobial treatment in the past 7 days
Interventions	**Autoinflation group (n = 19 randomised)** Modified Valsalva techniques - a disposable anaesthesia mask attached to a floating ball-type flowmeter with 2 plastic ring adaptors. Children were instructed to exhale through the nose through the mask (with the mouth closed); as the pressure increased, the ball in the flowmeter was propelled upwards. To be performed 3 times daily for 2 weeks **Control group (n = 22 randomised)** No treatment
Outcomes	**Primary outcomes relevant to this review:** • **Hearing** ○ Not reported • **Disease-specific quality of life** ○ Not reported • **Adverse events** ○ Not reported **Secondary outcomes relevant to this review:** • **Presence/persistence of OME: proportion of children** ○ Otological examination and tympanogram at 2 weeks **Other outcomes reported in the study:** Bilateral versus unilateral disease outcomes in control vs autoinflation groups
Funding sources	NIH grants
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • The trial was published prior to 2010, therefore prospective registration is not applicable • Baseline characteristics of the groups were not excessively similar • Some loss to follow-up was reported (1 participant) and the trial lasted for only 2 weeks, so this is plausible • No implausible results were reported

Chan 1989 *(Continued)*

- The groups did not include equal numbers of participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Within in each stratification, subjects were randomly assigned to either the autoinflation or the control group by the use of a set of random numbers". Comment: random numbers were used for randomisation.
Allocation concealment (selection bias)	Unclear risk	No information on concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	There is no description of whether the outcome assessors were blinded. It is likely that they were unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant was missing from follow-up.
Selective reporting (reporting bias)	Unclear risk	No protocol was identified.
Other bias	High risk	Follow-up is 2 weeks and therefore this is insufficient time for follow-up of no treatment.

Ercan 2005

Study characteristics

Methods	Two-arm, parallel-group randomised controlled trial with 6 weeks of treatment and follow-up at 3 and 9 months

Participants	**Setting:**
	
	Single-centre, conducted in an outpatient setting in Turkey between January 2002 and April 2004
	
	Sample size:
	
	• **Number randomised:** 60 participants (93 ears)
	• **Number completed:** 86 ears
	
	Participant (baseline) characteristics:
	
	• **Age:**
	  ◦ Mean 6.2 years
	  ◦ Range 4 to 10 years
	• **Gender:**
	  ◦ 32/60 (53%) male

Ercan 2005 *(Continued)*

- 28/60 (47%) female

- **Number with bilateral disease**
  - Autoinflation group: 18/30 (60%)
  - Control group: 15/30 (50%)

Inclusion criteria:

Children with middle ear effusion and free of signs of otitis media for at least a 4-week period (ear ache, ear discharge etc.)

Diagnosis of chronic otitis media with effusion was established by the typical appearance (fluid level or air bubbles in middle ear, white opacification in the tympanic membrane, vascularisation of the tympanic membrane without erythema, lack of mobility of the tympanic membrane in ventilation of the external ear canal, etc.) of the tympanic membrane at the pneumatic otoscopic examination and type B tympanogram at the end of the 3 months follow-up

Exclusion criteria:

- Hypersensitivity or significant adverse reactions to penicillin
- Previous tonsillectomy and/or adenoidectomy
- Previous ear surgery other than tympanocentesis or myringotomy with or without tube insertion
- History of seizure disorder, diabetes mellitus, asthma requiring daily medication or any health condition that could make entry potentially dangerous
- Medical conditions with a predisposition for MEE, such as cleft palate, Down syndrome, congenital malformations of the ear, cholesteatoma or chronic mastoiditis
- Severe retraction pockets
- Acute or chronic diffuse external otitis
- Perforation of the tympanic membrane
- Intracranial or intratemporal complications of MEE
- Upper respiratory obstruction attributable to tonsil or adenoid enlargement or both with cor pulmonale, sleep apnoea or severe dysphagia
- History of varicella exposure within the previous 30 days (if never had clinical varicella or varicella vaccine) or clinical varicella in the previous 3 weeks
- History of measles exposure in the previous 30 days
- Immunisation in the previous 30 days
- New otitis media attack in 3 months follow-up prior to study

Interventions	**Autoinflation group (n = 30 randomised (48 ears))** Otovent 3 times a day for 6 weeks, with nasal saline irrigation 3 times a day for 6 weeks **Control group (n = 30 randomised (45 ears))** Treated with nasal saline irrigation 3 times a day for 6 weeks **Information on treatment used before entry into the trial** Amoxicillin for 3 weeks, antihistamines (in case of allergy) and nasal saline irrigation

Outcomes	**Primary outcomes relevant to this review:**
	
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life**
	  ◦ Not reported
	• **Adverse events**
	  ◦ Not reported
	
	Secondary outcomes relevant to this review:

Ercan 2005 *(Continued)*

- **Presence/persistence of OME: proportion of ears with persistence of OME**
  - Measured at 6 weeks and 3 months

Funding sources	Not reported
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • As this study was published prior to 2010, prospective trial registration was not required • Very few baseline characteristics were reported, therefore it is difficult to assess whether there is excessive similarity between the groups; however, the distribution of bilateral/unilateral OME is different • Some loss to follow-up was reported • No implausible results were reported • Equal numbers were allocated to the groups and blocked randomisation was not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly divided into two groups". Comment: no information provided to indicate how the random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were randomly divided into two groups". Comment: no information provided to indicate how allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an open-label trial, with no mention of blinding, therefore the outcome assessors were unlikely to be blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There do not appear to be any missing outcome data.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration was found.
Other bias	Low risk	No concerns.

Scadding 2014

Study characteristics	
Methods	Four-arm, parallel-group, randomised controlled trial with up to 2 years of treatment and follow-up
Participants	**Setting:**

Scadding 2014 *(Continued)*

Single-centre, conducted in a specialist glue ear clinic in a hospital in the UK between 1994 and 2003

Sample size:

- **Number randomised:** 200 participants
- **Number completed:** 123 participants

Participant (baseline) characteristics:

- **Age:**
  - Nasal steroids group: mean 5.4 years (SD 1.2)
  - Autoinflation group: mean 5.7 (SD 1.3)
  - Autoinflation and nasal steroids group: mean 5.9 (SD 1.1)
  - Placebo group: mean 5.7 (SD 1.3)
- **Gender:**
  - Nasal steroids group:
    - 31 males (60%)
    - 21 females (40%)
  - Autoinflation group:
    - 25 males (48%)
    - 27 females (52%)
  - Autoinflation and nasal steroids group:
    - 29 males (60%)
    - 19 females (40%)
  - Placebo group:
    - 32 males (67%)
    - 16 females (33%)
- **Hearing thresholds**
  - Nasal steroids group:
    - Right: mean 23.3 (SD 8.5)
    - Left: mean 24.1 (SD 9.7)
  - Autoinflation group:
    - Right: mean 25.9 (SD 10.4)
    - Left: mean 24.3 (SD 10.1)
  - Autoinflation and nasal steroids group:
    - Right: mean 25.2 (12.3)
    - Left: mean 22.8 (SD 9.9)
  - Placebo group:
    - Right: mean 24.8 (SD 12.5)
    - Left: mean 25.8 (SD 11.8)

Inclusion criteria:

Aged 4 to 8 years with at least 3 months of glue ear or more than 2 episodes in the past 6 months, and a type B or C tympanogram

Exclusion criteria:

- Cleft palate
- Down's syndrome
- Cystic fibrosis

Interventions	**Nasal steroids group (n = 52 randomised; n = 32 completed)** 50 µg per spray, 1 puff per nostril twice daily for 2 weeks (2 puffs per nostril twice daily for children over 35 kg), i.e. total daily dose 200 µg (or 400 µg) initially Then reduced to 1 puff per nostril (100 µg) once daily. "The children were asked to use this on a regular basis". "Those who reported spray use on at least 3 days a week remained in the study"

Scadding 2014 *(Continued)*

	Autoinflation group (n = 52 randomised; n = 30 completed) Otovent autoinflation device. Used 3 times daily for the first box of balloons (i.e. 4 to 5 weeks) then stopped if hearing was not troublesome. Use was re-established if glue ear re-presented, especially after a cold. **Autoinflation and nasal steroids group (n = 48 randomised; n = 31 completed)** Otovent as above and nasal steroids as above **Placebo group (n = 48 randomised; n = 30 completed)** Matching placebo

Outcomes	**Primary outcomes relevant to this review:**
	
	• **Hearing**
	  ○ Not reported
	• **Disease-specific quality of life**
	  ○ Not reported
	• **Adverse events**
	  ○ Not reported
	
	Secondary outcomes relevant to this review:
	
	• **Presence/persistence of OME**
	  ○ Persistent hearing loss of greater than 30 dB or grommet insertion at 2 years
	• **Other adverse effects**
	  ○ Narrative summary only
	
	Other outcomes reported in the study:
	
	• Kaplan Meier plots of survival time without grommets or hearing loss > 30 dB HL
	• Change in specific symptoms over time
	• Number with recurrent URTIs

Funding sources	Glaxo Smith Kline, Inphormed and Merck
Declarations of interest	This study was conceived by Glenis Scadding and funded by Glaxo Smith Kline (including the salary of Abhijeet Parikh as a PhD student) together with Inphormed who provided Otovent devices free of charge. Merck Sharp and Dohme provided funding for further independent statistical analysis since this was advised by a referee when the paper was originally submitted. Glenis Scadding has received funding from GSK and MSD for other trials, serves on an advisory panel and has lectured for them at meetings. Helen Tate has worked as an independent statistical consultant for Merck, Sharp and Dohme. At the time of the study, DR was a full-time employee of GlaxoSmithKline R&D. None of the other authors has any interests to declare.
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • No prospective trial registration was identified; however, although the trial was published after 2010, we note that it was conducted from 1993 to 2003 • Baseline characteristics of the groups were not excessively similar • Some loss to follow-up was reported • No implausible results were reported • Block randomisation was used to allocate participants to the groups, but the numbers are not identical
Risk of bias	

Scadding 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomised to receive FP or matching placebo in a 1:1 ratio according to a computer-generated randomisation schedule using a block size of 8." "In addition those children entering the trial with an odd number were also given the Otovent device; this part of the study was open." Comment: computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Quote: "…computer-generated randomisation schedule using a block size of 8. This was held in the pharmacy, and both subjects and observers were blind as to the nature of this treatment." Comment: third party conducted randomisation and allocation. Even though personnel would know that an odd number is allocation to Otovent, it is unlikely that allocation could be interfered with.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "both subjects and observers were blind as to the nature of this treatment. In addition those children entering the trial with an odd number were also given the Otovent device; this part of the study was open." It is not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "both subjects and observers were blind as to the nature of this treatment." Comment: the above statement may refer to the steroid intervention, but it is likely that outcome assessors are not blinded to autoinflation allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	38% loss to follow-up; this may substantially impact results.
Selective reporting (reporting bias)	Unclear risk	No protocol found, so it was not possible to assess selective reporting bias.
Other bias	Low risk	No other concerns.

Stangerup 1992

Study characteristics	
Methods	Two-arm, parallel-group, randomised controlled trial with 2 weeks of treatment and 3 months of follow-up
Participants	**Setting:** Single-centre, conducted in a university ENT Department in China between June 2009 and March 2011 **Sample size:** • **Number randomised:** 100 participants • **Number completed:** 93 participants **Participant (baseline) characteristics:**

Stangerup 1992 *(Continued)*

- **Age:**
  - Autoinflation group: mean 5.3 years
  - Control group: mean 5.3 years
- **Gender:**
  - Autoinflation group
    - 26/46 (57%) male
    - 20/46 (43%) female
  - Control group
    - 28/47 (60%) male
    - 19/47 (40%) female
- **Number with bilateral disease**
  - 40 unilateral and 53 bilateral
- **Other measure of hearing status: tympanogram**
  - Autoinflation group:
    - Type C2 42.5% (31 ears)
    - Type B 57.5% (42 ears)
  - Control group:
    - Type C2 57.5% (42 ears)
    - Type B 42.5% (31 ears)

Inclusion criteria:

Aged 3 to 10 years, unilateral or bilateral secretory otitis media for at least 3 months as verified by tympanometry and otomicroscopy

Exclusion criteria:

None reported

Interventions	**Autoinflation group (n = 46 completed)** Tube designed by the author, with a balloon on the end, inserted in one nostril and blown up whilst occluding the other Three times per day for 2 weeks. If a type C2 or a type B tympanogram persisted after 2 weeks, the children where instructed to carry on for a further 2 weeks. To cease if they acquired a common cold or purulent rhinitis **Control group (n = 47 completed)** No treatment

Outcomes	**Primary outcomes relevant to this review:**
	
	• **Hearing**
	  ○ Not reported
	• **Disease-specific quality of life**
	  ○ Not reported
	• **Adverse events**
	  ○ Not reported
	
	Secondary outcomes relevant to this review:
	
	• **Presence/persistence of OME: proportion of children with persistence of OME**
	  ○ Tympanometry at 2 weeks
	• **Episodes of acute otitis media: mean (SD) number of episodes**
	  ○ Within 1 and 3 months

Funding sources	Not reported

Stangerup 1992 *(Continued)*

Declarations of interest	None reported
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • Prospective trial registration was not required, as this study was published prior to 2010 • Very few characteristics were reported for the individual groups, but different numbers of male and female children were enrolled in each group • Some loss to follow-up was reported • No implausible results were reported • The number randomised to each group is unclear, but assumed to be 50 in each group (i.e. numbers were equal, and block randomisation was not described)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "One hundred children were consecutively randomized to undergo either autoinflation, using a new device, or placed in a control group." "The patients were randomized to either a group performing autoinflation for 2 weeks or to a group being observed without treatment for 2 weeks." Comment: no information on how the random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Quote: "One hundred children were consecutively randomized to undergo either autoinflation, using a new device, or placed in a control group." "The patients were randomized to either a group performing autoinflation for 2 weeks or to a group being observed without treatment for 2 weeks." Comment: no information on how allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	It is not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	It is unlikely that outcome assessors were blind to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	Many results are reported as a per protocol analysis only for those who successfully carried out autoinflation.
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration was found.
Other bias	Low risk	No concerns.

Williamson 2015a

Study characteristics

Methods	Two-arm, parallel-group, randomised controlled trial with 3 months of follow-up

Williamson 2015a *(Continued)*

Participants	**Setting:**
	
	Multicentre, conducted in 43 general practices in the UK between January 2012 and February 2013
	
	Sample size:
	
	• **Number randomised:** 320 participants
	• **Number completed:** 245 participants
	
	Participant (baseline) characteristics:
	
	• **Age:**
	  ◦ Autoinflation group: mean 5.4 years (SD 1.24)
	  ◦ Control group: mean 5.4 years (SD 1.04)
	• **Gender:**
	  ◦ Autoinflation group: 83 (51.9%) male
	  ◦ Control group: 84 (52.5%) male
	• **Number with bilateral disease**
	  ◦ Autoinflation group: 68/160
	  ◦ Control group: 67/160
	• **Disease-specific quality of life score: OMQ-14 standardised at baseline**
	  ◦ Autoinflation group: 0.07 (SD 1.00) (n = 153)
	  ◦ Control group: -0.04 (SD 0.95) (n = 153)
	• **Number of doctor-diagnosed AOM episodes within a specified time frame:**
	  ◦ Number of episodes in the 12 months prior to assessment
	
	Inclusion criteria:
	
	Aged 4 to 11 years and attending school. At least one ear with a type B tympanogram in one or both ears and middle ear pressure of -400 with a flat trace, based on the modified Jerger classification, and fulfilled one of these 3 criteria:
	
	1. For children aged 4 to 6 years, identified through practice register – parental concern with report of at least one relevant symptom/concern associated with OME in the previous 3 months from the following list:
	  • Prolonged/bad cold, cough or chest infection
	  • Earache
	  • Appears to mishear what is said
	  • Hearing loss suspected by anyone
	  • Says ‘eh what’ or ‘pardon’ a lot
	  • Needs the television turned up
	  • May be irritable or withdrawn
	  • Appears to be lip-reading
	  • Not doing as well at school, e.g. with reading
	  • Noises in the ear/dizzy
	  • Snores, blocked nose or poor sleep
	  • Speech seems behind other children’s
	  • Any suspected ear problem
	2. For children in the targeted attendance screen (aged 7 to 11) – a history or recent and/or recurrent otitis media or OME in the previous 12 months recorded in the child's medical records OR ear-related problems in the previous year including suspected hearing loss, snoring, concerns about behaviour, speech or educational development
	3. For children newly presenting, relevant expressed clinical concern from the health team about OME as a cause
	
	Exclusion criteria:

Williamson 2015a *(Continued)*

- Current clinical features of acute otitis media (e.g. ear pain, fever or otoscopic features of acute inflammation)
- Children with a grommet already in the eardrum, or who have been referred or listed for surgery
- Children with a latex allergy
- Children with uncommon conditions and syndrome at high risk of recurrent disease, including cleft palate, Kartagener syndrome, primary ciliary dyskinesia and immunodeficiency states for whom early referral is indicated
- Children with a recent nosebleed in the previous 3 weeks, or more than one episode of nosebleeds in the preceding 6 months

Interventions	**Autoinflation group (n = 160 randomised, n = 125 followed up at 3 months)** Otovent was used. Children were required to inflate a purpose-manufactured balloon by blowing through each nostril into a connecting nozzle 3 times per day for 1 to 3 months. Children were shown the procedure, and a website with an instruction video was available for back-up. Children still showing a type B tympanogram in either ear at 1 month were advised to continue for a further 2 months. **Control group (n = 160 randomised, n = 120 followed up at 3 months)** No treatment **Background intervention common to both groups** Routine care was given to both groups as normal

Outcomes	**Primary outcomes relevant to this review:**
	
	• **Hearing**
	  ◦ Not reported
	• **Disease-specific quality of life: OMQ-14**
	  ◦ Mean (SD) at 3 months
	  ◦ Mean (SD) change and adjusted mean change from baseline at 3 months
	• **Adverse event**
	  ◦ Not reported
	
	Secondary outcomes relevant to this review:
	
	• **Presence/persistence of OME: proportion of children/ears with persistence of OME**
	  ◦ Tympanometry by ear at 1 month
	  ◦ Tympanometry by ear and by child at 3 months
	• **Receptive language: mean (SD) at endpoint**
	  ◦ Two alternative auditory disability and speech reception tests and hearing tests at 1 month
	• **Other adverse effects**
	  ◦ Nosebleeds
	  ◦ URTI
	  ◦ Unspecified RTI
	  ◦ Lower RTI
	  ◦ Otalgia
	  ◦ Headache
	  ◦ Hay fever
	• **Serious adverse events:**
	  ◦ Hospitalisation
	
	Other outcomes reported in the study:

Williamson 2015a *(Continued)*

	Parents were asked to complete a weekly diary recording the number of days (0 to 7) of their child's main symptoms of hearing loss, earache, difficulty concentrating, pain relief, disturbed sleep and absence from school. None of these are relevant outcomes. In addition, a second diary of items was included to systematically record a number of other symptoms including nosebleeds, clumsiness/off-balance, systemic illness, nasal discharge and nasal congestion/snoring. Not relevant outcomes. Those that we have listed as adverse events are recorded separately. Hearing disability was evaluated at baseline and at 1 month for all children using the TADAST web-based test. TADAST is a forced-choice test, originally developed in primary care, which evaluates hearing disability associated with glue ear. Only accounts for disability related to hearing, not an objective measure of hearing loss as required for our primary outcome. Not presented in text therefore cannot be used for hearing disability, due to few people completing questionnaire. Health economic analysis Qualitative outcomes Diary card of symptoms
Funding sources	Funded by the HTA programme. Project number 09/01/27.
Declarations of interest	One author is a member of the NIHR Editorial Board
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • The trial was prospectively registered: ISRCTN55208702 • Baseline characteristics of the groups were not excessively similar • Plausible loss to follow-up was reported (12.2% at 3 months) • No implausible results were reported • Minimisation was used to allocate equal numbers of participants to the 2 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent external agency provided a centralised web-based randomisation system (www.sealedenvelope.com) for nurses to access while recruiting children to the study". "The randomisation used an algorithm with minimisation based on three potential effect modifiers/confounders: age (< 6.5 years vs. > 6.5 years), sex and baseline severity of OME (one vs. two baseline type B tympanograms)". Comment: computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Quote: "An independent external agency provided a centralised web-based randomisation system (www.sealedenvelope.com) for nurses to access while recruiting children to the study". Comment: adequate concealment of allocation by third party.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Owing to the nature of the intervention, use of placebo was not possible and therefore nurses, children and families were not masked to treatment allocation."

Williamson 2015a *(Continued)*

		Comment: no blinding was possible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Tympanometry […] provides a reasonably objective outcome measure that can also be assessed blind to allocation arm. Two members of the trial team, trained in tympanometry, independently reviewed anonymised tympanometry printouts". Comment: outcome assessors were blinded to allocated group.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data were balanced across groups, with similar reasons in each group, however it is unclear whether the proportion of missing outcomes is likely to introduce significant bias in the effect direction or magnitude. Sensitivity analysis with multiple imputation to account for missing data resulted in similar effect size, but the difference between groups was then non-significant. Per protocol analysis reduced the effect size further.
Selective reporting (reporting bias)	Low risk	Study protocol is published, and all outcome measures are reported according to the pre-specified plan.
Other bias	Low risk	No other concerns.

Williamson 2015b

Study characteristics	
Methods	Two-arm, parallel-group randomised controlled trial with 3 months of follow-up These are pilot data from the same publication as Williamson 2015a

Participants	**Setting:**
	
	Multicentre, conducted in 4 general practices in the UK between January 2010 and May 2010
	
	Sample size:
	
	• **Number randomised:** 21 participants
	• **Number completed:** 17 participants (at 3 months)
	
	Participant (baseline) characteristics:
	
	• **Age:**
	  ◦ Autoinflation group:
	  ▪ 4 to 5 years: 3
	  ▪ 5 to 6 years: 4
	  ▪ 6 to 10 years: 0
	  ▪ 7 to 11 years: 2
	  ◦ Control group:
	  ▪ 4 to 5 years: 2
	  ▪ 5 to 6 years: 8
	  ▪ 6 to 10 years: 0
	  ▪ 7 to 11 years: 0
	• **Gender:**
	  ◦ Autoinflation group:
	  ▪ 5 female
	  ▪ 4 male
	  ◦ Control group:
	  ▪ 5 female

Williamson 2015b *(Continued)*

- 5 male

Inclusion criteria:

Aged 4 to 11 years and attending school. At least one ear with a type B tympanogram in one or both ears and middle ear pressure of -400 with a flat trace, based on the modified Jerger classification, and fulfilled one of the these 3 criteria:

1. For children aged 4 to 6 years, identified through practice register – parental concern with report of at least one relevant symptom/concern associated with OME in the previous 3 months from the following list:
   - Prolonged/bad cold, cough or chest infection
   - Earache
   - Appears to mishear what is said
   - Hearing loss suspected by anyone
   - Says 'eh what' or 'pardon' a lot
   - Needs the television turned up
   - May be irritable or withdrawn
   - Appears to be lip-reading
   - Not doing as well at school, e.g. with reading
   - Noises in the ear/dizzy
   - Snores, blocked nose or poor sleep
   - Speech seems behind other children's
   - Any suspected ear problem
2. For children in the targeted attendance screen (aged 7 to 11) – a history or recent and/or recurrent otitis media or OME in the previous 12 months recorded in the child's medical records OR ear-related problems in the previous year including suspected hearing loss, snoring, concerns about behaviour, speech or educational development
3. For children newly presenting, relevant expressed clinical concern from the health team about OME as a cause

Exclusion criteria:

- Current clinical features of acute otitis media (e.g. ear pain, fever or otoscopic features of acute inflammation)
- Children with a grommet already in the eardrum, or who have been referred or listed for surgery
- Children with a latex allergy
- Children with uncommon conditions and syndromes at high risk of recurrent disease, including cleft palate, Kartagener syndrome, primary ciliary dyskinesia and immunodeficiency states for whom early referral is indicated

Interventions	**Autoinflation group (n = 11 randomised, n = 9 followed up at 3 months)** Otovent was used. Children were required to inflate a purpose-manufactured balloon by blowing through each nostril into a connecting nozzle 3 times per day for 1 to 3 months. Children were shown the procedure, and a website with an instruction video was available for back-up. Children still showing a type B tympanogram in either ear at 1 month were advised to continue for a further 2 months. **Control group (n = 10 randomised, n = 8 followed up at 3 months)** No treatment **Background intervention common to both groups** Routine care was given to both groups as normal
Outcomes	**Primary outcomes relevant to this review:**

Williamson 2015b *(Continued)*

- **Hearing**
  - Not reported
- **Disease-specific quality of life**
  - Not reported
- **Adverse events**
  - Not reported

Secondary outcomes relevant to this review:

- **Presence/persistence of OME: proportion of children with persistence of OME**
  - Tympanometry at 1 and 3 months

Funding sources	Not reported
Declarations of interest	None reported
Notes	**Research integrity checklist** • No retraction notices or expressions of concern were identified • The trial was prospectively registered: ISRCTN55208702 • Baseline characteristics of the groups were not excessively similar • Plausible loss to follow-up was reported • No implausible results were reported • Different numbers of participants were allocated to the 2 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible children were individually randomised to autoinflation plus routine care or routine care alone via a telephone dial-in service" "The randomisation method used an algorithm with minimisation based on three previously found key variables: age, sex and baseline severity of OME." Comment: third party randomisation with the use of a minimisation algorithm implies computer-generated randomisation method.
Allocation concealment (selection bias)	Low risk	Quote: "Eligible children were individually randomised to autoinflation plus routine care or routine care alone via a telephone dial-in service" Comment: likely to be adequately concealed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Given the nature of the intervention it was not possible to blind participants and personnel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Tympanometric outcomes were assessed blind to intervention group by the chief investigator."
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/21 (19%) loss to follow-up at 3 months.
Selective reporting (reporting bias)	Low risk	All outcomes are reported according to the pre-specified plan.

Williamson 2015b *(Continued)*

Other bias	Low risk	No other concerns identified.

AOM: acute otitis media; dB: decibels; dB HL: decibels hearing level; ENT: ear, nose and throat; HTA: health technology assessment; kg: kilogram; µg: microgram; MEE: middle ear effusion; n/a: not applicable; NIH: National Institutes of Health; OME: otitis media with effusion; OMQ-14: Otitis Media Questionnaire-14; RTI: respiratory tract infection; SD: standard deviation; URTI: upper respiratory tract infection; VT: ventilation tube

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

Study	Reason for exclusion
Ardehali 2008	INTERVENTION: treatment with antibiotics, and is relevant for another review in this suite (Mulvaney 2022a)
Bidarian-Moniri 2016	ALLOCATION: not randomised
ChiCTR2000035008	INTERVENTION: wrong intervention
Choung 2008	INTERVENTION: treatment with steroids, and is relevant for another review in this suite (Mulvaney 2022b)
De Nobili 2008	INTERVENTION: included nasal decongestants
El Hachem 2012	INTERVENTION: no intervention of interest
Endo 1997	INTERVENTION: treatment with antibiotics, and is relevant for another review in this suite (Mulvaney 2022a)
Ferrara 2005	PARTICIPANTS: had recurrent acute otitis media
Gibson 1996	ALLOCATION: not randomised
Head 1992	STUDY DESIGN: commentary article, not an RCT
Heaf 1991	INTERVENTION: not an intervention of interest (nose blowing, not autoinflation)
Iino 1989	ALLOCATION: not randomised
Leunig 1995	COMPARISON: not a comparison of interest
Li 2020	PARTICIPANTS: adult patients
Li 2021	ALLOCATION: not randomised
Marchisio 1998	INTERVENTION: treatment with antibiotics, and is relevant for another review in this suite (Mulvaney 2022a)
NCT03534219	OTHER: study withdrawn/terminated
Paradise 1997	ALLOCATION: not randomised
Parlea 2012	ALLOCATION: not randomised
Rohail 2006	INTERVENTION: not a relevant intervention (no autoinflation)

Study	Reason for exclusion
Shubich 1996	ALLOCATION: not randomised
Silman 2005	ALLOCATION: not randomised
Starcevic 2011	INTERVENTION: treatment with ventilation tubes, and is relevant for another review in this suite (MacKeith 2022a)
Stenstrom 2005	ALLOCATION: not randomised
Tham 2018	ALLOCATION: not randomised

RCT: randomised controlled trial

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

Tawfik 2002

Methods	—
Participants	—
Interventions	—
Outcomes	—
Notes	Unable to obtain full text

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

INFLATE (ACTRN12617001652369)

Study name	'INFLATE: a protocol for a randomised controlled trial comparing nasal balloon autoinflation to no nasal balloon autoinflation for otitis media with effusion in Aboriginal and Torres Strait Islander children'
Methods	Multicentre, open-label, parallel-group randomised controlled trial
Participants	Aboriginal and Torres Strait Islander children aged 3 to 16 years old with unilateral or bilateral OME Estimated enrolment 400 participants
Interventions	Nasal balloon autoinflation using the Otovent device (2 times per day for 1 to 3 months) compared to no treatment
Outcomes	• Tympanometric improvement in OME at 1 month, 3 months and 6 months (change from type B to type A or C1 tympanogram in affected ears) • Hearing at 3 months • Ear health-related quality of life using the OMQ-14 • Adverse events • Adherence to treatment • Cost-effectiveness
Starting date	December 2017

INFLATE (ACTRN12617001652369) *(Continued)*

Contact information	P.Abbott@westernsydney.edu.au
Notes	—

NCT00393159

Study name	'The influence of the Ear Popper on serous otitis media and on the accompanying conductive hearing loss in children'
Methods	Single-centre, parallel-group, open-label randomised controlled trial with 7 weeks duration of intervention and follow-up at a maximum of 12 weeks
Participants	Children aged 3 to 18 years with OME for at least 3 months, a conductive hearing loss of more than 15 dB, and type B or C tympanogram
Interventions	Use of Ear Popper device (frequency of use not stated) compared to no treatment
Outcomes	• Audiometry and tympanometry results at 7 weeks and 3 months from start of treatment • Otoscopic findings at 7 weeks and 3 months from start of treatment • Hearing improvement at 7 weeks and 3 months from start of treatment • Rate of referral for tympanostomy tube insertion by 3 months
Starting date	Trial registered in October 2006. No details on starting date.
Contact information	dkyo@barak-online.net.il
Notes	We presume that this trial has been discontinued, due to the duration of time that has elapsed since the trial registration, however we have been unable to verify this

NCT02038400

Study name	'Efficacy of KNT® (KINETUBE) in recurrent chronic otitis media in children'
Methods	Parallel-group, open-label RCT
Participants	Children aged 7 to 15 years old with recurrent otitis media with effusion, or atelectasis, with presence of fluid behind the eardrum, and conductive hearing loss ≥ 30 dB NB: it is not clear if this study will recruit children with OME or only recurrent acute otitis media
Interventions	Use of the Kinetube compared to ventilation tube insertion Frequency and duration of treatment are not stated
Outcomes	Hearing threshold in dB HL measured with pure tone audiometry at up to 12 months
Starting date	Trial registration January 2014
Contact information	Loic Mondoloni, Assistance Publique Hopitaux De Marseille
Notes	It is not clear if this trial is ongoing, or was discontinued

NCT02546518

Study name	'A comparison of surgical and a new non-surgical treatment methods for secretory otitis media in children'
Methods	Single-centre, parallel-group randomised controlled trial
Participants	Children aged 30 months to 7 years with unilateral or bilateral OME for 3 months or longer
Interventions	The use of a custom-made autoinflation device (as described in Bidarian-Moniri 2014) for 5 minutes, twice a day for 1 month will be compared to the insertion of a tympanostomy tube
Outcomes	• Change from baseline in hearing level at 1 month, 3 months and 6 months of follow-up • Change from baseline in middle ear pressure, assessed with tympanometry at 1 month, 3 months and 6 months of follow-up • Presence of fluid in the middle ear at 1 month, 3 months and 6 months of follow-up • Health economics (number of days of parental leave in order to look after the child) • Otitis Media Questionnaire-14 (OMQ-14) at 1 month, 3 months and 6 months of follow-up • Number of health care or hospital visits due to ear associated problems
Starting date	September 2015 Estimated completion date December 2017
Contact information	mohammed.al-azzawe@vgregion.se hasse.ejnell@vgregion.se
Notes	Unable to locate any publication arising from this trial registration

NCT05324696

Study name	'Autoinflation: alternative in the treatment of otitis media with effusion'
Methods	Parallel-group randomised controlled trial, conducted in Portugal
Participants	Children aged 3 to 8 years with unilateral or bilateral OME, as diagnosed with otomicroscopy and tympanometry (type B or C2), audiogram with hearing loss ≥ 20 dB or air-bone gap Estimated enrolment 50 participants
Interventions	Autoinflation device (based on that used by Bidarian-Moniri 2014) compared to a sham device that does not generate pressure No details on frequency
Outcomes	Resolution of OME, assessed after 3 years of follow-up
Starting date	November 2020. Estimated completion December 2023.
Contact information	Joao Lino, Instituto de Ciências Biomédicas Abel Salazar
Notes	—

dB HL: decibels hearing level; OME: otitis media with effusion; OMQ-14: Otitis Media Questionnaire-14; RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Autoinflation versus watchful waiting/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Proportion of children whose hearing is normal (very short-term, < 6 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2 Proportion of children whose hearing is normal (short-term, > 6 weeks to ≤ 3 months)	1	94	Risk Ratio (M-H, Random, 95% CI)	2.67 [1.73, 4.12]
1.3 Hearing threshold (very short-term, < 6 weeks)	1	45	Mean Difference (IV, Random, 95% CI)	-5.00 [-10.10, 0.10]
1.4 Hearing threshold (short-term, > 6 weeks to ≤ 3 months)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 0.5 kHz	2	113	Mean Difference (IV, Random, 95% CI)	-9.13 [-15.14, -3.13]
1.4.2 1.0 kHz	2	113	Mean Difference (IV, Random, 95% CI)	-10.34 [-17.85, -2.83]
1.4.3 2.0 kHz	2	113	Mean Difference (IV, Random, 95% CI)	-9.04 [-14.84, -3.25]
1.4.4 4.0 kHz	2	113	Mean Difference (IV, Random, 95% CI)	-12.88 [-17.01, -8.75]
1.5 Disease-specific quality of life (short-term, > 6 weeks to ≤ 3 months)	1	247	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.62, -0.22]
1.6 Adverse events - pain and distress caused by the procedure (otalgia)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 Otalgia	1	320	Risk Ratio (M-H, Random, 95% CI)	3.50 [0.74, 16.59]
1.7 Persistence of OME (very short-term, < 6 weeks)	7	688	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.04]
1.7.1 Per ear data	6	670	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.69, 1.04]
1.7.2 Per child data	1	18	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.72, 1.39]
1.8 Persistence of OME (short-term, > 6 weeks to ≤ 3 months)	4	483	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.80, 0.97]
1.8.1 Per ear data	3	466	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.79, 0.96]

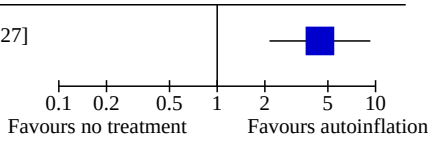
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8.2 Per child data	1	17	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.61, 2.07]
1.9 Episodes of acute otitis media (short-term, > 6 weeks to ≤ 3 months)	2	403	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.49, 1.36]
1.10 Sensitivity analysis: Proportion of children whose hearing is normal (very short-term, < 6 weeks). Per ear data (ICC of 1, complete correlation between ears)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.11 Sensitivity analysis: Proportion of children whose hearing is normal (very short-term, < 6 weeks). Per ear data (ICC of 0, no correlation between ears)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.12 Sensitivity analysis: Hearing threshold (short-term, > 6 weeks to ≤ 3 months). Right ear data	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.12.1 0.5 kHz	2	117	Mean Difference (IV, Random, 95% CI)	-9.13 [-15.35, -2.92]
1.12.2 1.0 kHz	2	117	Mean Difference (IV, Random, 95% CI)	-10.91 [-20.07, -1.76]
1.12.3 2.0 kHz	2	117	Mean Difference (IV, Random, 95% CI)	-9.59 [-17.74, -1.44]
1.12.4 4.0 kHz	2	117	Mean Difference (IV, Random, 95% CI)	-13.37 [-20.66, -6.08]
1.13 Sensitivity analysis: Hearing threshold (short-term, > 6 weeks to ≤ 3 months). Left ear data	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.13.1 0.5 kHz	2	115	Mean Difference (IV, Random, 95% CI)	-8.97 [-14.88, -3.06]
1.13.2 1.0 kHz	2	115	Mean Difference (IV, Random, 95% CI)	-9.64 [-15.50, -3.78]
1.13.3 2.0 kHz	2	115	Mean Difference (IV, Random, 95% CI)	-8.06 [-12.16, -3.97]
1.13.4 4.0 kHz	2	115	Mean Difference (IV, Random, 95% CI)	-10.92 [-15.42, -6.41]
1.14 Sensitivity analysis: Persistence of OME (very short-term, < 6 weeks). Per ear data (ICC of 0)	6	862	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.68, 1.04]
1.15 Sensitivity analysis: Persistence of OME (very short-term, < 6 weeks). Per ear data (ICC of 1)	6	551	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16 Sensitivity analysis: Persistence of OME (very short-term, < 6 weeks). Per child data, where available	7	621	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.68, 1.04]
1.16.1 Per ear data, adjusted for correlation for those with bilateral disease	4	300	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.55, 1.12]
1.16.2 Per child data: persistence in any affected ear	1	40	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.88, 1.25]
1.16.3 Per child data: persistence in all affected ears	2	281	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.68, 1.00]
1.17 Sensitivity analysis: Persistence of OME (short-term, > 6 weeks to ≤ 3 months). Per ear data (ICC of 0)	4	617	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.82, 0.97]
1.17.1 Per ear data	3	600	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.82, 0.97]
1.17.2 Per child data	1	17	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.61, 2.07]
1.18 Sensitivity analysis: Persistence of OME (short-term, > 6 weeks to ≤ 3 months). Per ear data (ICC of 1)	4	402	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.81, 1.00]
1.18.1 Per ear data	3	385	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.00]
1.18.2 Per child data	1	17	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.61, 2.07]
1.19 Sensitivity analysis: Persistence of OME (short-term, > 6 weeks to ≤ 3 months). Per child data, where available	4	441	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.78, 0.96]
1.19.1 Per ear data	2	179	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.68, 1.06]
1.19.2 Per child data	2	262	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.66, 1.02]

Analysis 1.1. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 1: Proportion of children whose hearing is normal (very short-term, < 6 weeks)

Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Risk Ratio M-H, Random, 95% CI
Bidarian-Moniri 2014 (1)	25	29	6	31	4.45 [2.14 , 9.27]

Test for subgroup differences: Not applicable



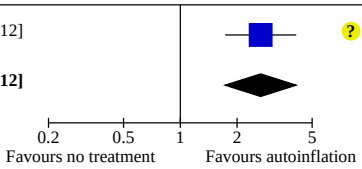
Footnotes

(1) Data from 4 weeks. Number with hearing threshold of <20dB HL. Per ear data, adjusted with an ICC of 0.5 (see methods).

Analysis 1.2. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 2: Proportion of children whose hearing is normal (short-term, > 6 weeks to ≤ 3 months)

Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Arick 2005 (1)	40	47	15	47	100.0%	2.67 [1.73 , 4.12]	? ? − ? + ? +
Total (95% CI)		**47**		**47**	**100.0%**	**2.67 [1.73 , 4.12]**	
Total events:	40		15				

Heterogeneity: Not applicable
Test for overall effect: Z = 4.43 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes

(1) Data from 11 weeks. Per child data. Number in whom hearing returned to normal in at least one ear (no definition of 'normal hearing').

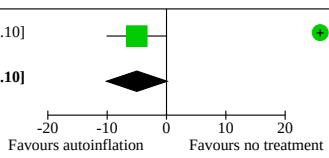
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Autoinflation versus watchful waiting/ no treatment, Outcome 3: Hearing threshold (very short-term, < 6 weeks)

Study or Subgroup	Autoinflation Mean	Autoinflation SD	Autoinflation Total	No treatment Mean	No treatment SD	No treatment Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A B C D E F G
Bidarian-Moniri 2014 (1)	-6	5.5	22	-1	11.15	23	100.0%	-5.00 [-10.10 , 0.10]	+ ? − + + ? −
Total (95% CI)			**22**			**23**	**100.0%**	**-5.00 [-10.10 , 0.10]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.92 (P = 0.05)
Test for subgroup differences: Not applicable



Footnotes

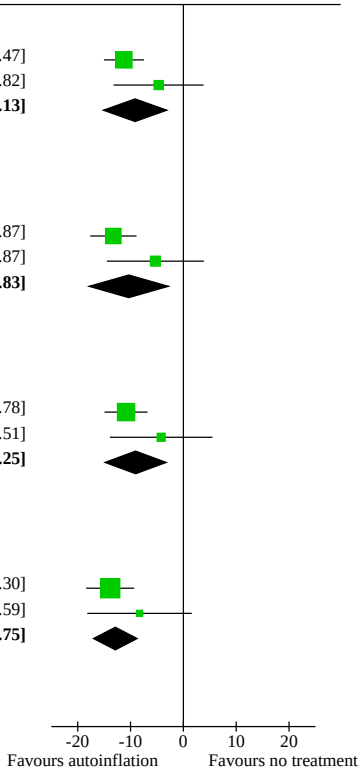
(1) Change from baseline in pure tone air conduction threshold. Data from 4 weeks. SD estimated from reported median and range.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.4. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 4: Hearing threshold (short-term, > 6 weeks to ≤ 3 months)

Study or Subgroup	Autoinflation Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 0.5 kHz								
Arick 2005 (1)	18.65	7.78	43	29.9	9.75	41	67.7%	-11.25 [-15.03 , -7.47]
Banigo 2016 (2)	32.2	13.11	15	36.9	10.22	14	32.3%	-4.70 [-13.22 , 3.82]
Subtotal (95% CI)			**58**			**55**	**100.0%**	**-9.13 [-15.14 , -3.13]**
Heterogeneity: Tau² = 10.13; Chi² = 1.89, df = 1 (P = 0.17); I² = 47%								
Test for overall effect: Z = 2.98 (P = 0.003)								
1.4.2 1.0 kHz								
Arick 2005	16.4	8.45	43	29.65	11.69	41	63.4%	-13.25 [-17.63 , -8.87]
Banigo 2016	28.5	9.68	15	33.8	14.8	14	36.6%	-5.30 [-14.47 , 3.87]
Subtotal (95% CI)			**58**			**55**	**100.0%**	**-10.34 [-17.85 , -2.83]**
Heterogeneity: Tau² = 18.16; Chi² = 2.35, df = 1 (P = 0.13); I² = 57%								
Test for overall effect: Z = 2.70 (P = 0.007)								
1.4.3 2.0 kHz								
Arick 2005	8.3	6.97	43	19.15	11.44	41	72.9%	-10.85 [-14.92 , -6.78]
Banigo 2016	23	10.72	15	27.2	15.37	14	27.1%	-4.20 [-13.91 , 5.51]
Subtotal (95% CI)			**58**			**55**	**100.0%**	**-9.04 [-14.84 , -3.25]**
Heterogeneity: Tau² = 7.68; Chi² = 1.53, df = 1 (P = 0.22); I² = 35%								
Test for overall effect: Z = 3.06 (P = 0.002)								
1.4.4 4.0 kHz								
Arick 2005	13.35	7.76	43	27.2	12.77	41	82.6%	-13.85 [-18.40 , -9.30]
Banigo 2016	23.8	13.98	15	32.1	13.19	14	17.4%	-8.30 [-18.19 , 1.59]
Subtotal (95% CI)			**58**			**55**	**100.0%**	**-12.88 [-17.01 , -8.75]**
Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 1 (P = 0.32); I² = 0%								
Test for overall effect: Z = 6.11 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 3 (P < 0.00001), I² = 0%								

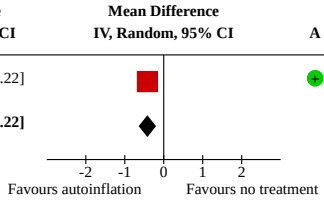


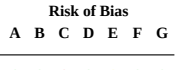
Footnotes

(1) Data from 11 weeks. Pooled data from both ears used for analysis, assumed correlation of 0.5 between ears.
(2) Data from 7 weeks.

Analysis 1.5. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 5: Disease-specific quality of life (short-term, > 6 weeks to ≤ 3 months)

Study or Subgroup	Mean Difference	SE	Autoinflation Total	No treatment Total	Weight	Mean Difference IV, Random, 95% CI
Williamson 2015a (1)	-0.42	0.104077	126	121	100.0%	-0.42 [-0.62 , -0.22]
Total (95% CI)			**126**	**121**	**100.0%**	**-0.42 [-0.62 , -0.22]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.04 (P < 0.0001)						
Test for subgroup differences: Not applicable						





Footnotes

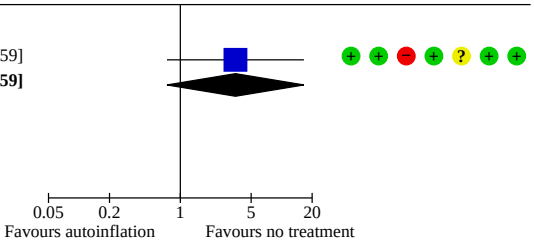
(1) Mean difference in standardised OMQ-14 scores at 3 months. Lower score is favourable.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 6: Adverse events - pain and distress caused by the procedure (otalgia)

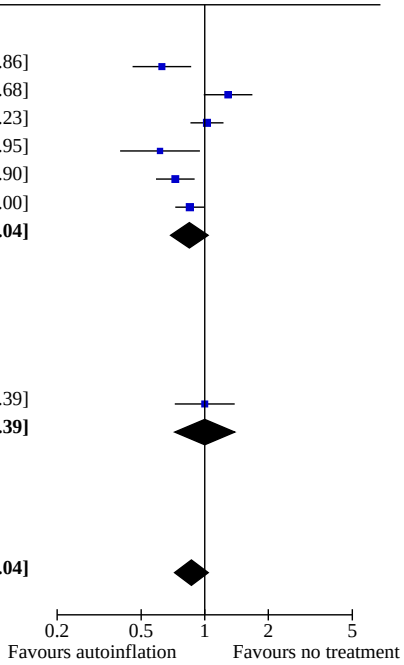
Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 Otalgia						
Williamson 2015a	7	160	2	160	100.0%	3.50 [0.74 , 16.59]
Subtotal (95% CI)		**160**		**160**	**100.0%**	**3.50 [0.74 , 16.59]**
Total events:	7		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

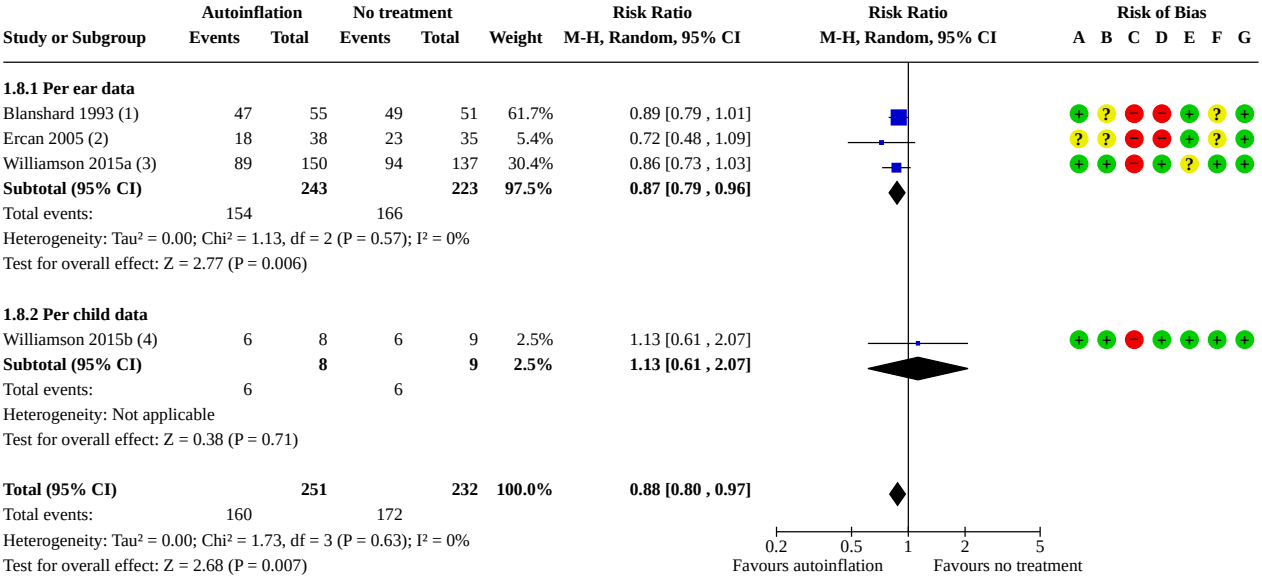
Analysis 1.7. Comparison 1: Autoinflation versus watchful waiting/ no treatment, Outcome 7: Persistence of OME (very short-term, < 6 weeks)

Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Per ear data						
Bidarian-Moniri 2014 (1)	17	29	29	31	12.6%	0.63 [0.46 , 0.86]
Brooker 1992 (2)	26	28	18	25	14.4%	1.29 [0.99 , 1.68]
Chan 1989 (3)	26	29	28	32	17.1%	1.02 [0.86 , 1.23]
Ercan 2005 (4)	16	38	24	35	9.5%	0.61 [0.40 , 0.95]
Stangerup 1992 (5)	37	57	51	57	16.1%	0.73 [0.59 , 0.90]
Williamson 2015a (6)	95	155	111	154	17.8%	0.85 [0.73 , 1.00]
Subtotal (95% CI)		**336**		**334**	**87.6%**	**0.85 [0.69 , 1.04]**
Total events:	217		261			
Heterogeneity: Tau² = 0.05; Chi² = 22.40, df = 5 (P = 0.0004); I² = 78%						
Test for overall effect: Z = 1.61 (P = 0.11)						
1.7.2 Per child data						
Williamson 2015b (7)	8	9	8	9	12.4%	1.00 [0.72 , 1.39]
Subtotal (95% CI)		**9**		**9**	**12.4%**	**1.00 [0.72 , 1.39]**
Total events:	8		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**345**		**343**	**100.0%**	**0.86 [0.72 , 1.04]**
Total events:	225		269			
Heterogeneity: Tau² = 0.04; Chi² = 23.29, df = 6 (P = 0.0007); I² = 74%						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Chi² = 0.73, df = 1 (P = 0.39), I² = 0%						



Footnotes
(1) Data from 4 weeks. Type B or C2 tympanogram. Per ear data adjusted with ICC of 0.5 (see appendix).
(2) Data from 3 weeks. Children with a persistent flat tympanogram. Per ear data adjusted with ICC of 0.5.
(3) Data from 2 weeks. No details on assessment method. Per ear data adjusted with ICC of 0.5.
(4) Data from 6 weeks. Assessed with pneumatic otoscopy and tympanometry. Per ear data adjusted with ICC of 0.5.
(5) Data from 2 weeks. Type B or C2 tympanogram. Per ear data adjusted with ICC of 0.5.
(6) Data from 1 month. Type B or C2 tympanogram. Per ear data adjusted with ICC of 0.5.
(7) Data from 1 month. Type B or C2 tympanogram. Persistence in at least one ear.

Analysis 1.8. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 8: Persistence of OME (short-term, > 6 weeks to ≤ 3 months)



Footnotes

(1) Data from 3 months. Type B or C2 tympanogram. Per ear data adjusted with ICC of 0.5 (see methods).
(2) Data from 3 months. Assessed with pneumatic otoscopy and tympanometry. Per ear data adjusted with ICC of 0.5.
(3) Data from 3 months. Type B or C2 tympanogram. Per ear data adjusted with ICC of 0.5.
(4) Data from 3 months. Type B or C2 tympanogram. Persistence in at least one ear.

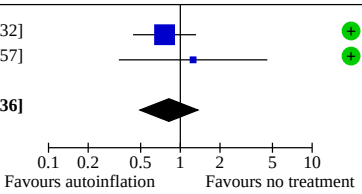
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.9. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 9: Episodes of acute otitis media (short-term, > 6 weeks to ≤ 3 months)

Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Blanshard 1993 (1)	14	42	18	41	84.7%	0.76 [0.44 , 1.32]
Williamson 2015a (1)	5	160	4	160	15.3%	1.25 [0.34 , 4.57]
Total (95% CI)		**202**		**201**	**100.0%**	**0.82 [0.49 , 1.36]**
Total events:	19		22			

Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



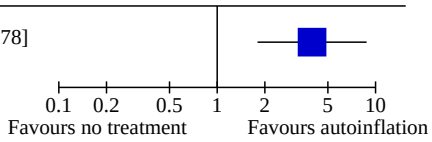
Footnotes
(1) Data from 3 months.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.10. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 10: Sensitivity analysis: Proportion of children whose hearing is normal (very short-term, < 6 weeks). Per ear data (ICC of 1, complete correlation between ears)

Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Risk Ratio M-H, Random, 95% CI
Bidarian-Moniri 2014 (1)	19	22	5	23	3.97 [1.80 , 8.78]

Test for subgroup differences: Not applicable

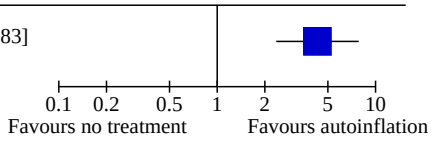


Footnotes
(1) Data from 4 weeks. Number with hearing threshold of < 20 dB HL. Per ear data, adjusted with an ICC of 1 (see appendix).

Analysis 1.11. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 11: Sensitivity analysis: Proportion of children whose hearing is normal (very short-term, < 6 weeks). Per ear data (ICC of 0, no correlation between ears)

Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Risk Ratio M-H, Random, 95% CI
Bidarian-Moniri 2014 (1)	37	44	9	46	4.30 [2.36 , 7.83]

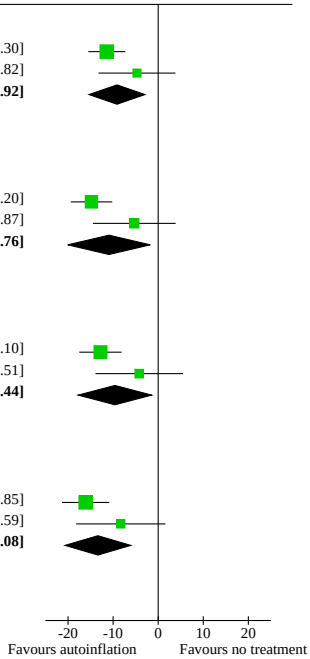
Test for subgroup differences: Not applicable



Footnotes
(1) Data from 4 weeks. Number with hearing threshold of < 20 dB HL. Per ear data, adjusted with an ICC of 0 (see appendix).

Analysis 1.12. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 12: Sensitivity analysis: Hearing threshold (short-term, > 6 weeks to ≤ 3 months). Right ear data

Study or Subgroup	Autoinflation Mean [dB HL]	SD [dB HL]	Total	No treatment Mean [dB HL]	SD [dB HL]	Total	Weight	Mean Difference IV, Random, 95% CI [dB HL]
1.12.1 0.5 kHz								
Arick 2005 (1)	18.3	7.6	43	29.7	11.7	45	66.2%	-11.40 [-15.50 , -7.30]
Banigo 2016 (2)	32.2	13.11	15	36.9	10.22	14	33.8%	-4.70 [-13.22 , 3.82]
Subtotal (95% CI)			**58**			**59**	**100.0%**	**-9.13 [-15.35 , -2.92]**
Heterogeneity: Tau² = 10.79; Chi² = 1.93, df = 1 (P = 0.17); I² = 48%								
Test for overall effect: Z = 2.88 (P = 0.004)								
1.12.2 1.0 kHz								
Arick 2005	15.5	8.4	43	30.3	13.2	45	59.1%	-14.80 [-19.40 , -10.20]
Banigo 2016	28.5	9.68	15	33.8	14.8	14	40.9%	-5.30 [-14.47 , 3.87]
Subtotal (95% CI)			**58**			**59**	**100.0%**	**-10.91 [-20.07 , -1.76]**
Heterogeneity: Tau² = 31.42; Chi² = 3.29, df = 1 (P = 0.07); I² = 70%								
Test for overall effect: Z = 2.34 (P = 0.02)								
1.12.3 2.0 kHz								
Arick 2005	7.9	7.9	43	20.7	13.9	45	62.7%	-12.80 [-17.50 , -8.10]
Banigo 2016	23	10.72	15	27.2	15.37	14	37.3%	-4.20 [-13.91 , 5.51]
Subtotal (95% CI)			**58**			**59**	**100.0%**	**-9.59 [-17.74 , -1.44]**
Heterogeneity: Tau² = 21.84; Chi² = 2.44, df = 1 (P = 0.12); I² = 59%								
Test for overall effect: Z = 2.31 (P = 0.02)								
1.12.4 4.0 kHz								
Arick 2005	12	9.8	43	28.1	14.9	45	65.0%	-16.10 [-21.35 , -10.85]
Banigo 2016	23.8	13.98	15	32.1	13.19	14	35.0%	-8.30 [-18.19 , 1.59]
Subtotal (95% CI)			**58**			**59**	**100.0%**	**-13.37 [-20.66 , -6.08]**
Heterogeneity: Tau² = 14.11; Chi² = 1.86, df = 1 (P = 0.17); I² = 46%								
Test for overall effect: Z = 3.60 (P = 0.0003)								
Test for subgroup differences: Chi² = 0.00, df = 3 (P < 0.00001), I² = 0%								

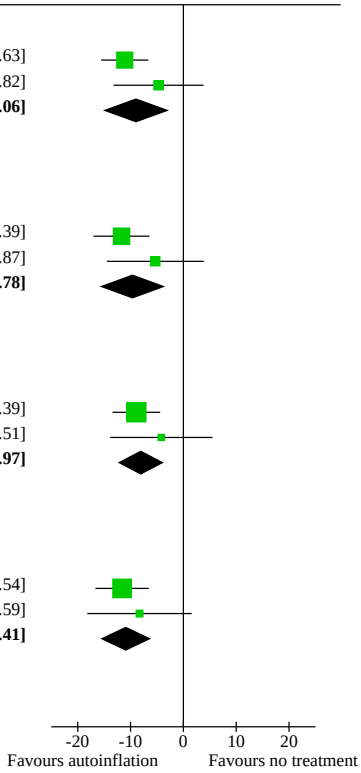


Footnotes

(1) Data from 11 weeks. Right ear used for analysis. Final hearing air conduction threshold.
(2) Data from 7 weeks. Final hearing air conduction threshold.

Analysis 1.13. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 13: Sensitivity analysis: Hearing threshold (short-term, > 6 weeks to ≤ 3 months). Left ear data

Study or Subgroup	Autoinflation Mean	SD	Total	No treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.13.1 0.5 kHz								
Arick 2005 (1)	19	10.3	45	30.1	10.8	41	66.7%	-11.10 [-15.57 , -6.63]
Banigo 2016 (2)	32.2	13.11	15	36.9	10.22	14	33.3%	-4.70 [-13.22 , 3.82]
Subtotal (95% CI)			**60**			**55**	**100.0%**	**-8.97 [-14.88 , -3.06]**
Heterogeneity: Tau² = 8.42; Chi² = 1.70, df = 1 (P = 0.19); I² = 41%								
Test for overall effect: Z = 2.98 (P = 0.003)								
1.13.2 1.0 kHz								
Arick 2005	17.3	11	45	29	13.8	41	67.8%	-11.70 [-17.01 , -6.39]
Banigo 2016	28.5	9.68	15	33.8	14.8	14	32.2%	-5.30 [-14.47 , 3.87]
Subtotal (95% CI)			**60**			**55**	**100.0%**	**-9.64 [-15.50 , -3.78]**
Heterogeneity: Tau² = 5.87; Chi² = 1.40, df = 1 (P = 0.24); I² = 29%								
Test for overall effect: Z = 3.22 (P = 0.001)								
1.13.3 2.0 kHz								
Arick 2005	8.7	8.2	45	17.6	12.5	41	82.2%	-8.90 [-13.41 , -4.39]
Banigo 2016	23	10.72	15	27.2	15.37	14	17.8%	-4.20 [-13.91 , 5.51]
Subtotal (95% CI)			**60**			**55**	**100.0%**	**-8.06 [-12.16 , -3.97]**
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%								
Test for overall effect: Z = 3.86 (P = 0.0001)								
1.13.4 4.0 kHz								
Arick 2005	14.7	8.1	45	26.3	14.6	41	79.3%	-11.60 [-16.66 , -6.54]
Banigo 2016	23.8	13.98	15	32.1	13.19	14	20.7%	-8.30 [-18.19 , 1.59]
Subtotal (95% CI)			**60**			**55**	**100.0%**	**-10.92 [-15.42 , -6.41]**
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%								
Test for overall effect: Z = 4.75 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.00, df = 3 (P < 0.00001), I² = 0%								



Footnotes

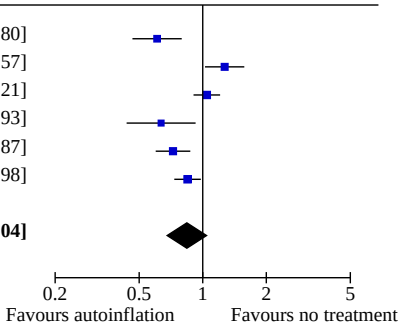
(1) Data from 11 weeks. Left ear used for analysis.

(2) Data from 7 weeks.

Analysis 1.14. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 14: Sensitivity analysis: Persistence of OME (very short-term, < 6 weeks). Per ear data (ICC of 0)

Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Bidarian-Moniri 2014 (1)	25	44	43	46	15.5%	0.61 [0.46 , 0.80]
Brooker 1992 (2)	38	41	27	37	17.0%	1.27 [1.03 , 1.57]
Chan 1989 (3)	35	38	37	42	18.7%	1.05 [0.90 , 1.21]
Ercan 2005 (4)	21	48	31	45	12.5%	0.64 [0.44 , 0.93]
Stangerup 1992 (5)	47	73	65	73	17.6%	0.72 [0.60 , 0.87]
Williamson 2015a (6)	115	188	135	187	18.7%	0.85 [0.73 , 0.98]
Total (95% CI)		**432**		**430**	**100.0%**	**0.84 [0.68 , 1.04]**
Total events:	281		338			

Heterogeneity: Tau² = 0.06; Chi² = 34.18, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 1.58 (P = 0.11)
Test for subgroup differences: Not applicable



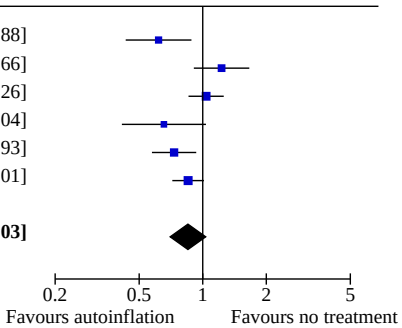
Footnotes

(1) Data from 4 weeks. Type B or C2 tympanogram. Per ear data.
(2) Data from 3 weeks. Children with a persistent flat tympanogram. Per ear data.
(3) Data from 2 weeks. No details on assessment method. Per ear data.
(4) Data from 6 weeks. Assessed with pneumatic otoscopy and tympanometry. Per ear data.
(5) Data from 2 weeks. Type B or C2 tympanogram. Per ear data.
(6) Data from 1 month. Type B or C2 tympanogram. Per ear data.

Analysis 1.15. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 15: Sensitivity analysis: Persistence of OME (very short-term, < 6 weeks). Per ear data (ICC of 1)

Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
Bidarian-Moniri 2014 (1)	13	22	22	23	13.6%	0.62 [0.43 , 0.88]
Brooker 1992 (2)	19	21	14	19	15.8%	1.23 [0.91 , 1.66]
Chan 1989 (3)	21	23	22	25	20.5%	1.04 [0.86 , 1.26]
Ercan 2005 (4)	14	31	20	29	10.5%	0.65 [0.41 , 1.04]
Stangerup 1992 (5)	30	47	41	47	18.3%	0.73 [0.57 , 0.93]
Williamson 2015a (6)	81	132	95	132	21.3%	0.85 [0.72 , 1.01]
Total (95% CI)		**276**		**275**	**100.0%**	**0.85 [0.70 , 1.03]**
Total events:	178		214			

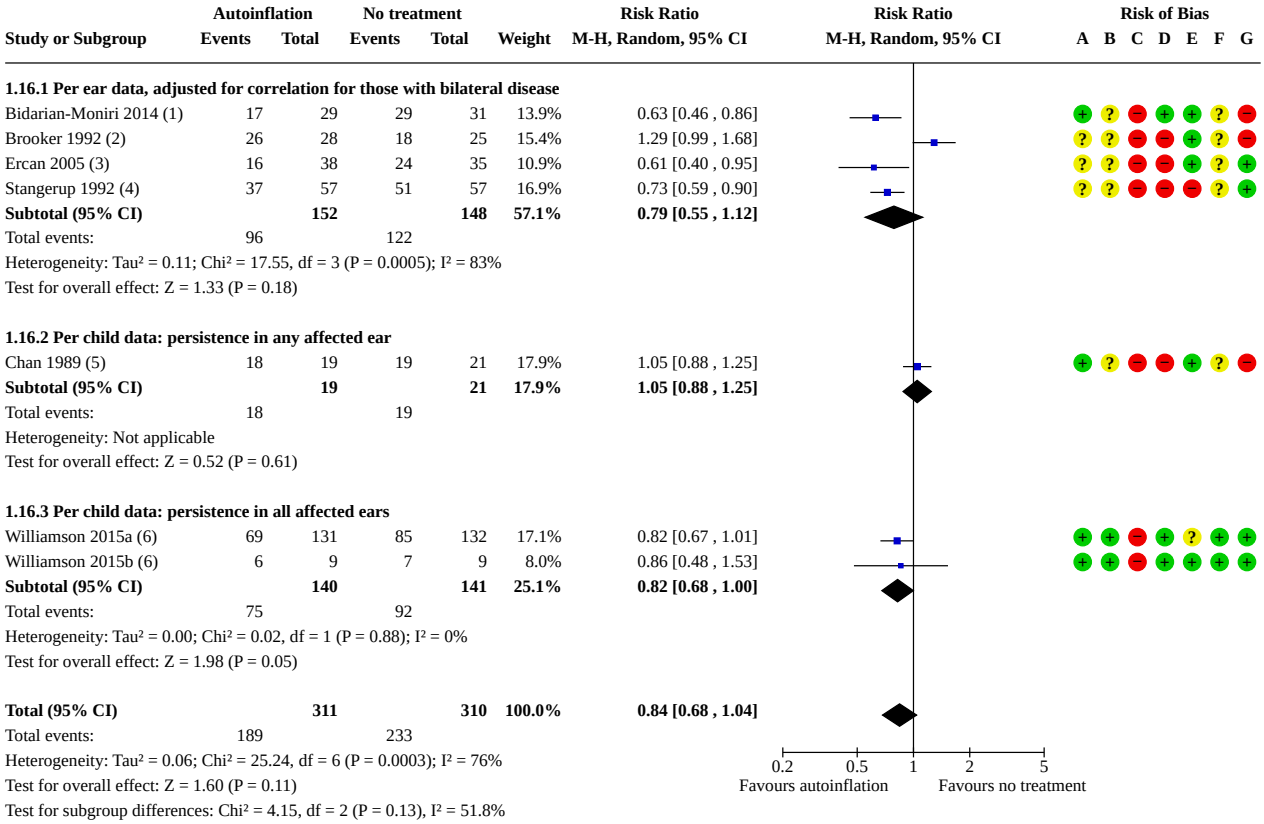
Heterogeneity: Tau² = 0.04; Chi² = 16.37, df = 5 (P = 0.006); I² = 69%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable



Footnotes

(1) Data from 4 weeks. Type B or C2 tympanogram. Per ear data adjusted with ICC of 1 (see appendix).
(2) Data from 3 weeks. Children with a persistent flat tympanogram. Per ear data adjusted with ICC of 1.
(3) Data from 2 weeks. No details on assessment method. Per ear data adjusted with ICC of 1.
(4) Data from 6 weeks. Assessed with pneumatic otoscopy and tympanometry. Per ear data adjusted with ICC of 1.
(5) Data from 2 weeks. Type B or C2 tympanogram. Per ear data adjusted with ICC of 1.
(6) Data from 1 month. Type B or C2 tympanogram. Per ear data adjusted with ICC of 1.

Analysis 1.16. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 16: Sensitivity analysis: Persistence of OME (very short-term, < 6 weeks). Per child data, where available



Footnotes

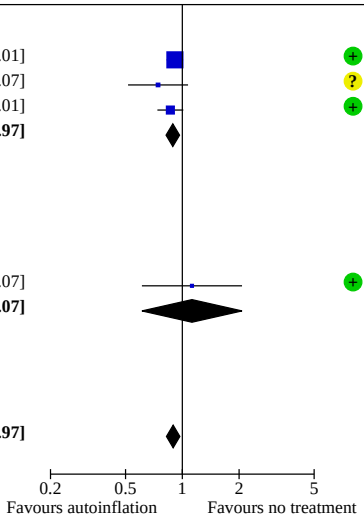
(1) Data from 4 weeks. Type B or C2 tympanogram. Per ear data adjusted with ICC of 0.5 (see appendix).
(2) Data from 3 weeks. Children with a persistent flat tympanogram. Per ear data adjusted with ICC of 0.5.
(3) Data from 6 weeks. Assessed with pneumatic otoscopy and tympanometry. Per ear data adjusted with ICC of 0.5.
(4) Data from 2 weeks. Type B or C2 tympanogram. Per ear data adjusted with ICC of 0.5.
(5) Data from 2 weeks. No details on assessment method. Per child data (persistence in at least one affected ear).
(6) Data from 1 month. Type B or C2 tympanogram. Per child data (persistence in all affected ears)

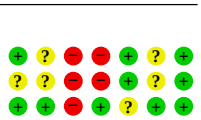
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.17. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 17: Sensitivity analysis: Persistence of OME (short-term, > 6 weeks to ≤ 3 months). Per ear data (ICC of 0)

Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 Per ear data						
Blanshard 1993 (1)	71	82	73	77	66.6%	0.91 [0.83 , 1.01]
Ercan 2005 (2)	23	48	29	45	5.0%	0.74 [0.52 , 1.07]
Williamson 2015a (1)	108	182	114	166	26.6%	0.86 [0.74 , 1.01]
Subtotal (95% CI)		**312**		**288**	**98.2%**	**0.89 [0.82 , 0.97]**
Total events:	202		216			
Heterogeneity: Tau² = 0.00; Chi² = 1.81, df = 2 (P = 0.40); I² = 0%						
Test for overall effect: Z = 2.76 (P = 0.006)						
1.17.2 Per child data						
Williamson 2015b (3)	6	8	6	9	1.8%	1.13 [0.61 , 2.07]
Subtotal (95% CI)		**8**		**9**	**1.8%**	**1.13 [0.61 , 2.07]**
Total events:	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
Total (95% CI)		**320**		**297**	**100.0%**	**0.89 [0.82 , 0.97]**
Total events:	208		222			
Heterogeneity: Tau² = 0.00; Chi² = 2.27, df = 3 (P = 0.52); I² = 0%						
Test for overall effect: Z = 2.69 (P = 0.007)						
Test for subgroup differences: Chi² = 0.55, df = 1 (P = 0.46), I² = 0%						





Footnotes

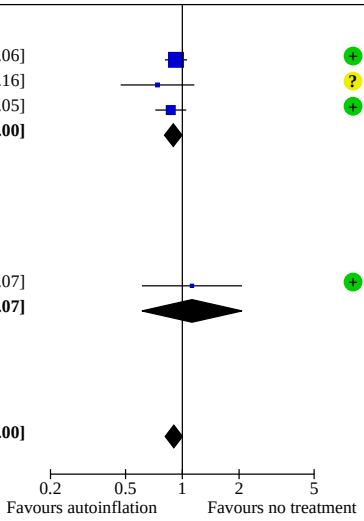
(1) Data from 3 months. Type B or C2 tympanogram. Per ear data.
(2) Data from 3 months. Assessed with pneumatic otoscopy and tympanometry. Per ear data.
(3) Data from 3 months. Type B or C2 tympanogram. Persistence in at least one ear.

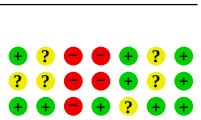
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.18. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 18: Sensitivity analysis: Persistence of OME (short-term, > 6 weeks to ≤ 3 months). Per ear data (ICC of 1)

Study or Subgroup	Autoinflation Events	Autoinflation Total	No treatment Events	No treatment Total	Weight	Risk Ratio M-H, Random, 95% CI
1.18.1 Per ear data						
Blanshard 1993 (1)	36	41	37	39	60.5%	0.93 [0.81 , 1.06]
Ercan 2005 (2)	15	31	19	29	5.5%	0.74 [0.47 , 1.16]
Williamson 2015a (3)	76	128	80	117	31.1%	0.87 [0.72 , 1.05]
Subtotal (95% CI)		**200**		**185**	**97.0%**	**0.90 [0.80 , 1.00]**
Total events:	127		136			
Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 2.03 (P = 0.04)						
1.18.2 Per child data						
Williamson 2015b (4)	6	8	6	9	3.0%	1.13 [0.61 , 2.07]
Subtotal (95% CI)		**8**		**9**	**3.0%**	**1.13 [0.61 , 2.07]**
Total events:	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.71)						
Total (95% CI)		**208**		**194**	**100.0%**	**0.90 [0.81 , 1.00]**
Total events:	133		142			
Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 3 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.93 (P = 0.05)						
Test for subgroup differences: Chi² = 0.52, df = 1 (P = 0.47), I² = 0%						





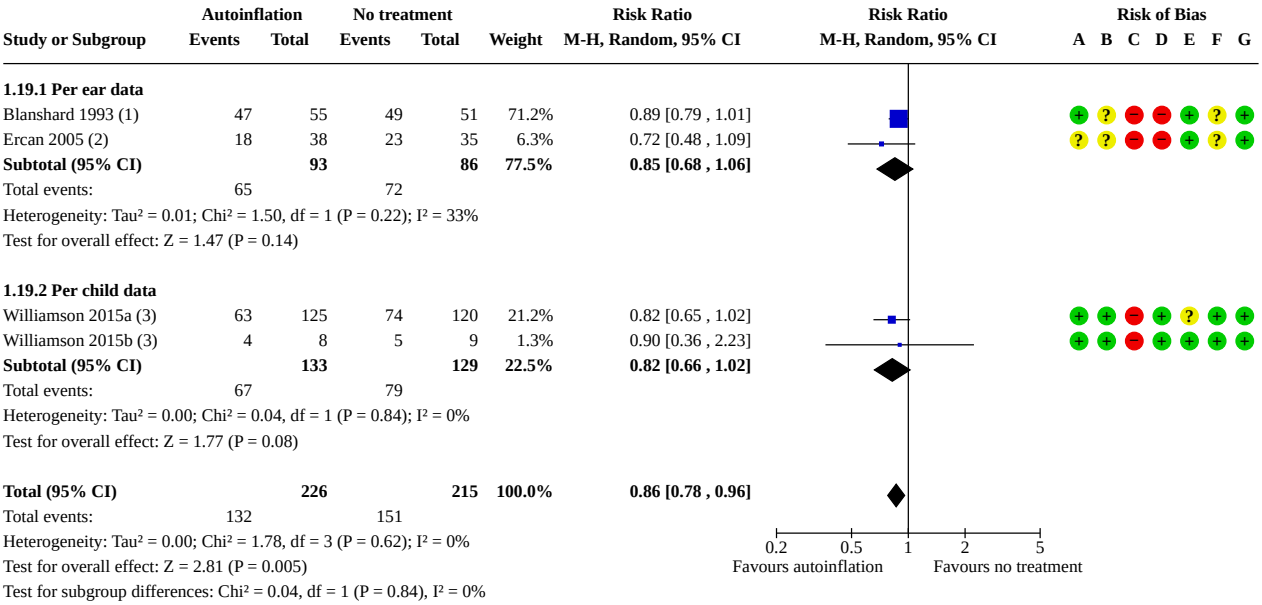
Footnotes

(1) Data from 3 months. Type B or C2 tympanogram. Per ear data adjusted with ICC of 1 (see appendix).
(2) Data from 3 months. Assessed with pneumatic otoscopy and tympanometry. Per ear data adjusted with ICC of 1.
(3) Data from 3 months. Type B or C2 tympanogram. Per ear data, adjusted with ICC of 1.
(4) Data from 3 months. Type B or C2 tympanogram. Persistence in at least one ear.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.19. Comparison 1: Autoinflation versus watchful waiting/no treatment, Outcome 19: Sensitivity analysis: Persistence of OME (short-term, > 6 weeks to ≤ 3 months). Per child data, where available



Footnotes

(1) Data from 3 months. Type B or C2 tympanogram. Per ear data adjusted with ICC of 0.5.
(2) Data from 3 months. Assessed with pneumatic otoscopy and tympanometry. Per ear data adjusted with ICC of 0.5 (see appendix).
(3) Data from 3 months. Type B or C2 tympanogram. Persistence in all affected ears.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. RCTs identified through Cochrane Crowd and the RCT classifier

	Possible RCTs	Rejected
Known assessments	34	50
RCT classifier	2559	1514
Cochrane Crowd	1130	1313
Total	1280	2877

RCT: randomised controlled trial

Table 2. Key characteristics of studies and participants

Study	Participants and ears randomised (N)	Autoinflation method	Age (years) and whether unilateral or bilateral (if stated)	Outcomes assessed by study	Final follow-up
Arick 2005	94 174 ears	Modified Politzer device, used twice daily for 7 weeks	4 to 11 Minimum 2-month history of middle ear effusion	• Proportion children with hearing returned to normal • Mean (SD) final hearing thresholds (dB) per ear assessed	11 weeks
Banigo 2016	30	EarPopper device, used twice daily for 7 weeks	4 to 11 3-month history of persistent OME	• Mean (SD) final hearing thresholds (dB), air conduction at 7 weeks • Mean (SD) change in hearing thresholds (dB) from baseline, air conduction thresholds • Presence/persistence of OME • Adverse events: narrative summary	7 weeks
Bidari-an-Moniri 2014	45	New autoinflation device consisting of an inflatable facemask, a T-shaped junction tube connecting at one end to the facemask, another end to a balloon and the third end to a handheld pump covered by a teddy bear to improve compliance Used twice daily for 4 weeks	2 to 8 All bilateral Persistent OME with a duration of at least 3 months	• Proportion of ears with hearing returned to normal: hearing thresholds > 20 dB • Mean (SD) change in hearing thresholds (dB) from baseline (best ear): pure tone air conduction thresholds • Presence/persistence of OME • Adverse events: narrative summary	4 weeks (Additional data at 1-year follow-up, but not relevant for this review)
Blanshard 1993	85	Otovent device, used 3 times daily for 3 months	3 to 10 Bilateral Confirmation of type B or C2 tympanograms on 2 occasions separated by ≥ 3 months	• Mean (SD) change in hearing thresholds (dB) from baseline: pure tone audiometry • Presence/persistence of OME • Episodes of acute otitis media	3 months
Brooker 1992	40 78 ears	Device comprised of a toy balloon attached to a carnival blower mouthpiece; used 3 times daily for 3 weeks	< 10 years Unilateral or bilateral	• Presence/persistence of OME	3 weeks
Chan 1989	41	Modified Valsalva techniques - a disposable anaesthesia mask attached to a floating	3 to 18 Unilateral or bilateral	• Presence/persistence of OME • Adverse events: narrative summary	2 weeks

Table 2. Key characteristics of studies and participants *(Continued)*

		ball-type flowmeter. Child instructed to exhale through the nose through the mask (with mouth closed), as the pressure increased the ball in the flowmeter was propelled upwards. Used 3 times daily for 2 weeks.	Aimed to include those that had persistence for ≥ 3 months (although this was not everyone)		
Ercan 2005	60 93 ears	Otovent, used 3 times daily for 6 weeks	Unilateral and bilateral Chronic OME for 3 months	• Presence/persistence of OME	3 months
Scadding 2014	200	Otovent, used 3 times daily for 4 to 5 weeks	4 to 8 With ≥ 3 months of glue ear or > 2 episodes in the past 6 months	• Presence/persistence of OME • Adverse effects: narrative summary	2 years
Stangerup 1992	100	Tube designed by the author, with a balloon on the end, inserted in one nostril and blown up whilst occluding the other. Used 3 times daily for 2 to 4 weeks.	3 to 10 Unilateral and bilateral Secretory OM for ≥ 3 months	• Presence/persistence of OME • Episodes of acute otitis media	3 months

Williamson 2015a	320	Otovent, used 3 times daily for between 1 and 3 months	4 to 11
			
			Unilateral and bilateral
			
			Parental concern with report of ≥ 1 relevant symptom/concern associated with OME in previous 3 months
				• Disease-specific quality of life: OMQ-14
				• Presence/persistence of OME
				• Receptive language: mean (SD) at endpoint
				  ◦ Auditory disability and speech reception tests and hearing tests
				• Other adverse effects
				  ◦ Nosebleeds
				  ◦ URTI
				  ◦ Unspecified RTI
				  ◦ Lower RTI
				  ◦ Otalgia
				  ◦ Headache
				  ◦ Hay fever
				  ◦ Serious adverse event: hospitalisation
					3 months

Williamson 2015b	21	Otovent, used 3 times daily for between 1 and 3 months	4 to 11 Unilateral and bilateral Parental concern with report of ≥	• Presence/persistence of OME • Adverse events: narrative summary	3 months

Table 2. Key characteristics of studies and participants *(Continued)*

			1 relevant symptom/concern associated with OME in previous 3 months	

OME: otitis media with effusion; RTI: respiratory tract infection; SD: standard deviation; URTI: upper respiratory tract infection

Table 3. Compliance with autoinflation

Study	Treatment requirements	Compliance monitoring and definition	Age	Compliance
Arick 2005	Twice a day, alternating nostrils with each treatment for 7 weeks	Daily log to track compliance	4 to 11 years	Complete compliance in 46 of 47 experimental patients (97.9%), moderate compliance in remaining patient
Banigo 2016	Use twice a day and on each occasion to be used twice in each nostril for 7 weeks	Diary card, no definition	Treatment Mean 5.94 years (range 4.36 to 8.19) Control Mean 5.55 (range 3.96 to 7.79)	94% on average
Bidarian-Moniri 2014	Use the device twice a day to perform 20 inflations at each session (approximately 5 to 10 minutes) for 4 weeks	Diary and full compliance was defined as using the device twice a day to perform 20 inflations at each session (approximately 5 to 10 minutes) during a period of 4 weeks	Treatment: 68 months Control: 53 months	All children from 2 years and 9 months of age were able to use the device after demonstration by a doctor or nurse. In one case, the compliance was not satisfactory to complete the 4-week treatment. The overall compliance for the total treatment time was satisfactory.
Blanshard 1993	One nostril 3 times a day	Compliance was measured as the number of times the device was used as a percentage of the maximum possible	Treatment HC (high compliance) n = 19 Mean 62.7 months (SD 17.5) LC (low compliance) n = 23 Mean 52.8 months (SD 8.9) Control n = 41 Mean 59.9 months (SD 18.3)	Of 42 children in the treatment group, 19 (45%) used it as prescribed (> 70%), 18 (43%) used it irregularly and 5 (12%) were unable to use it at all. Treatment group was divided into those with a high compliance (HC) of greater than 70%, (n = 19) and those with a low compliance (LC) of < 70% (n = 23). In the LC group compliance deteriorated from 45% to 29% over the course of the treatment. See table 1 in Blanshard 1993 for further information
Brooker 1992	Inflate balloon nasally 3 times a day for 3 weeks	No information on compliance	Age 3 to 10 years, mean 5.7	No information on compliance

Table 3. Compliance with autoinflation *(Continued)*

Chan 1989	3 times daily for 2 weeks	Participants stratified according to their ability of tubal opening during autoinflation Parents asked to record number of exercise cycles completed each day and to hand in a score card at the end of the 2-week study as a method to monitor patient compliance Ability to autoinflate Autoinflation No 4 (21.1) Yes 15 (78.9) Control No 5 (22.7) Yes 17 (77.3)	Age between 3 and 18 years of age Autoinflation 3 to 6 years: 14 (73.6) 7 to 11 years: 4 (21.1) > 12 years: 1 (5.3) Control 3 to 6 years: 13 (59.1) 7 to 11 years: 7 (31.8) > 12 years: 2 (9.2)	No further details on compliance
Ercan 2005	Autoinflation 3 times a day for 6 weeks	—	Mean age 6.2 years (range 4 to 10 years)	"The compliance of the children to the autoinflation was satisfactory and the autoinflation was somehow amusing for the children"
Scadding 2014	Otovent 3 times daily for approximately 4 to 5 weeks	Compliance assessed by questioning child and parent/guardian and by number of bottles used. Those who reported spray use on at least 3 days a week remained in the study.	Aged between 4 and 8 years Treatment 5.7 (SD 1.3) Placebo 5.7 years (SD 1.3)	Those who reported spray use on at least 3 days a week remained in the study
Stangerup 1992	3 times a day for 2 weeks	At second visit the use of the nose balloon was scored: 0 not used, 1 used a few times, 2 used as prescribed	Aged 3 to 10 years "some children younger than 3 years of age had difficulty performing autoinflation" Median age 5.3 years	3 children had not performed autoinflation, 10 only once, 33 had followed instructions
Williamson 2015a	Otovent 3 times per day for 1 to 3 months	Weekly diary of compliance, sticker book	Autoinflation group: mean 5.4 years (SD 1.24) Control group: mean 5.4 years (SD 1.04)	89% (116/130) used 'most' or 'all of the time' in the first month 80% in months 2 and 3 (68/85, 805) See table 22 in Williamson 2015a for more information
Williamson 2015b	Otovent 3 times per day for 1 to 3 months	Recorded using a daily sticker reward chart	Age: Autoinflation group:	Compliance described as "excellent" and pilot study answered major unknown issue about "whether or not children were able to perform

Table 3. Compliance with autoinflation *(Continued)*

	4 to 5 years: 3 5 to 6 years: 4 6 to 10 years: 0 7 to 11 years: 2 Control group: 4 to 5 years: 2 5 to 6 years: 8 6 to 10 years: 0 7 to 11 years: 0	the technique and achieve sufficient compliance over 1 month in a primary care setting" See table 4 in Williamson 2015a for more information

SD: standard deviation

Table 4. Sensitivity analyses

Outcome	Main analysis result	Sensitivity analysis	Sensitivity analysis result
1.5.1 Hearing threshold (short-term, > 6 weeks to ≤ 3 months): 0.5 kHz	MD -9.13 (-15.14 to -3.13)	Fixed-effect model	MD -10.17 (-13.63 to -6.71)
1.5.2 Hearing threshold (short-term, > 6 weeks to ≤ 3 months): 1 kHz	MD -10.34 (-17.85 to -2.83)	Fixed-effect model	MD -11.77 (-15.73 to -7.82)
1.5.3 Hearing threshold (short-term, > 6 weeks to ≤ 3 months): 2 kHz	MD -9.04 (-14.84 to -3.25)	Fixed-effect model	MD -9.85 (-13.61 to -6.10)
1.5.4 Hearing threshold (short-term, > 6 weeks to ≤ 3 months): 4 kHz	MD -12.88 (-17.01 to -8.75)	Fixed-effect model	MD -12.88 (-17.01 to -8.75)
1.7 Persistence of OME (very short-term, < 6 weeks)	RR 0.86 (0.72 to 1.04)	Fixed-effect model	RR 0.83 (0.76 to 0.92)
1.7 Persistence of OME (very short-term, < 6 weeks)	RR 0.86 (0.72 to 1.04)	Excluding studies at high risk using the trustworthiness tool	RR 0.94 (0.81 to 1.09)
1.8 Persistence of OME (short-term, > 6 weeks to ≤ 3 months)	RR 0.88 (0.80 to 0.97)	Fixed-effect model	RR 0.86 (0.77 to 0.97)
1.8 Persistence of OME (short-term, > 6 weeks to ≤ 3 months)	RR 0.88 (0.80 to 0.97)	Excluding studies at high risk using the trustworthiness tool	RR 0.88 (0.74 to 1.04)
1.9 Episodes of acute otitis media (short-term, > 6 weeks to ≤ 3 months)	RR 0.82 (0.49 to 1.36)	Fixed-effect model	RR 0.85 (0.51 to 1.41)
1.9 Episodes of acute otitis media (short-term, > 6 weeks to ≤ 3 months)	RR 0.82 (0.49 to 1.36)	Excluding studies at high risk using the trustworthiness tool	RR 1.25 (0.34 to 4.57)

MD: mean difference; OME: otitis media with effusion; RR: risk ratio

Numbers in brackets represent 95% confidence intervals.

APPENDICES

Appendix 1. Search strategies

The search strategies were designed to identify all relevant studies for a suite of reviews on various interventions for otitis media with effusion.

CENTRAL (CRS)	Cochrane ENT Register (CRS)	MEDLINE (Ovid)
1 MESH DESCRIPTOR Otitis Media with Effusion EXPLODE ALL AND CENTRAL:TARGET	1 MESH DESCRIPTOR Otitis Media EXPLODE ALL AND INREGISTER	1 exp Otitis Media with Effusion/
2 ("otitis media" adj6 effusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET	2 ("otitis media" OR OME OR "glue ear" OR middle-ear effusion OR middle-ear perfusion):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER	2 ("otitis media" adj6 effusion).ab,ti.
3 (OME):TI,TO AND CENTRAL:TARGET	3 #1 OR #2	3 OME.ti.
4 (Secretory otitis media):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET	4 (effusion or Recurrent or persistent or serous or secretory or perfusion):AB,EH,KW,KY,MC,MH,TI,TO AND INREGISTER	4 Secretory otitis media.ab,ti.
5 (Serous otitis media):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET	5 #3 AND #4	5 Serous otitis media.ab,ti.
6 (Middle-ear effusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET		6 Middle-ear effusion.ab,ti.
7 (glue ear):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET		7 Glue ear.ab,ti.
8 (middle-ear perfusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET		8 middle-ear perfusion.ab,ti.
9 MESH DESCRIPTOR Otitis Media AND CENTRAL:TARGET		9 Otitis Media/
10 (otitis media):TI,TO AND CENTRAL:TARGET		10 otitis media.ti.
11 #9 OR #10 AND CENTRAL:TARGET		11 9 or 10
12 (((effusion or Recurrent or persistent or serous or secretory or perfusion) adj3 otitis)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET		12 ((effusion or Recurrent or persistent or serous or secretory or perfusion) adj3 otitis).ab,ti.
13 #11 AND #12 AND CENTRAL:TARGET		13 11 and 12
14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #13 AND CENTRAL:TARGET		14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 13
		15 randomized controlled trial.pt.
		16 controlled clinical trial.pt.
		17 randomized.ab.
		18 placebo.ab.
		19 drug therapy.fs.
		20 randomly.ab.
		21 trial.ab.
		22 groups.ab.

(Continued)

		23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 24 exp animals/ not human-s.sh. 25 23 not 24 26 14 and 25
Embase (Ovid)	**Web of Science (Web of knowledge)**	**Trial registries (CRS)**
1 exp secretory otitis media/ 2 ("otitis media" adj6 effusion).ab,ti. 3 OME.ti. 4 Secretory otitis media.ab,ti. 5 Serous otitis media.ab,ti. 6 Middle-ear effusion.ab,ti. 7 glue ear.ab,ti. 8 middle-ear perfusion.ab,ti. 9 otitis media/ 10 otitis media.ti. 11 9 or 10 12 ((effusion or Recurrent or persistent or serous or secretory or perfusion) adj3 otitis).ab,ti. 13 11 and 12 14 1 or 2 or 4 or 5 or 6 or 7 or 8 or 13 15 (random* or factorial* or placebo* or assign* or allocat* or crossover*).tw. 16 (control* adj group*).tw. 17 (trial* and (control* or comparative)).tw. 18 ((blind* or mask*) and (single or double or triple or treble)).tw. 19 (treatment adj arm*).tw. 20 (control* adj group*).tw. 21 (phase adj (III or three)).tw. 22 (versus or vs).tw. 23 rct.tw. 24 crossover procedure/ 25 double blind procedure/ 26 single blind procedure/	11 #10 AND #9 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 10 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 9 TS=(randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple))) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 8 (TI=(otitis media)) AND TS=((effusion or Recurrent or persistent or serous or secretory or perfusion) NEAR/3 otitis) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 7 TOPIC: ((middle-ear perfusion)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 6 TOPIC: ((glue ear)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 5 TOPIC: ((Middle-ear effusion)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 4 TOPIC: ((Serous otitis media)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 3 TOPIC: ((Secretory otitis media)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 2 TITLE: (OME)	1 ("otitis media" OR OME OR "glue ear" OR middle-ear effusion OR middle-ear perfusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 2 (effusion or Recurrent or persistent or serous or secretory or perfusion):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 3 #1 AND #2 4 http*:SO AND CENTRAL:TARGET 5 (NCT0* or ACTRN* or ChiCTR* or DRKS* or EUCTR* or eudract* or IRCT* or ISRCTN* or JapicCTI* or JPRN* or NTR0* or NTR1* or NTR2* or NTR3* or NTR4* or NTR5* or NTR6* or NTR7* or NTR8* or NTR9* or SRCTN* or UMIN0*):AU AND CENTRAL:TARGET 6 #4 OR #5 7 #3 AND #6

(Continued)

27 randomization/ 28 placebo/ 29 exp clinical trial/ 30 parallel design/ 31 Latin square design/ 32 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 33 exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/ 34 exp human/ 35 33 not 34 36 32 not 35 37 14 and 36	Indexes=SCI-EXPANDED, CPCI-S Timespan=All years 1 TOPIC: ("otitis media" NEAR/6 effusion) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

ClinicalTrials.gov	ICTRP
(EXPAND[Concept] "otitis media" OR EXPAND[Concept] "glue ear" OR middle-ear) AND (effusion OR Recurrent OR persistent OR serous OR secretory OR perfusion) | Interventional Studies	(otitis media AND effusion) OR glue ear OR middle-ear effusion OR middle-ear perfusion

Appendix 2. Tool for screening eligible studies for scientific integrity/trustworthiness

This screening tool has been developed by Cochrane Pregnancy and Childbirth. It includes a set of predefined criteria to select studies which, based on available information, are deemed to be sufficiently trustworthy to be included in the analysis.

Criteria questions	Assessment		Comments and concerns
	High risk	Low risk	
Research governance			
Are there any retraction notices or expressions of concern listed on the Retraction Watch Database relating to this study?	Yes	No	
Was the study prospectively registered (for those studies published after 2010) If not, was there a plausible reason?	No	Yes	
When requested, did the trial authors provide/share the protocol and/or ethics approval letter?	No	Yes	
Did the trial authors engage in communication with the Cochrane Review authors within the agreed timelines?	No	Yes	
Did the trial authors provide IPD data upon request? If not, was there a plausible reason?	No	Yes	

(Continued)

Baseline characteristics		
Is the study free from characteristics of the study participants that appear too similar? (e.g. distribution of the mean (SD) excessively narrow or excessively wide, as noted by Carlisle 2017)	No	Yes
Feasibility		
Is the study free from characteristics that could be implausible? (e.g. large numbers of women with a rare condition (such as severe cholestasis in pregnancy) recruited within 12 months)	No	Yes
In cases with (close to) zero losses to follow-up, is there a plausible explanation?	No	Yes
Results		
Is the study free from results that could be implausible? (e.g. massive risk reduction for main outcomes with small sample size)?	No	Yes
Do the numbers randomised to each group suggest that adequate randomisation methods were used (e.g. is the study free from issues such as unexpectedly even numbers of women 'randomised' including a mismatch between the numbers and the methods, if the authors say 'no blocking was used' but still end up with equal numbers, or if the authors say they used 'blocks of 4' but the final numbers differ by 6)?	No	Yes
For abstracts only:		
Have the study authors confirmed in writing that the data to be included in the review have come from the final analysis and will not change?	No	Yes

HISTORY

Protocol first published: Issue 4, 2022

CONTRIBUTIONS OF AUTHORS

Katie Webster: screened the search results and selected studies, conducted data extraction and carried out statistical analyses. Drafted the text of the review.

Caroline A Mulvaney: drafted the protocol. Screened the search results and selected studies, conducted data extraction, carried out statistical analyses and GRADE assessment. Drafted the text of the review.

Kevin Galbraith: drafted the protocol. Screened the search results and selected studies, conducted data extraction, carried out statistical analyses and GRADE assessment. Drafted the text of the review.

Mridul Rana: conducted data extraction. Reviewed the analyses and reviewed and edited the text of the review.

Tal Marom: reviewed the protocol. Reviewed the analyses and reviewed and edited the text of the review.

Mat Daniel: reviewed the protocol. Reviewed the analyses and reviewed and edited the text of the review.

Roderick P Venekamp: co-wrote and edited the protocol. Reviewed the analyses and reviewed and edited the text of the review.

Anne GM Schilder: co-wrote and edited the protocol. Reviewed the analyses and reviewed and edited the text of the review.

Samuel MacKeith: drafted the protocol. Screened the search results and selected studies. Reviewed the analyses and reviewed and edited the text of the review.

DECLARATIONS OF INTEREST

Katie Webster: none known.

Caroline A Mulvaney: none known.

Kevin Galbraith: none known.

Mridul Rana: none known.

Samuel MacKeith: treats patients with OME in his NHS and private practice and is Assistant Co-ordinating Editor of Cochrane ENT but has not been involved in the editorial process for this review.

Tal Marom: treats patients with OME in his public sector and private practice.

Mat Daniel: treats patients with OME in his NHS practice. He has a financial interest in Aventamed, a company that produces a ventilation tube insertion device.

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

Anne GM Schilder: Professor Anne Schilder was joint Co-ordinating Editor of Cochrane ENT until April 2020, but had no role in the editorial process for this review. She treats patients with OME in her NHS practice. Her evidENT team at the UCL Ear Institute is supported by the National Institute of Health Research (NIHR) University College London Hospitals (UCLH) Biomedical Research Centre (BRC), with research projects being supported by the NIHR, Wellcome Trust, RNiD, ENT UK and industry. She is the National Specialty Lead for the NIHR Clinical Research Network ENT and Surgical Specialty Lead for ENT for the Royal College of Surgeons of England's Clinical Research Initiative. In her role as director of the NIHR UCLH BRC Deafness and Hearing Problems Theme, she advises CRO, biotech and pharma companies in the hearing field on clinical trial design and delivery.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We noted some overlap in the outcomes related to adverse events that were specified in our protocol (Galbraith 2022). The original list of primary and secondary outcomes was as follows:

Primary outcomes

- Hearing
- Disease-specific quality of life
- Adverse events - pain and distress caused by the procedure

Secondary outcomes

- Presence/persistence of OME
- Adverse events:
  - Eardrum perforation
  - Middle ear infection
  - Otalgia
  - Acute otitis media (AOM)
- Compliance

- Receptive language skills
- Speech development
- Cognitive development
- Psychosocial outcomes
- Listening skills
- Generic health-related quality of life
- Parental stress
- Vestibular function
- Number of doctor-diagnosed AOM episodes within a specified time frame

However, when we came to extract outcome data from the studies, we noted that there was some duplication in this list:

- Our primary outcome of 'pain and distress caused by the procedure' overlapped with the outcome 'otalgia', listed as a secondary outcome.
- Our secondary outcomes of middle ear infection and acute otitis media (listed under adverse events) overlapped with the outcome 'number of doctor diagnosed AOM episodes within a specified time frame'.

No studies reported specifically on 'pain and distress caused by the procedure'. However, some studies gave information on the number of children experiencing otalgia. We considered that this should be assessed within this primary outcome, rather than as a separate, secondary outcome. Therefore, data on otalgia have been included under this outcome in the summary of findings table, and are reported in the abstract.

Due to the overlap in outcomes considering infection, we have only reported on the 'number of doctor diagnosed AOM episodes within a specified time frame'.

In our protocol we planned to use the Trustworthiness Tool developed by Cochrane Pregnancy and Childbirth to determine which studies would be included in the main analyses. As described in the text, we used this tool to assess the studies, but did not use it to determine whether a study should be included in the main analysis.