Comparative Effectiveness Review
Number 185

# Tympanostomy Tubes in Children With Otitis Media



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This report is based on research conducted by the Brown Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00002-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

**None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.**

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.



This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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# Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.
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# Tympanostomy Tubes in Children With Otitis Media

## Structured Abstract

**Objectives.** The objectives for the systematic review are to synthesize information on the effectiveness of tympanostomy tubes (TT) in children with chronic otitis media with effusion and recurrent acute otitis media, summarize the frequency of adverse effects or complications associated with TT placement, synthesize information on the necessity for water precautions in children with TT, and assess the effectiveness of available treatments for otorrhea in children who have TT.

**Data sources.** We conducted literature searches in MEDLINE®, the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, Embase®, and CINAHL®. Additionally, we perused the reference lists of published relevant clinical practice guidelines and narrative and systematic reviews, and examined Scientific Information Packages from manufacturers. Citations were independently screened by two researchers.

**Review methods.** Each study was extracted by one methodologist and confirmed by at least one other methodologist. Data were extracted into customized forms in the Systematic Review Data Repository (SRDR) online system. All included studies were summarized in narrative form and in summary tables. We conducted random effects meta-analyses of comparative studies that were sufficiently similar in population, interventions, and outcomes, and network meta-analyses to compare treatment alternatives across studies. Specific methods and metrics (summary measures) meta-analyzed were chosen based on available reported study data. The PROSPERO protocol registration number is CRD42015029623.

**Results and conclusions.** The literature search yielded 13,334 citations, of which 172 articles are included in the report. Overall, the evidence suggests that TT placed in children with persistent middle-ear effusion improve hearing at 1 to 3 months compared to watchful waiting, but there is no benefit at 12 to 24 months. TT did not consistently improve language, cognition, behavior, or quality of life. However, evidence is sparse, limiting definitive conclusions, and is applicable only to otherwise healthy children. The current evidence base provides little guidance for the treatment of children with cleft palate or Down syndrome. Children with recurrent acute otitis media may have fewer episodes after TT placement, but the evidence base is limited and there is insufficient evidence to assess the impact on quality of life. The benefits of TT placement must be weighed against a variety of adverse events. There is no compelling evidence for children with TT to avoid swimming or bathing, or use earplugs or bathing caps. Should otorrhea develop, the evidence supports topical treatment rather than oral antibiotics or watchful waiting.

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# Executive Summary

## Background and Objectives

Otitis media is often preceded by a viral upper respiratory tract infection that causes Eustachian tube obstruction, negative middle ear pressure, and accumulation of fluid in the normally air-filled space of the middle ear. Acute otitis media (AOM) is defined as the presence of fluid in the middle ear with signs and symptoms of an acute infection, such as fever and ear pain. Otitis media with effusion (OME) is defined as the presence of fluid in the middle ear behind an intact tympanic membrane without signs and symptoms of an acute infection. [1,2] OME is defined as chronic OME, if effusion persists for 3 months or longer.[1] Acute otitis media and chronic OME have shared causes. Children with chronic OME are prone to recurrent AOM episodes, and after an AOM episode all children have OME for some time.[3] Chronic OME can result in hearing deficits, which put a child at risk for speech and language delays, behavioral changes, and poor academic achievement. Recurrent AOM has been shown to impact quality of life for patients and their caregivers.[4]

Certain children, including those with Down syndrome and cleft palate, have a very high risk for middle ear disease. The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) clinical practice guideline (CPG) identifies a subpopulation of children who may be at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors.[1,5]

Myringotomy with TT placement is the most common ambulatory surgery performed on children in the United States[6], with 667,000 TT placed in children under the age of 15 in 2006.[7] The proceedings of the National Summit on Overuse, convened in 2012, based on sample of continually enrolled children into a treatment pathways database and a Medicaid database, reported that 2.5 percent of all U.S. children 2 years old and older had TT inserted in 2010.[8]

The effectiveness of TT for chronic OME and recurrent AOM is likely influenced by the many factors that affect the prognosis for middle ear disease in children, including current age, age at first diagnosis, frequency of respiratory tract infections, and day care exposure.[9]

The AAO-HNS CPG recommends that clinicians offer TT to children with recurrent AOM who have middle ear effusion at the time of assessment for tube candidacy, and that clinicians do not perform TT insertion when middle ear effusion is not present.[1]

TT placement may result in acute otorrhea in some patients and conversely watchful waiting may result in continued episodes of recurrent AOM, which may include tympanic membrane perforation and otorrhea.

In children with TTs, episodes of otorrhea that reflect acute bacterial infection may be otherwise asymptomatic and less troublesome than AOM episodes in children with intact eardrums.[10] However, otorrhea may be associated with a foul odor, fever, or pain, and it may negatively affect quality of life. Treatment is aimed at eradicating bacterial infection and reducing the duration and severity of symptoms.[11]

The objectives for this systematic review are to synthesize information on the effectiveness of TT in children with chronic otitis media with effusion and recurrent acute otitis media, summarize the frequency of adverse effects or complications associated with TT placement, synthesize information on the necessity for water precautions in children with TT, and assess the effectiveness of available treatments for otorrhea in children who have TT.

## Key Questions

With input from clinical experts during Topic Refinement, and from the public, during a public review period, we developed the following Key Questions (KQs) and study eligibility criteria.

**Key Question 1:** For children with chronic otitis media with effusion, what is the effectiveness of TT, compared to watchful waiting, on resolution of middle ear effusion, hearing and vestibular outcomes, quality of life, and other patient-centered outcomes?

a. What factors (such as age, age of onset, duration of effusion, comorbidities, and sociodemographic risk factors) predict which children are likely to benefit most from the intervention?
b. Does obtaining a hearing test help identify which children are more likely to benefit from the intervention?

**Key Question 2:** For children with recurrent acute otitis media, what is the effectiveness of TT, compared to watchful waiting with episodic or prophylactic antibiotic therapy, on the frequency and severity of otitis media, quality of life, and other patient-centered outcomes?

a. What factors (such as age, age of onset, number of recurrences, presence of persistent middle ear effusion, comorbidities, sociodemographic risk factors, history of complications of acute otitis media, antibiotic allergy or intolerance) predict which children are likely to benefit most from the intervention?

**Key Question 3:** What adverse events, surgical complications, and sequelae are associated with inserting TT in children with either chronic otitis media with effusion or recurrent acute otitis media?

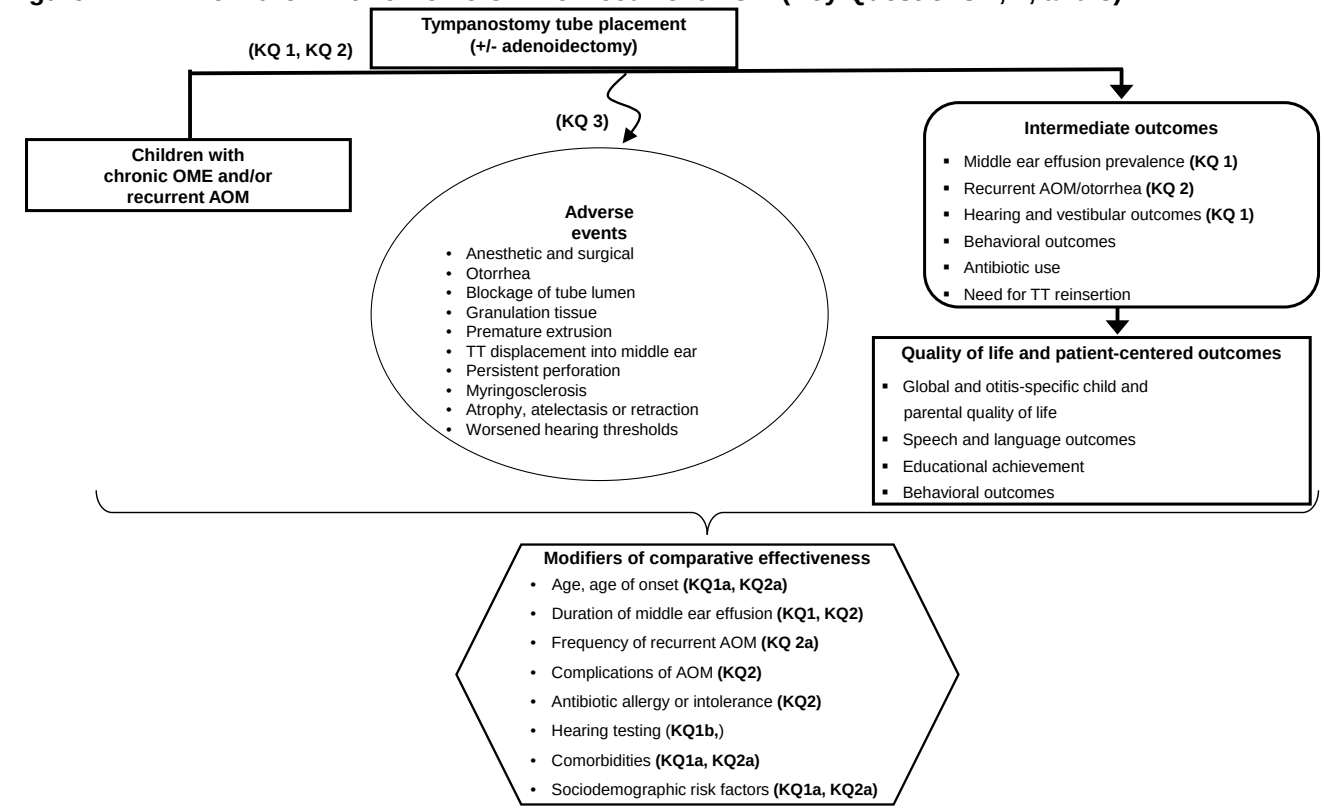
**Key Question 4:** Do water precautions reduce the incidence of TT otorrhea or affect quality of life?

**Key Question 5:** In children with TT otorrhea, what is the comparative effectiveness of topical antibiotic drops versus systemic antibiotics or watchful waiting on duration of otorrhea, quality of life, or need for tube removal?

# Analytic Frameworks

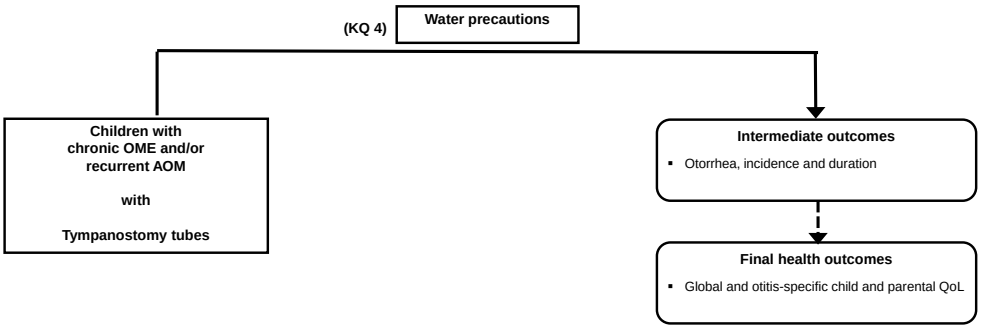
The analytic frameworks in Figures A through C describe the specific linkages associating the populations of interest, exposures, modifying factors, and outcomes of interest in the assessment of studies that examine the association between TT placement, intermediate and final health outcomes, and harms (KQs 1, 2 and 3; Figure A); need for water precautions (KQ 4; Figure B); and treatment of otorrhea (KQ 5; Figure C).

**Figure A. TT in children with chronic OME or recurrent AOM (Key Questions 1, 2, and 3)**



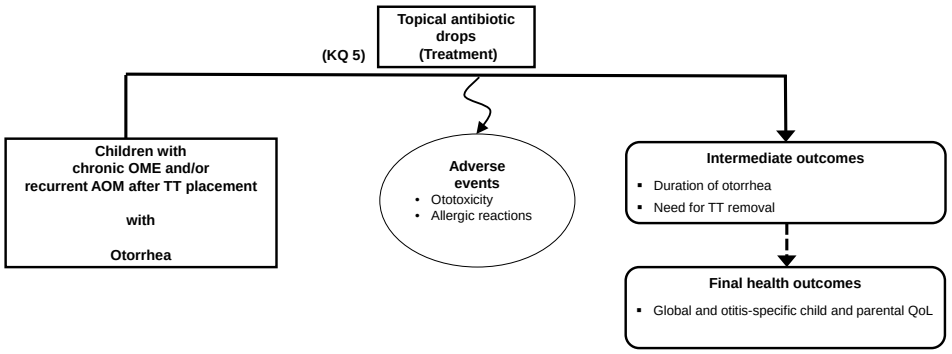

OME=otitis media with effusion; AOM=acute otitis media; TT=tympanostomy tubes; KQ=Key Question

**Figure B. Need for water precautions in children with TT (Key Question 4)**




OME=otitis media with effusion; AOM=acute otitis media; QoL= Quality of Life

**Figure C. Treatment of otorrhea in children with TT (Key Question 5)**




OME=otitis media with effusion; AOM=acute otitis media; QoL= Quality of Life; TT=tympanostomy tube

# Methods

The Brown Evidence-based Practice Center (EPC) conducted this review based on a systematic review of the published scientific literature using established methodologies as outlined in the Agency for Healthcare Research and Quality's (AHRQ) Methods Guide for

Comparative Effectiveness Reviews.[12] The PROSPERO protocol registration number is CRD42015029623.

# Eligibility Criteria

We use the Population, Intervention, Comparator, Outcomes, and Designs (PICOD) formalism to define the characteristics of the eligible studies for this review.

## Populations

For all KQs, studies of children and adolescents from 1 month to 18 years old were eligible. Subpopulations of interest included children at high risk of recurrent AOM or OME, such as children with Down syndrome, cleft palate, other craniofacial anomalies, and primary ciliary dyskinesia; and children at high risk of adverse clinical or developmental outcomes, such as those with preexisting hearing loss, speech and language problems, or developmental disorders. We were also interested in the population of children who have sociodemographic risk factors, such as day care exposure or low socioeconomic status.

For KQ 1, we included studies of children with chronic OME. We preferred the standard definition of effusion that persists for at least three months,[1] but included results based on studies' alternative definitions if our preferred one was not reported. We excluded children with chronic suppurative otitis media since it is usually associated with a persistently perforated tympanic membrane.

For KQ 2, we included children with recurrent AOM with or without middle ear effusion, defined as three or more well-documented and separate AOM episodes in the past 6 months or at least four well-documented and separate AOM episodes in the past 12 months with at least one in the past 6 months.[1] For studies that did not report the preferred definition, we recorded the study specific definition.

For KQ 3 and 4, we included studies in children with TT placed for OME or AOM. For KQ 5, we included studies of symptomatic or asymptomatic children with acute TT otorrhea beyond the immediate postoperative period. We defined the immediate postoperative period as 30 days after surgery, but included studies reporting results near that period (e.g., 28 days, 4 weeks).

## Interventions/Exposures

For KQs 1, 2 and 3, we considered all studies that included myringotomy with TT placement, with or without adenoidectomy. Tubes were classified as short-term tubes (generally in place for 10-18 months) and long-term tubes (which typically remain in place for several years).

In KQ 4, we distinguished three categories of interventions; avoidance of swimming or head immersion while bathing, canal occlusion methods (e.g. earplugs or headbands), and postexposure prophylaxis using ototopical antibiotics.

KQ 5 compares ototopical preparations, and includes products approved by the U.S. Food and Drug Administration (FDA) (i.e., ofloxacin otic 0.3%, ciprofloxacin 0.3% and dexamethasone 0.1%), and other non–FDA-approved agents, such as hydrocortisone, bacitracin, and colistin.

## Comparators

For KQ 1, comparisons of primary interest were watchful waiting or adenoidectomy. Comparators for KQ 2 included watchful waiting, systemic or topical antibiotic therapy for recurrent episodes of AOM, prophylactic antibiotics, and adenoidectomy. KQ 3 did not address

comparative harms. In KQ 4, comparators included no water precautions with or without avoidance of higher risk activities (e.g. diving or underwater swimming), and ear plugs or swimming caps. The primary comparators for KQ5 were watchful waiting and oral antibiotic therapy.

### Outcomes

For KQs 1 and 2, which address the effectiveness of TT, we considered intermediate outcomes, including the prevalence of middle ear effusion, measures of hearing and vestibular function, such as improved hearing thresholds (audibility), tests of auditory perception and discrimination (clarity), and balance and coordination (vestibular function). For KQ 2, measures of recurrent AOM, including otorrhea were extracted.

Quality of life and patient-centered outcomes were considered, including global and otitis-specific child and parental quality of life, speech and language outcomes, educational achievement, behavioral outcomes such as disobedience, enuresis, or tantrums.

The following outcomes were extracted for KQ 3: Intraoperative and immediate postoperative anesthetic and surgical adverse events, otorrhea beyond the postoperative period, blockage of the tube lumen, granulation tissue, premature extrusion, TT displacement into the middle ear, persistent perforation of the tympanic membrane, myringosclerosis, tympanic membrane atrophy, atelectasis and retraction pockets, worsened hearing thresholds, and other reported (plausibly related to tubes).

Outcomes for KQ 4 included final health and patient-centered outcomes related to child and parental quality of life and intermediate outcomes related to the incidence and duration of otorrhea. Outcomes evaluated relating to KQ 5 (treatment of otorrhea) included global and otitis-specific child and parental quality of life, duration of otorrhea, and need for removal of TT.

### Timing

We included studies with any duration of followup.

### Setting

We included studies performed in both primary and specialty care settings.

## Study Design

We evaluated published, peer-reviewed studies only. For KQs 1, 2, 4, and 5, we included randomized comparative trials and nonrandomized comparative studies, prospective and retrospective where treatment was assigned on a per patient basis. Studies with per ear assignment were excluded (e.g. tubes placed by design in one ear only). For KQ 3, we included prospective surgical single group studies enrolling at least 50 subjects (including arms treated with TT that were part of randomized controlled trials [RCTs] or nonrandomized comparative studies [NRCSs]) and population based retrospective single group studies (registry studies) with at least 1000 subjects.

## Searching for the Evidence

We conducted literature searches of all studies in MEDLINE®, the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, Embase®, and CINAHL® databases (details in Appendix A of the full report). The last search was run on May 19, 2016. Additionally, we perused the reference lists of published clinical practice guidelines, relevant

narrative and systematic reviews, and Scientific Information Packages from manufacturers. Citations were independently screened by two researchers in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/).

## Data Extraction and Data Management

Each study was extracted by one methodologist and confirmed by at least one other methodologist. Data was extracted into customized forms in the Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov). Excluded studies are listed in Appendix B of the full report. Details of included studies are summarized in Appendix C, D and E of the full report.

## Assessment of Risk of Bias of Individual Studies

We assessed the methodological quality of each study based on predefined criteria. For RCTs, we used the Cochrane risk of bias tool.[13] For observational studies, we used relevant questions from the Newcastle Ottawa Scale.[14]

## Data Synthesis

All included studies were summarized in narrative form and in summary tables that record the important features of the study populations, design, intervention, outcomes, and results.

We performed network meta-analysis of clinical outcomes to compare treatment alternatives across studies for KQs 1 and 5. We also conducted pairwise comparisons by means of random effects meta-analyses of comparative studies. Specific methods and metrics (summary measures) meta-analyzed were chosen based on available, reported study data. When available, these were summarized as odds ratios of categorical outcomes and net change of continuous outcomes (e.g., mean hearing thresholds). Statistical heterogeneity was explored qualitatively. We explored subgroup differences within across studies based on the list of comparisons described in the KQs.

## Grading the Strength of Evidence

We graded the strength of evidence (SOE) as per the AHRQ Methods Guide on assessing the strength of evidence.[15]

## Assessing Applicability

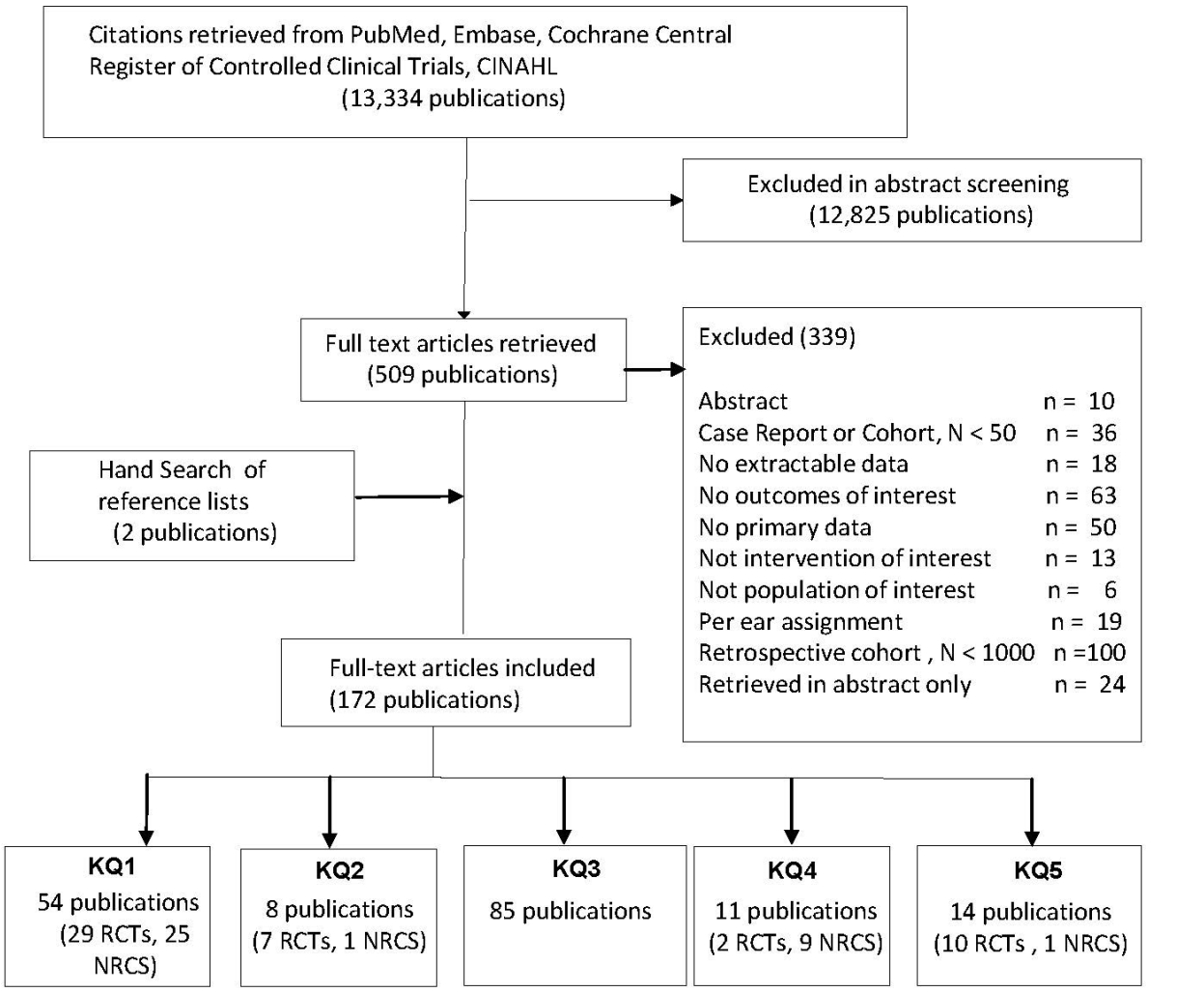
We assessed the direct applicability within and across studies with reference to children with specific comorbidities (Down syndrome, cleft palate, etc.), and whether interventions and comparators are used in current practice.

# Results

The literature search yielded 10,129 citations (Figure D). We identified 481 of these as potentially relevant full-text studies, and retrieved them for further evaluation. Overall, 306 full text articles did not meet eligibility criteria (see Appendix B of the full report for a list of rejected articles along with reasons for rejection); thus 184 articles are included in this report.

A trial registry search did not turn up any completed trial that was not already identified through literature searches. As shown in Figure D, the majority of included publications (n=98) related to KQ3, with 50 related to KQ1. There is a relative paucity of studies available for the other KQs.

**Figure D. Literature flow diagram**




CINAHL = Cumulative Index to Nursing and Allied Health Literature; KQ = Key Question; NRCS = nonrandomized comparative study; RCT = randomized controlled trial; Some publications reported data from the same study. The KQ3 publications included 70 cohorts, 12 NRCSs and 3 RCTs (from which the cohort most closely matching usual care was extracted). Detailed reasons for exclusion of studies reviewed in full text but not considered further are presented in Appendix B of the full report.

# Key Question 1

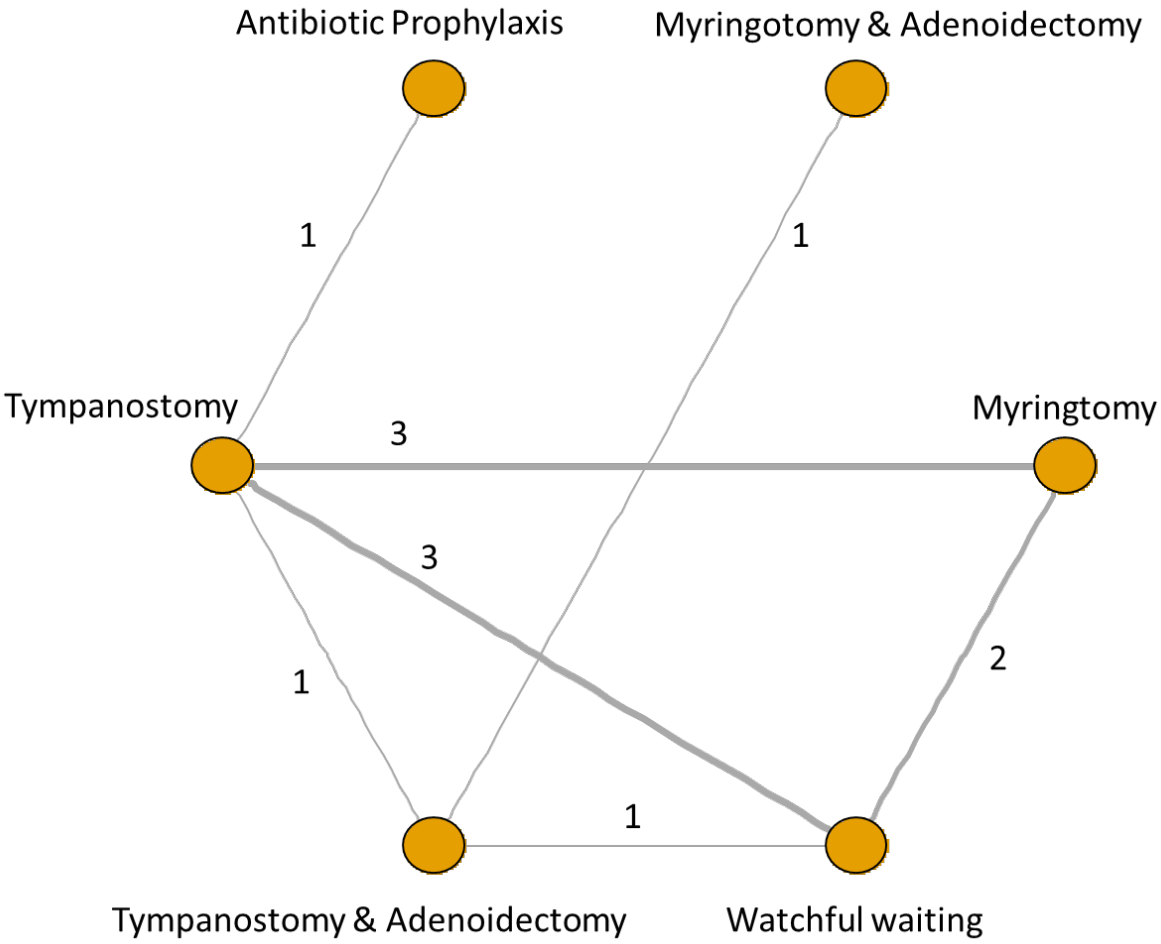
We identified 54 publications Of these, there were 29 papers reporting results of 16 RCTs. There were 24 publications reporting 24 NRCSs that assessed the effectiveness of TT in pediatric patients with chronic middle ear effusion. These studies evaluated multiple interventions (TT, TT with adenoidectomy, myringotomy with adenoidectomy, myringtomy alone, adenoidectomy alone, oral antibiotic prophylaxis, and watchful waiting). Two studies

included at least some patients with recurrent AOM with or without persistent middle ear effusion.

## Randomized Comparative Studies

Hearing thresholds were measured in 16 RCTs. In 10 of these, mean hearing thresholds were reported by arm at various time points. For the network meta-analysis of these RCTs, we classified hearing thresholds obtained at one to three months as "early". Similarly, hearing thresholds obtained between 12 and 24 months where were classified "late". Not all studies had interventions at both "early" and "late" time points. Thus, the network of comparators differs for "early" and "late" comparisons. Figure E shows the topology of the network for early hearing thresholds at 1 to 3 months. Such network plots are a visual representation of the evidence base.

**Figure E. Network graph of comparators for early (1 to 3 months) hearing thresholds**

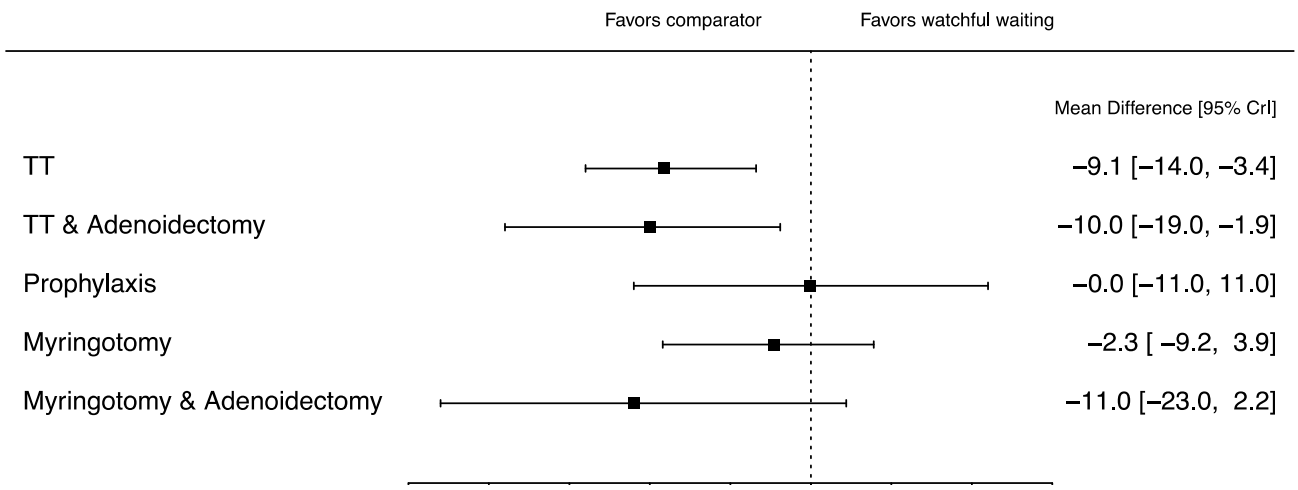



The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

Figure F illustrates the effectiveness of various interventions at 1 to 3 months, compared with watchful waiting. Mean hearing thresholds improved (decreased) by average of 9.1 dB following TT, and by 10 dB following TT with adenoidectomy. Credible intervals for these effects exclude

zero. The credible intervals for comparisons between watchful waiting and myringotomy alone, myringotomy with adenoidectomy, and oral antibiotic prophylaxis were wide.

**Figure F. Early (1 to 3 months) decrease (improvement) in mean hearing thresholds compared with watchful waiting**




TT= tympanostomy tubes; CrI=Credible Interval

As shown in Table A, the strategies with the highest probability of being among the three most effective interventions with respect to early improvements in hearing thresholds were TT, TT with adenoidectomy, and myringotomy with adenoidectomy.

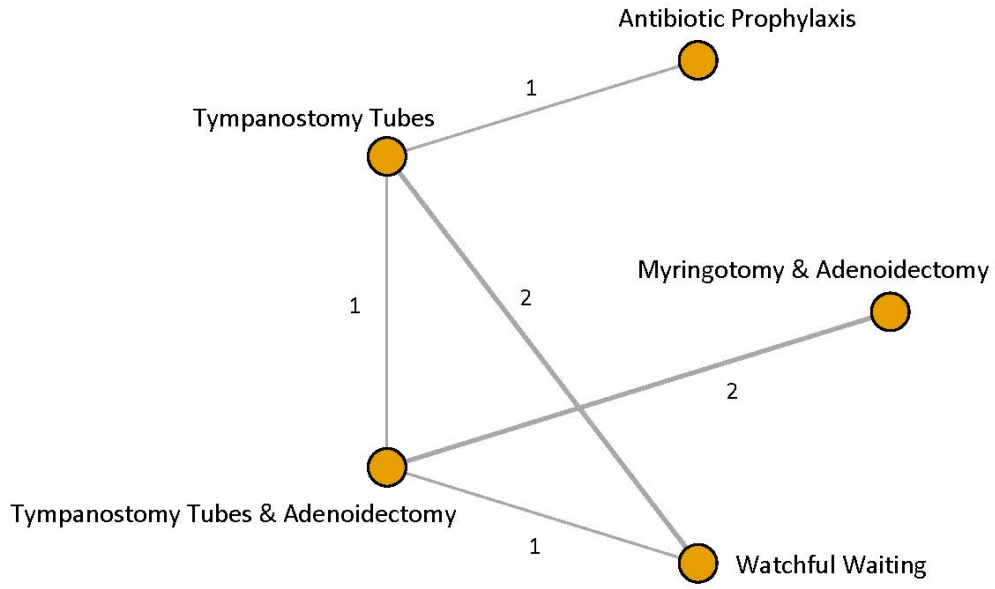
**Table A. Probabilities (percent) that an intervention is among the three most effective with respect to early hearing thresholds**

| Intervention | Probability (%) of Being Among the 3 Most Effective Interventions | Probability (%) of Being Among the 3 Least Effective Interventions |
|---|---|---|
| TT | 97 | 3 |
| TT + Adenoidectomy | 96 | 4 |
| Myringotomy | 8 | 92 |
| Myringotomy + Adenoidectomy | 91 | 9 |
| Antibiotic Prophylaxis | 6 | 94 |
| Watchful Waiting | 1 | 99 |

TT= tympanostomy tubes

Five RCTs reported hearing thresholds at 12 to 24 months. Figure G shows the topology of the network of comparisons at this time interval.

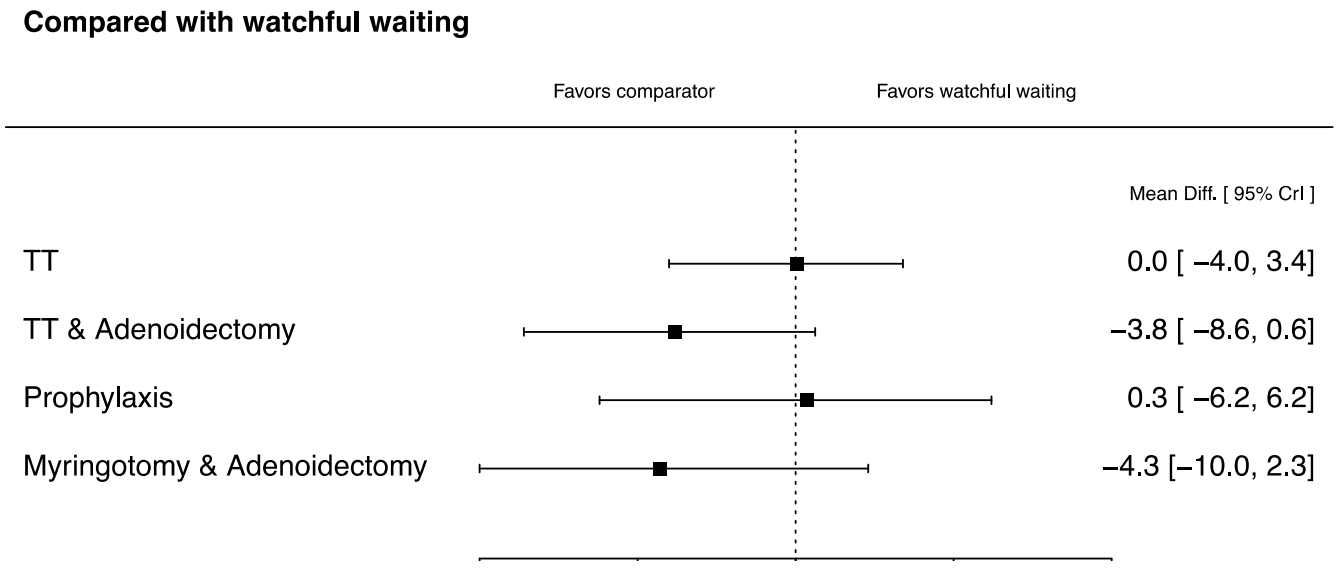
**Figure G. Network graph of comparators for late (12 to 24 months) hearing thresholds**




The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number.

As shown in Figure H, by 12 to 24 months, the mean difference in hearing thresholds for TT alone, compared to watchful waiting was 0 dB (95% CrI [credible interval] -4 to 3). Compared to watchful waiting, myringotomy with adenoidectomy and TT with adenoidectomy have better hearing outcomes by about 4 dB, but the 95 percent credible intervals include zero.

**Figure H. Late (12 to 24 months) decrease (improvement) in mean hearing thresholds compared with watchful waiting**




TT= tympanostomy tubes; CrI=Credible Interval

As can be seen in Table B, TT with adenoidectomy and myringotomy with adenoidectomy were the two most effective strategies with respect to late hearing thresholds. TT alone, antibiotic prophylaxis, and watchful waiting were among the three least effective ones.

**Table B. Probabilities (percent) that an intervention is among the two most effective with respect to late hearing thresholds**

| Intervention | Probability (%) of Being Among the 2 Most Effective Interventions | Probability (%) of Being Among the 3 Least Effective Interventions |
|---|---|---|
| TT | 5 | 95 |
| TT + Adenoidectomy | 92 | 8 |
| Myringotomy + Adenoidectomy | 88 | 12 |
| Antibiotic Prophylaxis | 10 | 90 |
| Watchful Waiting | 4 | 96 |

The results for the studies that reported measuring hearing thresholds, but did not report mean hearing thresholds are summarized in the full report.

A network meta-analysis of the mean duration of middle ear effusion is presented in the full report.

## Nonrandomized Comparative Studies

The nonrandomized comparative studies (NRCSs) are summarized in the full report. The NRCSs evaluated special populations and are summarized here. Six studies reported results in the populations with comorbidities of interest, including cleft palate/lip and primary ciliary dyskinesia. Three studies (two in cleft palate and one in primary ciliary dyskinesia) compared TT placement with nonsurgical treatment, while one study compared early versus delayed TT in different settings. Two studies assessed the effects of TT and cleft repairing versus cleft repairing alone. Hearing thresholds reported as pure tone averages were reported in four studies. In patients with cleft palate/lip and primary ciliary dyskinesia, respectively, average hearing threshold was lower in TT than non-surgical control, but the difference was not significant. TT in addition to cleft repair improved hearing thresholds with unknown significance. The improvement by early (mean age 3 months) compared to delayed (mean age 40.8 months or not at all in two subjects) TT procedures in patients with cleft palate was marginally significant (P=0.05 for ears with better hearing and P=0.10 for ear with worse hearing). The rate of normal hearing, defined as hearing threshold < 20 dB bilaterally, was significantly higher in TT than control (P <0.05).

## Quality of Life and Patient-Centered Outcomes

Eight studies (five RCTs, three NRCSs, and one that combined both designs) in 12 papers reported on 119 quality of life and patient-centered outcomes (cognitive, language, and behavioral) in 1665 children over multiple time points and arms. These studies reported only 14 outcomes with significant results. In general, the results were not significant and varied in magnitude and direction, even across subscales of the same test.

Only two studies reported specifically on quality of life outcomes: Paradise reported on measures of parental stress at various ages, and Vlastos reported on pediatric health related quality of life. Neither found any significant differences. Full details for all outcomes are in Appendix G of the full report.

# Key Question 2

We identified 8 publications, reporting 7 RCTs and 2 NRCSs. The Matilla 2003 paper reported two groups, an RCT which randomly allocated treatment in 137 patients, and a NRCS in which parental choice determined treatment in169 patients. Three RCTs compared TT placement with daily oral antibiotic prophylaxis. Two of these studies included a comparison with placebo and the third compared TT placement with no treatment. The effectiveness of TT alone versus TT with adenoidectomy was evaluable in three studies.

## Randomized Comparative Studies

### Frequency and Severity of Recurrent Acute Otitis Media

The majority of studies were done prior to widespread use of the conjugate pneumococcal vaccine, in an era where antibiotic resistance was less common, and prophylactic oral antibiotic therapy was more commonly used in clinical practice. Results are summarized by comparison below.

## TT Versus Placebo or No Treatment

Gonzalez 1986 reported that in the placebo group three of 20 children had no further episodes of AOM, compared to 12 of 22 in the TT group (P = 0.01, an attack rate of 2.0 in the placebo group, compared to 0.86 in the TT group (P = 0.006). In a post-hoc subgroup comparison of children who had middle ear effusion upon entering the study, attack rate and number of patients who had no further bouts of AOM was significantly better (P < 0.05) in those children without middle ear effusion. However, this group consisted of only 22 patients.

Casselbrant 1992 reported the rate of new episodes per arm was 1.08 in the placebo group versus 1.02 in the TT group (P = 0.25). In the placebo group, 40 percent had no further episodes of AOM, compared to 35 percent in the TT group. In addition, TT placement significantly decreased the percentage of time with AOM compared to placebo (P < 0.001).

Kujala 2012 reported failure rates (defined as at least two episodes of AOM in 2 months, three in 6 months or persistent effusion lasting at least 2 months), percent of children with no recurrent AOM, cumulative number of AOM episodes, and one-year incidence rates. There was an absolute difference in the proportion of failures of −13 percent (95% CI −25 to −01) between the TT and control groups, favoring TT. The one year incidence rate (infections per child per year) was 0.55 (95% CI 0.93 to 0.17) lower in the TT group compared to the control group.

## TT Versus Antibiotic Prophylaxis

In the Gonzalez 1986 RCT, 54.5 percent of children in the TT group and 24 percent in the sulfisoxazole prophylaxis group had no recurrent AOM (P = 0.02). The attack rate was 0.86 infections per child in the TT group and 1.4 in prophylaxis group (P = 0.08).

Casselbrant 1992 reported a rate of 0.6 episodes of recurrent AOM per child-year children treated with Amoxicillin and a rate of 1.02 in their TT group (P = 0.001).

El-Sayed found no difference in the treatment outcomes of children treated with trimethoprim/sulfamethoxazole compared to children treated with TT (P = 0.37).

## TT Versus TT and Adenoidectomy

An RCT by Mattila 2003 found no difference in cumulative hazard of recurrent AOM or in efficacy, defined as one minus the adjusted relative risk in randomized and nonrandomized comparisons of children who underwent TT with adenoidectomy compared with TT alone.

In the Kujala 2012 study, there was no significant difference in the TT with adenoidectomy group compared to the TT only group in the number of failures (absolute difference −5%, 95% CI −16 to 6, P = 0.37), in the time to failure (P = 0.29) or to the first AOM (P = 0.6), or in the proportion of children with no AOM episodes (absolute difference 1%, CI −13 to 15, P =1.0).

A subsequent 2005 RCT, which enrolled 217 children, 162 of whom had recurrent AOM, again found no differences in the mean number of otitis media episodes overall or in the subgroup of children with recurrent AOM at enrollment.

## Quality of Life Outcomes

Although Kujala 2014 found that insertion of TT tubes, with or without adenoidectomy, significantly reduced the risk of recurrent AOM, a subsequent publication from the same trial examining quality of life outcomes at study entry, 4 months and 12 months found no differences in overall ear-related quality of life (Otitis Media-6 questionnaire [OM-6]), or for the subscales of caregiver concern, emotional distress, physical suffering, activity limitations, hearing loss, or speech impairment between surgically treated and no surgery groups.

## Nonrandomized Comparative Studies

In a cross-sectional study, Grindler 2014 reported both disease-specific quality of life outcomes, utilizing OM-6 score, and health related quality of life, using the PedsWL Infant Impact Module, in 1208 patients. The OM-6 score was higher (reflecting worse otitis specific quality of life) in children in otolaryngology practices who had been recommended to undergo TT placement than in children with prior TT placement.

## Key Question 2a

There are no prospective planned comparisons evaluating whether the presence of middle ear effusion (at time of surgical evaluation) modifies the effectiveness of TT placement for recurrent AOM. Gonzalez 1986 report a retrospective subgroup comparison based on the presence or absence of middle ear effusion at initial evaluation and conclude that the attack rate, as well as the number of patients who had no further bouts of AOM, was significantly better ($p < 0.05$) in those children without middle ear effusion. However, this group consisted of only 22 patients. Two studies specifically excluded patients with middle ear effusion at time of surgical evaluation.

Casselbrant 1992 analyzed data with a multivariable Poisson model, and concluded that TT reduced the number of episodes of AOM/otorrhea only in those subjects whose episodes of AOM occurred year round. In their model, younger age and white race were significantly associated with higher rates of recurrent AOM, but there treatment by age and treatment by race interactions were not found.

# Key Question 3

We extracted data on the occurrence of 11 adverse events from 85 cohorts and from RCTs and NRCSs included in KQs 1 and 2. The adverse events considered were: perioperative complications, otorrhea, tube blockage, granulation tissue formation, premature extrusion, displacement of the TT into the middle ear space, persistent perforation, myringosclerosis (tympanosclerosis), presence of atrophy, atelectasis or retraction, cholesteatoma and long term hearing loss. We did not consider other adverse events, such as antibiotic resistance, gastrointestinal side effects of antibiotics or pain related to ear drops. The number of publications reporting each event, and the median (with $25^{th}$ and $75^{th}$ percentiles) percent of patients and ears are summarized in Table C.

**Table C. Median percentage of patients and ears with adverse events associated with TT placement**

| Adverse Event | N Publications | Patients: Median Percent [25%, 75th%] | Ears: Median Percent (25%, 75th%) |
|---|---|---|---|
| Perioperative Complications | 4 | NA | NA |
| Otorrhea | 39 | 20.6 [13.1, 47.3] | 10.4 [9.1, 28.2] |
| Tube Blockage | 18 | 9.0 [ 2.6, 10.7] | 4.0 [2.8, 17.1] |
| Granulation Tissue | 12 | 3.3 [ 2.9, 5.7] | 3.9 [1.8, 5.7] |
| Premature Extrusion | 18 | 13.3 [ 7.1,47.9] | 4.1 [1.6, 14.0] |
| TT Displacement into middle ear | 8 | NA | 0.8 [0.7, 0.9] |
| Persistent Perforation | 48 | 2.7 [1.8, 6.7] | 2.9 [ 2.0, 5.3 ] |
| Myringosclerosis | 22 | 33.5 [5.0, 38.0] | 17.1 [6.8, 43.9] |
| Atrophy, Atelectasis or Retraction | 22 | 13.9 [7.5, 25.9] | 14.4 [ 5.0, 32.8] |
| Cholesteatoma | 24 | 0.9 [0.2, 1.8] | 0.7 [ 0.1 ,3.2 ] |
| Hearing Loss | 10 | 8.0 [ 1.2, 19.2] | NA |

NA: Not calculated when number of patients (ears) < 5; TT=Tympanosotomy Tubes

See Appendix G of the full report for adverse event details by study, and for study specific details, including design, recruitment period, tube type(s) used, age, proportion with recurrent AOM, followup time, and study specific definitions. In general, the study specific definitions of adverse events are poorly reported and/or highly variable between studies.

# Key Question 4

We identified 11 publications which reported 2 RCTs and 9 NRCSs, which evaluate a range of interventions, from complete water restriction (e.g., no swimming or head immersion while bathing), physical protection while swimming (utilizing ear plugs or bathing caps), postexposure prophylactic ear drops, avoidance of high risk activities (e.g., diving), to completely unrestricted exposure to water. All studies compared either no-swimming or ear plugs with a second group of swimmers with or without post-exposure antibiotic ear drops.

In the two RCTs, Goldstein 2005 reported a slightly higher average rate of otorrhea per month in children who did not wear ear plugs (mean 0.10 episodes/month, compared to a mean of 0.07; P = 0.05) in a Poisson regression model adjusting for compliance. Parker 1994 reported identical mean otorrhea rates in nonswimmers and swimmers. Table D summarizes the occurrence of one or more episodes of otorrhea in the RCTs.

**Table D. RCTs: Water precautions—one or more episodes of otorrhea**

| Study PMID<br>Enrollment dates<br>Country (Design) | Followup time | Intervention | Population | n/N (%) | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| Goldstein 2005 15689760<br>7/1996-6/1999<br>U.S. | 1 year | Ear plugs | All Participants | 42/90 (46.7) | 0.68 (0.37 – 1.25) |
| | | No precautions | All Participants | 46/82 (56.1) | [reference] |
| | | Ear plugs | Children who each had ≥ 125 instances of water exposure | 29/39 (74.3) | 2.69 (0.95 – 7.64) |
| | | No precautions | Children who each had ≥ 125 instances of water exposure | 14/27 (51.8) | [reference] |
| Parker 1994 8024107<br>12/1989-2/1991<br>U.S. | 1 year | Nonswimming | All Participants | 18/30 (60.0) | 0.71 (0.29 – 1.76) |
| | | Ear plugs† | All Participants | 13/15 (86.7) | 3.10 (0.64 – 15.04) |
| | | No precautions | All Participants | 42/62 (67.7) | [reference] |

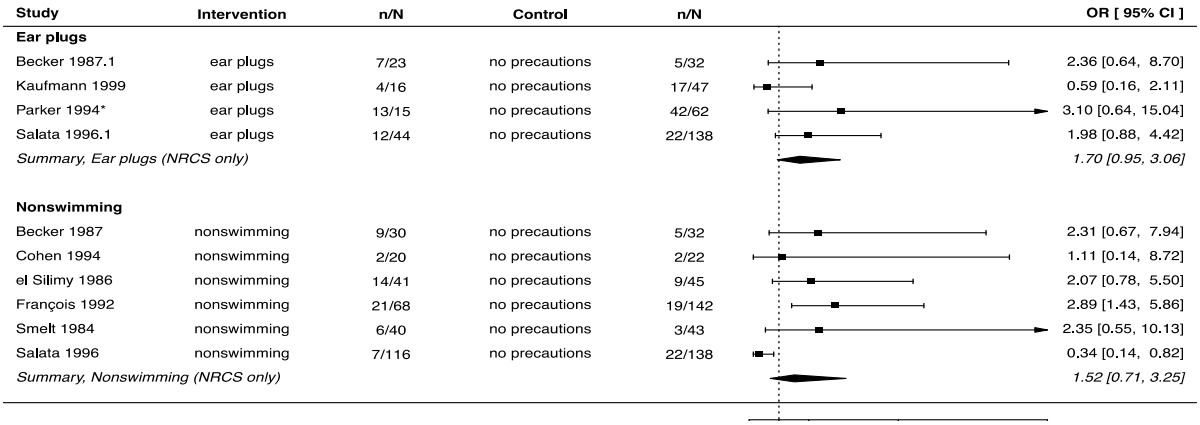
†Randomized to the nonswimming group, but self-selected to swim using ear precautions (e.g., ear plugs, wax, cotton with petroleum jelly) – considered an NRCS in the meta-analysis.

RCT=Randomized Control Trial; NRCS=Nonrandomized Comparative Trial; CI=Confidence Interval

The forest plot in Figure I, summarizes the results of a random effects meta-analysis from the NRCSs only with separate summary estimates for ear plugs and avoidance of swimming. The summary odds ratio comparing ear plugs versus no precautions of having one or more episodes of otorrhea was 1.70 (95% CI 0.95 to 3.06). The odds ratio for nonswimming compared to no precautions was 1.52 (95% CI 0.71 to 3.25). It is notable that events rates in the RCTs are systematically higher in both control and intervention arms in the RCTs compared with event rates in NRCSs. A possible explanation is more complete ascertainment of outcomes in RCTs.

There appears to be a statistically nonsignificant trend in the NRCSs, which favor no ear plugs and no precautions. This trend may reflect a possible bias (e.g. patients who chose to swim may be less likely to report minor degrees of otorrhea).

**Figure I. Nonrandomized comparative studies only, children with one or more episodes of otorrhea**




CI= Confidence Interval; NRCS= Nonrandomized Comparative Study; OR = Odds ratio (values > 1 favor 'no precautions' arms; values < 1 favor intervention (ear plugs or nonswimming)

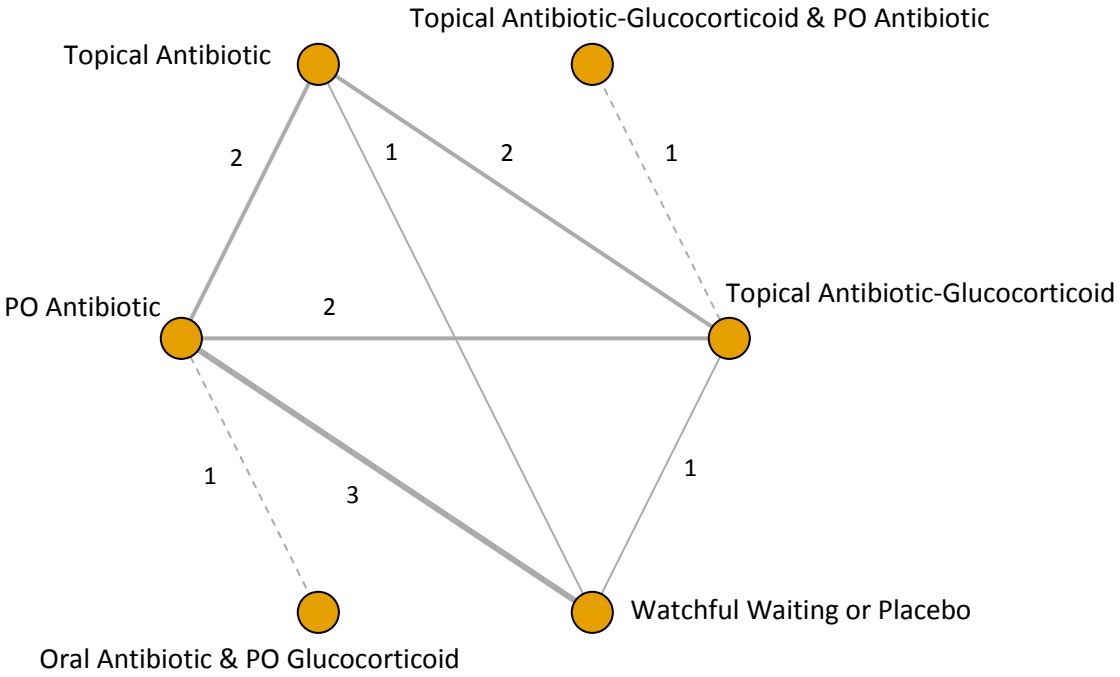
Overall, aside from the small reduction in mean number of episodes of otorrhea found in the Goldstein RCT, the available evidence does not support the conclusion that either ear plugs or avoidance of swimming reduces the risk of otorrhea related to swimming.

# Key Question 5

We identified 12 papers, representing 11 studies, reporting 10 RCTs and 1 NRCS, with a total of 1811 patients analyzed (1405 in RCTs and 406 in NRCSs) that assessed the effectiveness of various interventions to treat TT otorrhea. The studies reported multiple comparisons, including oral antibiotics (amoxicillin and amoxicillin/clavulanate), various antibiotic drops and antibiotic-glucocorticoid drops, oral corticosteroids, and combinations. Several studies had a watchful waiting or placebo arm.

Two studies were excluded from our meta-analysis, the NRCS by Dohar where specific treatments used in the historical practice group and concurrent practice group were not reported and a study which compared an antibiotic-glucocorticoid topical drop containing neomycin sulfate, polymyxin B sulfate and hydrocortisone with a topical spray formulation containing neomycin sulfate and dexamethasone. The network of available comparisons is shown in Figure J.

**Figure J. Network of treatment comparisons (RCTs)**




RCT= Randomized Control Trial; PO=Oral The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

# Outcomes

## Clinical Cure

Eleven studies reported the number of clinically cured patients in each arm, often at multiple time points. All studies reported additional intermediate outcomes (e.g., cessation, improvement or duration of otorrhea).

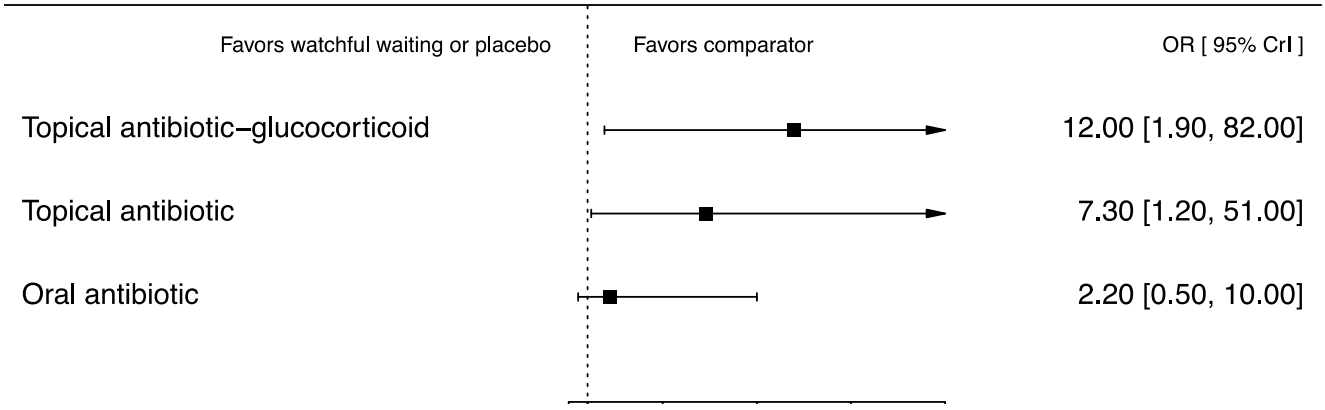
After excluding 4 studies, 7 studies were included in the network meta-analysis. We chose the time designated by each study as the test of cure (range 7 to 20 days after initiation of treatment). As shown in Table E, treatment strategies that include topical antibiotic drops predominate over both oral antibiotics and watchful waiting or placebo.

**Table E. Probabilities (percent) that an intervention is among the three most effective with respect to clinical resolution of otorrhea**

| Intervention | 1st | 2nd | 3rd | 4th |
|---|---|---|---|---|
| Topical Antibiotic-Glucocorticoid | 77 | 21 | 1 | 0 |
| Topical Antibiotic | 22 | 73 | 5 | 1 |
| Oral antibiotic | 1 | 5 | 83 | 12 |
| Watchful waiting/placebo | 0 | 1 | 12 | 87 |

The plots show that topical antibiotic-glucocorticoid and antibiotic-only drops are superior to watchful waiting (Figure K).

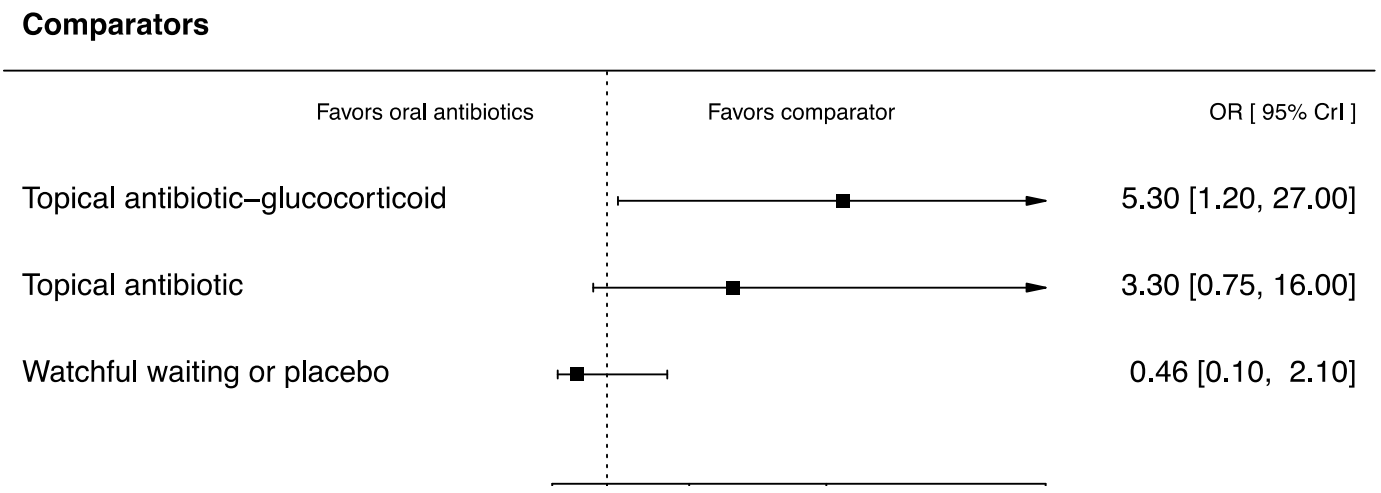
**Figure K. Relative effectiveness of interventions compared to watchful waiting or placebo therapy**




OR=Odds Ratio, CrI=Credible Interval

When compared to oral antibiotics, topical antibiotic-glucocorticoid drops are superior to oral antibiotics and there is a suggestion that topical antibiotic drops are also superior, although the credible interval overlaps the null effect (Figure L).

**Figure L. Relative effectiveness of interventions compared to treatment with oral antibiotics**




OR=Odds Ratio, CrI=Credible Interval

## Quality of Life

Van Dongen 2014 was the only study to report quality of life outcomes. They evaluated quality of life in 230 children with otorrhea who received watchful waiting, oral antibiotics, or antibiotic- glucocorticoid drops for 7 days. At baseline, the generic and disease-specific health-related quality-of-life scores indicated good quality of life and were similar across the groups. At 2 weeks of follow-up, the change in the generic health-related quality-of-life scores did not differ significantly among the study groups. The changes in the disease-specific health-related quality-of-life scores at 2 weeks were small but consistently favored eardrops. Confidence intervals were relatively wide.

# Discussion

## Overall Summary and Strength of Evidence

Our systematic review of 172 publications focused on five Key Questions (KQ), which evaluate the evidence for effectiveness of TT in children with chronic middle ear effusion and recurrent acute otitis media, the adverse events (harms) associated with this procedure, the need for water precautions in children with TT, and the treatment of TT otorrhea. Table E summarizes our dispositions about the strength of the evidence.

## Key Question 1

In children with chronic otitis media with effusion, 54 publications reported results of 29 RCTs.

Risk of bias for evaluation of hearing and middle ear effusion outcomes was rated as moderate to high. Limited information on quality of life and other patient-centered outcomes (cognitive, language, and behavioral) suggests that effects for these outcomes varied in magnitude and direction, even across subscales of the same test, and were not significantly different across the compared interventions. Risk of bias for quality of life outcomes as rated as low to moderate. Risk of bias for various outcomes in high risk populations was rated as high.

TT placement (compared to watchful waiting) resulted in improved average hearing thresholds 1 to 3 months after surgery (a period when the majority of tubes are functioning). Mean hearing thresholds after TT placement with or without adenoidectomy improved by approximately 10 dB when assessed at 1 to 3 months.

By 1 to 2 years, when most tubes have extruded, hearing thresholds are no longer different, reflecting the favorable natural history of spontaneous resolution of middle ear effusion in most children. There was a trend suggesting improved thresholds in children undergoing adenoidectomy, but credible intervals (CrI) are wide and include the null effect. The individual patient data meta-analysis (IPD) by Boonacker et. al., which relied on a composite outcome, concluded that adenoidectomy is most beneficial in children four years or older with persistent otitis media with effusion. In this group at 12 months, 51 percent of those who had adenoidectomy failed whereas 70 percent of those who did not have adenoidectomy failed (Risk Difference 19%: 95% Crl 12% - 26%; NNT (Number Needed to Treat) = 6). No significant benefit of adenoidectomy was found in children less than 4 years old.[3]

Data were very sparse with respect to which factors might predict those children more likely to benefit from TT. The individual patient data (IPD) meta-analysis reported by Rovers et al. focused on interactions between treatment and baseline characteristics. They found significant interactions between daycare attendance in children 3 years or younger, and in children over 4 years of age with a hearing level of 25 dB or greater in both ears, and concluded that TT might be used in young children attending day-care; or in older children with a hearing level of 25 dB or baseline hearing level persisting for at least 12 weeks. They noted that average hearing level at baseline did not obviously modify the effect estimate.[16]

There is limited evidence regarding quality of life outcomes, but neither of the two studies that evaluated parental stress and health related quality of life found significant improvements in surgically treated children. Evidence for improved cognitive, language, or behavioral outcomes after TT, compared to watchful waiting, is similarly lacking.

## Key Question 2

In children with recurrent acute otitis media, seven publications reported results of six RCTs. We were unable to provide pooled results due to the small number of studies, multiple interventions, and heterogeneity in reported outcomes. The limited available evidence suggests that TT placement decreases the number of further episodes and the overall number of episodes of recurrent AOM. Three RCTs consistently found no difference in recurrent episodes of AOM when comparing TT versus TT and adenoidectomy.

Very little evidence from RCTs is available to evaluate factors that identify children most likely to benefit from TT placement. Only one study addressed any predisposing factors. A *post hoc* subgroup (n=22) comparison in one study concluded that patients with middle ear effusion at the time of surgical evaluation had improved outcomes.[17] Risk of bias across outcomes ranged from moderate to high.

## Key Question 3

In general, the study specific definitions of adverse events were poorly reported and/or highly variable between studies. Not all cohorts followed all patients until extrusion of the tube, nor was followup complete in all studies. Several adverse event categories have very wide interquartile ranges (e.g. otorrhea, premature extrusion, and myringosclerosis). This is likely due to highly variable definitions. For example, in some studies counts of patients with at least one episode of otorrhea were included, while other studies included only patients with purulent ear discharge. Otorrhea is particularly complex to characterize, as it may with respect to frequency, duration, volume, character, and associated symptoms. Other adverse events, such as hearing loss and cholesteatoma, are likely confounded by the severity of preexisting and ongoing middle ear disease.

## Key Question 4

We identified nine studies, two RCTs and seven NRCSs that evaluated physical ear protection (e.g. ear plugs) or water restriction (e.g. no swimming or head immersion while bathing) in children after TT placement. One RCT reported a slightly higher average rate of otorrhea (after adjusting for compliance) in children who did not wear ear plugs.[18] A second RCT, with high risk of bias, found a statistically nonsignificant difference in the odds ratio in nonswimmers versus swimmers.[19] A meta-analysis of NRCSs with evaluated ear protection and nonswimming tended to favor no precautions and swimming, but these RCTs are subject to high risk of bias and the analysis did not exclude a null effect. For the comparison of ear plugs vs. no precautions, risk of bias was rated as moderate. For those comparisons and outcomes where the evidence consists of nonrandomized comparative studies only, risk of bias was rated as high.

## Key Question 5

Seven RCTs were included in a network meta-analysis of the comparative effectiveness of various treatments for TT otorrhea.

Seven studies were included in a network meta-analysis of the comparative effectiveness of various treatments for TT otorrhea. The common outcome evaluated was clinical cure, defined as absence of otorrhea after completion of treatment.

The odds of clinical cure were 12-fold (95% CrI: 1.9 – 82) higher [NNT 2.2 (assuming a baseline rate 0.45)][a] for antibiotic-glucocorticoid drops, compared to watchful waiting/placebo. Similarly, the odds of clinical cure were 7.3-fold (95% CrI: 1.2 – 51) higher [NNT 2.5 (assuming a baseline rate of 0.45)][b] for topical antibiotic drops (compared to watchful waiting/placebo).

Compared to oral antibiotics, treatment with topical-glucocorticoid drops demonstrated higher effectiveness, odds ratio 5.3 (95% CrI: 1.2 to 27) [NNT 3.2 (assuming a baseline rate 0.56)].[c] The odds ratio for topical antibiotic drops was 3.3 (95% CrI: 0.74 – 16)[NNT 5 (assuming a baseline rate of 0.69)][d], although the credible interval includes 1. Risk of bias was low for random sequence generation and allocation concealment. However, 8 of 10 studies had high risk of bias due to open label design, which precluded blinding of personnel and care providers. Risk of bias was rated moderate overall.

[a] As seen in: van Dongen TM, van der Heijden GJ, Venekamp RP, et al. A trial of treatment for acute otorrhea in children with tympanostomy tubes. N Engl J Med. 2014 Feb 20;370(8):723-33. doi: 10.1056/NEJMoa1301630. PMID: 24552319. (34 of 75 in watchful waiting arm)

[b] As seen in: Heslop A, Lildholdt T, Gammelgaard N, et al. Topical ciprofloxacin is superior to topical saline and systemic antibiotics in the treatment of tympanostomy tube otorrhea in children: the results of a randomized clinical trial. Laryngoscope. 2010 Dec;120(12):2516-20. doi: 10.1002/lary.21015. PMID: 20979100. (12/26 cured in saline rinse (placebo) arm)
[c] As seen in: van Dongen TM, van der Heijden GJ, Venekamp RP, et al. A trial of treatment for acute otorrhea in children with tympanostomy tubes. N Engl J Med. 2014 Feb 20;370(8):723-33. doi: 10.1056/NEJMoa1301630. PMID: 24552319. (43 of 77 cured in oral antibiotic arm)
[d] As seen in: Goldblatt EL, Dohar J, Nozza RJ, et al. Topical ofloxacin versus systemic amoxicillin/clavulanate in purulent otorrhea in children with tympanostomy tubes. Int J Pediatr Otorhinolaryngol. 1998 Nov 15;46(1-2):91-101. PMID: 10190709. (101 of 146 cured in oral antibiotic arm)

An overall summary of main conclusions with an assessment of the strength of evidence is summarized in Table F.

**Table F. Summary of conclusions and associated strength of evidence dispositions**

| Conclusion | Strength of Evidence | Comments |
|---|---|---|
| *Key Question 1- effectiveness of TT in children with chronic otitis media with effusion* | | |
| Treatment with TT results in short term improvements in hearing thresholds, compared to Watchful waiting | Moderate | Network metaanlysis<br>-9.1 (CrI: -14.5, -3.2) dB at 1 to 3 months |
| Improvements in hearing thresholds are not sustained at 12 to 24 months. | Moderate | Network meta-analysis<br>0.03 (CrI: -3.9, 3.3) dB at 12 to 24 months |
| Concurrent Adenoidectomy with TT is associated with longer term improvements in hearing thresholds | Low | Network meta-analysis<br>-3.8 (CrI: -8.5, 0.62) at 12-24 months (92% probability one of 3 most effective interventions) |
| Periods of watchful waiting do not result in consistently worse cognitive, language, behavioral or quality of life outcomes in children without comorbidities. | Low | Limited number of studies (8), each using different outcome definitions<br>No quantitative synthesis done |
| *Key Question 2 - Comparative effectiveness of TT in recurrent acute otitis media* | | |
| Treatment with TT does not improve quality of life | Low | Limited number of RCTs (1)<br>No quantitative synthesis done |
| *Key Question 4 – Effectiveness of ear plugs or avoidance of swimming* | | |
| Ear plugs or avoidance of swimming does not reduce the risk of otorrhea after swimming | Low | Limited number of studies (2 RCTs) Meta-analysis of 7 NRCSs |
| *Key Question 5 – Effectiveness of topical antibiotic drops vs. systemic antibiotics or watchful waiting* | | |
| Topical antibiotic-glucocorticoid drops are superior to oral antibiotics in achieving clinical cure | Moderate | Network meta-analysis<br>OR: 5.3 (CrI: 1.2, 27.0) |
| Topical antibiotic drops are superior to oral antibiotics in achieving clinical cure | Low | Network meta-analysis<br>OR: 3.3 (CrI: 0.75, 16.0)<br>(95% probability one of 2 most effective interventions) |
| Topical antibiotic-glucocorticoid drops and topical antibiotic drops are both superior to Watchful waiting in achieving clinical cure of otorrhea | Moderate | Network meta-analysis<br>OR: 12.0 (CrI: 1.9, 82) [antibiotic-glucocorticoid]<br>OR: 7.2 (CrI: 1.2, 51.0) [antibiotic only] |

CrI = credible interval; OR = odds ratio; TT=Tympanostomy Tubes; NRCS=Nonrandomized Comparative Study; RCT=Randomized Control Trial

## Limitations

The available evidence base is composed of studies that evaluate multiple interventions. Several of these (e.g. myringotomy alone and oral antibiotic prophylaxis) are rarely used in current practice. Thus, the direct evidence relating to the comparisons of interest relies on a smaller subset of studies or must be augmented with indirect evidence from network meta-analysis. Many of these trials were performed prior to widespread use of conjugate pneumococcal vaccines and in an era where antibiotic resistance was less common. It is unclear whether these or other factors affect the relative (current vs. historical) benefits of TT placement for recurrent AOM.

The majority of trials utilized similar inclusion criteria and subgroup analysis of higher or lower risk groups is sparse. The generalizability of results to infants and young toddlers and to school age children is also uncertain, given that children in these age groups are underrepresented in available trials. With the exception of two older trials that included children with chronic middle ear effusion (MEE) and/or recurrent AOM, most enrolled predominately children with chronic MEE. The degree to which patients in clinical practice may have both chronic MEE and recurrent AOM is unclear.

Reporting of possible sociodemographic risk factors is sparse and inconsistent, which limits the ability to draw conclusion about which of these factors might influence the relative effectiveness of TT.

With the exception of a few NRCSs, patients with cleft palate and Down syndrome have been systematically excluded from comparative trials, limiting the applicability of the evidence to these and other small subgroups, who experience a higher burden of middle ear disease. Similarly, patients at increased risk of developmental or behavioral sequelae from middle ear disease are not included (or at least identified) in trials to date.

Across RCTs relative to KQs 1 and 2, there was universal lack of blinding of participants and, in many cases, of outcome assessors. Given the intervention in question, placement of a tube in a visible anatomic structure, blinding of participants is not easily accomplished. In addition, many studies are at risk for attrition bias due to dropouts and incomplete followup.

Our meta-analysis of hearing levels used average pure tone hearing levels (typically reported as an average over frequencies of 500, 1000, 2000 and 4000 Hz). This simple measurement is likely insufficient to fully elucidate the complex relationships between hearing and speech perception and development in children.

Assessment of the effectiveness of TT in children with recurrent acute otitis media is particularly challenging, since an episode of AOM in control children (with intact tympanic membrane) results in otalgia and inflammatory changes, whereas children with a functioning TT may present with varying degrees of otorrhea. Bacterial cultures performed in the setting of research may assist in differentiating infections due to organisms associated with AOM from superinfections or colonization with other organisms (e.g. *Staphylococcus* or *Pseudomonas* species). Intermediate outcomes, which rely on simple counts or rates of otorrhea, fail to account for the variable nature of otorrhea with respect to duration, character, and patient impact.

Our network meta-analysis of the effectiveness of treatments for otorrhea combines trials of fluoroquinolones with other non FDA approved preparations. This presumes equivalent effectiveness and does not consider variable side effects such as ototoxicity, which may be associated with some agents.

## Future Research Recommendations

Current indications for TT placement largely reflect the inclusion criteria used in clinical trials. Prognostic models are urgently needed to stratify children with regard to their risk of persistence of middle ear effusion or recurrent AOM.

Pragmatic trials are needed, particularly in children with recurrent AOM, but also in children with chronic MEE and children with risk factors, such as cleft palate or Down syndrome. If possible, trials should be powered with planned subgroup analyses in groups at higher versus lower risk of outcomes.

Since TT are no longer effective after extrusion, future trials should record per-ear and per-patient outcomes that are conditional on whether the TT has extruded. Trialists should explore methods to control for high rates of potential cross-over from watchful waiting to surgical intervention.

Outcome assessment in children with recurrent acute otitis media is challenging, since an episode of AOM in children with an intact tympanic membrane results in otalgia and inflammatory changes, whereas children with a functioning TT exhibit otorrhea. Reliance on outcomes based on simple counts or rates of otorrhea fail to account for the variable character of otorrhea, which can be transient (of little to no concern), recurrent (of more concern, but usually readily managed), or chronic (of considerable concern and difficult to manage). Future trials would benefit from standardization and consistent definition of adverse events. In some cases, e.g. premature extrusion, one author's premature extrusion may be another's time extrusion, depending on the duration of anticipated need.[20]

Bacteriologic evaluations performed in the research setting may assist in differentiating otorrhea resulting from infection with organisms associated with AOM (e.g. *Streptoccus pneumoniae*, nontypable *Haemophilus influenza*)from superinfections with organisms associated with chronic otorrhea (e.g. *Staphylococcus aureus* and *Pseudomonas aeruginosa*).[21]

# Conclusions

Overall, the evidence suggests that TT placed in children with persistent middle-ear effusion result in short term improvements in hearing compared to watchful waiting. However, there is no evidence of a sustained benefit.

Our network meta-analysis of hearing thresholds suggests the possibility of a more sustained improvement in hearing thresholds in at least some children who undergo adenoidectomy and TT placement. However, a nuanced understanding of which children may benefit from adenoidectomy is limited by the small evidence base and our use of aggregate data.

The evidence suggests that a period of watchful waiting does not worsen language, cognition, behavior, or quality of life. However, the current evidence base provides little guidance for the treatment of children who may be at increased risk for speech, language, or learning problems because of baseline sensory, physical, cognitive or behavioral factors.

Children with recurrent AOM may have fewer episodes after TT placement, but the evidence base is severely limited. It is unclear that quality of life outcomes are improved. The benefits of TT placement must be weighed against a variety of adverse events associated with TT placement.

In children in whom TT have been placed, there is no compelling evidence for the need to either avoid swimming or bathing or use ear plugs or bathing caps

Should otorrhea develop, the available evidence supports topical treatment of TT otorrhea.

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# Introduction

## Background and Objectives

Uncertainty about the effectiveness of tympanostomy tubes (TT) for children with otitis media, indications for tympanostomy in children, effectiveness of antibiotics for children with tube otorrhea, and the need for prophylactic water precaution devices prompted the Agency for Healthcare Research and Quality to commission a review of the evidence to help inform recommendations concerning surgical indications and management strategies for TT placement.

Otitis media is often preceded by a viral upper respiratory tract infection that causes Eustachian tube obstruction, negative middle ear pressure, and accumulation of fluid in this normally air-filled space. Acute otitis media (AOM) is defined as the presence of fluid in the middle ear with signs and symptoms of an acute infection, such as fever and ear pain. Otitis media with effusion (OME) is defined as the presence of fluid in the middle ear behind an intact tympanic membrane without signs and symptoms of an acute infection.[1,2] OME is defined as chronic OME, if effusion persists for 3 months or longer.[1] Acute otitis media and chronic OME have shared causes. Children with chronic OME are prone to recurrent AOM episodes, and after an AOM episode all children have OME for some time.[3]

Myringotomy with TT placement is the most common ambulatory surgery performed on children in the United States[4], with 667,000 TT placed in children under the age of 15 in 2006.[5] The proceedings of the National Summit on Overuse, convened in 2012, based on sample of continually enrolled children into a treatment pathways database and a Medicaid database, reported that 2.5 percent of all U.S. children 2 years old and older had TT inserted in 2010.[6]

A 1994 study reported indications for TT placement in children: 30 percent were for chronic OME, 24 percent for recurrent AOM, and 46 percent of surgical candidates had both recurrent AOM and chronic OME.[7]

Chronic OME can result in hearing deficits, which put a child at risk for speech and language delays, behavioral changes, and poor academic achievement. Recurrent AOM has been shown to impact quality of life for patients and their caregivers.[8] The comparative effectiveness of TT for chronic OME and recurrent AOM is likely influenced by the many factors that affect the prognosis for middle ear disease in children, including current age, age at first diagnosis, frequency of respiratory tract infections, and day care exposure.[9] Children with middle ear effusions that are bilateral and continuously present are likely at higher risk. Tube lifespan is likely to be an important mediator of effectiveness.

Because recurrent AOM and chronic OME have shared causes, and for many patients represent a continuum, it may be important to consider children's risk of these conditions and risk of important outcomes under various treatments for these conditions when researching or planning a child's optimal management. A risk-centered approach might involve differential management of children with otitis media by their risk of important outcomes, as obtained from risk prediction models, which may be preferable to algorithms that use a single threshold for duration or frequency of a diagnosis.[10]

Along these lines we note that certain children, including those with Down syndrome and cleft palate, have a very high risk for middle ear disease. In a retrospective review of patients with Down syndrome, the authors found that the majority of patients required two or more sets of tubes during their childhood.[11] Due to the effects of palatal dysfunction on Eustachian tube function, children with cleft palate also have a high incidence of OME and associated hearing loss.[12] The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) clinical practice guideline

(CPG) identifies a subpopulation of children who may be at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors.[1] The inclination to treat OME more aggressively in these children is reflected in a study that found that approximately 1 in 6 children with autism spectrum disorder underwent TT placement.[13]

The AAO-HNS CPG concludes that the efficacy of TT for preventing recurrent AOM is unclear, with systematic reviews reporting insufficient evidence, small short-term benefits, or moderate benefits of similar magnitude to antibiotic prophylaxis. They note the overall favorable natural history of otitis media without persistent middle ear effusion.[14] The AAO-HNS CPG recommends that clinicians should offer TT to children with recurrent AOM and middle ear effusions based on shared decisionmaking with the child's caregiver. They conclude that there is no benefit if one considers only randomized controlled trials with AOM that clears between episodes (without chronic OME) and recommend that tubes not be placed in children with recurrent AOM who have a normal ear examination at the time of assessment for tube candidacy.[1] The American Academy of Pediatrics CPG discourages routine use of prophylactic antibiotics to prevent recurrent AOM.[15] The reluctance to use antibiotic prophylaxis because of concerns about antibiotic resistance may result in increased use of TT in children with recurrent AOM. Attempts to promote the use of more rigorous criteria for the diagnosis of AOM may also result in improved effectiveness of TT.

A 2014 review by Tsao and Goode provides a narrative summary of their search for evidence regarding water precautions to prevent post-TT otorrhea.[16] They discuss systematic reviews published in 1999 and 2002 and a randomized controlled a trial published in 2005 and conclude that water precautions should not be routinely advised.

Acute otorrhea is common after TT placement.[17] Postoperative otorrhea (up to 30 days after surgery) is common and reflects, in part, underlying (preoperative) middle ear glandular changes and inflammation. Some otorrhea is to be expected, since the role of the tube is to ventilate the middle ear. Episodes of otorrhea that reflect acute bacterial infection may be otherwise asymptomatic and less troublesome than AOM episodes in children with intact eardrums.[18] However, otorrhea may be associated with a foul odor, fever, or pain, and may negatively affect quality of life. Treatment is aimed at eradicating bacterial infection and reducing the duration and severity of symptoms.[19] A number of subgroups of acute otorrhea exist, including: 1) otorrhea in the immediate postoperative period, 2) otorrhea caused by the same pathogens as AOM, including *Moraxella catarrhalis, Haemophilus influenzae,* and *Streptococcus pneumoniae,* and 3) otorrhea resulting from superinfection with *Staphylococcus aureus,* including methicillin resistant *Staphylococccus aureus* (MRSA), and *Pseudomonas* associated with biofilms.[20]

The objectives for the systematic review are to synthesize information on the effectiveness of TT in children with chronic otitis media with effusion and recurrent acute otitis media, to summarize the frequency of adverse effects and/or complications associated with TT placement, to synthesize information on the necessity for water precautions in children with TT, and to assess the effectiveness of available treatments for otorrhea in children who have TT.

## Key Questions

With input from clinical experts during Topic Refinement, and from the Public, during a public review period, we developed the following Key Questions and study eligibility criteria.

**Key Question 1:** For children with chronic otitis media with effusion, what is the effectiveness of TT, compared to watchful waiting, on

resolution of middle ear effusion, hearing and vestibular outcomes, quality of life, and other patient-centered outcomes?

a) What factors (such as age, age of onset, duration of effusion, comorbidities, and sociodemographic risk factors) predict which children are likely to benefit most from the intervention?
b) Does obtaining a hearing test help identify which children are more likely to benefit from the intervention?

**Key Question 2:** For children with recurrent acute otitis media, what is the effectiveness of TT, compared to watchful waiting with episodic or prophylactic antibiotic therapy, on the frequency and severity of otitis media, quality of life, and other patient-centered outcomes?

a) What factors (such as age, age of onset, number of recurrences, presence of persistent middle ear effusion, comorbidities, sociodemographic risk factors, history of complications of acute otitis media, antibiotic allergy or intolerance) predict which children are likely to benefit from the intervention?

**Key Question 3:** What adverse events, surgical complications, and sequelae are associated with inserting TT in children with either chronic otitis media with effusion or recurrent acute otitis media?

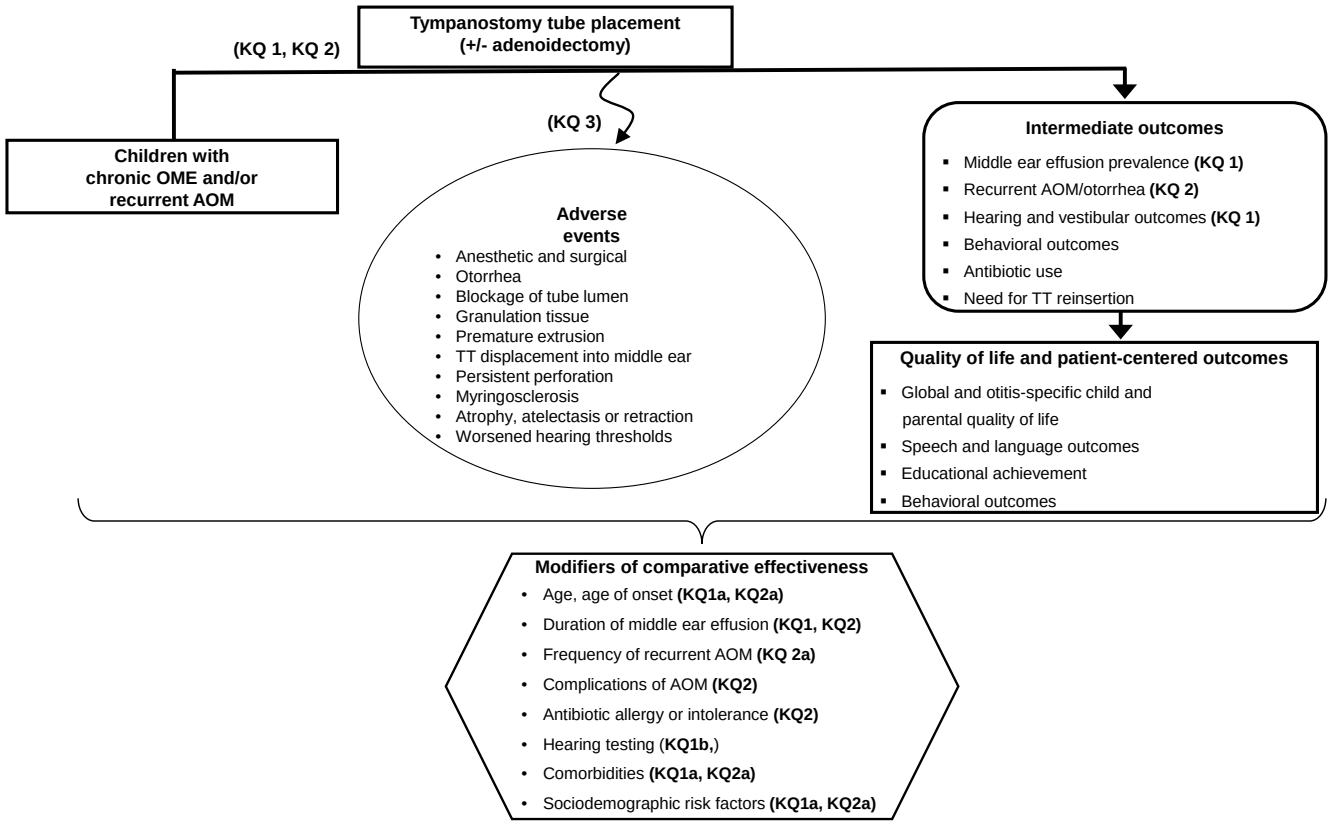
**Key Question 4:** Do water precautions reduce the incidence of TT otorrhea or affect quality of life?

**Key Question 5:** In children with TT otorrhea, what is the comparative effectiveness of topical antibiotic drops versus systemic antibiotics or watchful waiting on duration of otorrhea, quality of life, or need for tube removal?

## Analytic Frameworks

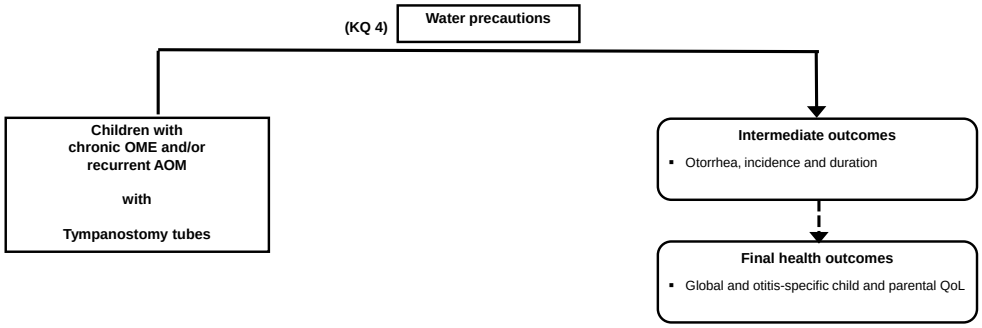
The analytic frameworks in Figures 1 through 3 describe the specific linkages associating the populations of interest, exposures, modifying factors, and outcomes of interest the assessment of studies that examine the association between TT placement and intermediate and final health outcomes and harms (KQs 1, 2 and 3; Figure 1), need for water precautions (KQ 4; Figure 2), and treatment of otorrhea (KQ 5; Figure 3).

**Figure 1. TT in Children with chronic OME or recurrent AOM (Key Questions 1, 2, and 3)**



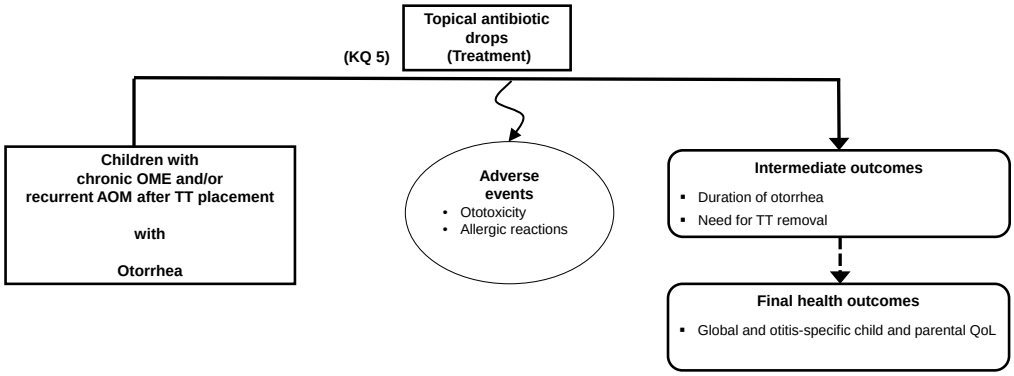

OME=otitis media with effusion; AOM=acute otitis media; TT=tympanostomy tubes; KQ=Key Question

**Figure 2. Need for water precautions in children with TT (Key Question 4)**




OME=otitis media with effusion; AOM=acute otitis media; TT=tympanostomy tubes; KQ=Key Question

**Figure 3. Treatment of otorrhea in children with TT (Key Question 5)**




OME=otitis media with effusion; AOM=acute otitis media; TT=tympanostomy tubes; KQ=Key Question

# Methods

The Brown Evidence-based Practice Center (EPC) conducted this review based on a systematic review of the published scientific literature using established methodologies as outlined in the Agency for Healthcare Research and Quality's (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[21] The PROSPERO protocol registration number is CRD42015029623.

## Eligibility Criteria

We use the Population, Intervention, Comparator, Outcomes, and Designs (PICOD) formalism to define the characteristics of the eligible studies for this review.

### Populations

For all KQs, studies of children and adolescents from 1 month to 18 years old were eligible. We defined five age groups, namely infants (28 days to 12 months), toddlers (13 months to 2 years), early childhood (2 to 5 years), middle childhood (6 to 11 years), and early adolescence (12 to 18 years).[22] Subpopulations of interest included children at high risk of recurrent AOM or OME, such as children with Down syndrome, cleft palate, other craniofacial anomalies, or primary ciliary dyskinesia; and children at high risk of adverse clinical or developmental outcomes, such as those with preexisting hearing loss, speech and language problems, or various developmental disorders. We were also interested in the population of children who have sociodemographic risk factors (e.g. day care exposure or low socioeconomic status).

For Key Question (KQ) 1, we included studies of children with chronic OME. We preferred the standard definition of effusion that persists for at least 3 months,[1] but also included results based on studies' alternative definitions, if our preferred one was not reported. We excluded studies of children with chronic suppurative otitis media since it is associated with a persistently perforated tympanic membrane.

For KQ 2, we included children with recurrent AOM with or without middle ear effusion, defined as three or more well-documented and separate AOM episodes in the past 6 months or at least four well-documented and separate AOM episodes in the past 12 months with at least one in the past 6 months.[23] For studies that did not report the preferred definition we recorded the study specific definition.

For KQ 3 and 4, we included studies in children with TT placed for OME or AOM. For KQ 5, we included studies of symptomatic or asymptomatic children with acute TT otorrhea beyond the immediate postoperative period. We defined the immediate postoperative period as 30 days after surgery, but included studies reporting results near that period (e.g., 28 days, 4 weeks).

### Interventions/Exposures

For KQs 1, 2, and 3 we considered all studies that included myringtomy with TT placement, with or without adenoidectomy. Tubes were classified as short-term tubes (generally in place for 10-18 months) and long-term tubes (e.g. T-tubes, which typically remain in place for several years).

In KQ 4, we distinguished three categories of interventions; avoidance (e.g. of swimming or head immersion while bathing), canal occlusion methods (e.g. earplugs or headbands), and postexposure prophylaxis using ototopical antibiotics.

In KQ 5 we compared ototopical preparations, including FDA approved products (i.e. ofloxacin otic 0.3%, ciprofloxacin 0.3% & dexamethasone 0.1%), and other non FDA-approved agents (e.g. hydrocortisone & bacitracin & colistin).

## Comparators

For KQ 1, comparisons of primary interest were watchful waiting or adenoidectomy. Comparators for KQ2 included watchful waiting, with systemic or topical antibiotic therapy for recurrent episodes of AOM, prophylactic antibiotics and adenoidectomy. KQ 3 did not address comparative harms. In KQ 4, comparators included no water precautions with or without avoidance of higher risk activities (e.g. diving or underwater swimming and ear plugs or swimming caps). The primary comparators for KQ5 were watchful waiting and oral antibiotic therapy.

## Outcomes

For KQs 1 and 2, which address the effectiveness of TT, we considered intermediate outcomes, including prevalence of middle ear effusion, measures of hearing and vestibular function, such as improved hearing thresholds (audibility), tests of auditory perception and discrimination (clarity), and balance and coordination (vestibular function). For KQ 2, measures of recurrent AOM, including otorrhea were also extracted.

Quality of life and patient-centered outcomes included global and otitis-specific child and parental quality of life, speech and language outcomes, educational achievement, and behavioral outcomes, such as disobedience, enuresis, or tantrums.

The following adverse event outcomes were extracted for KQ 3: Intraoperative and immediate postoperative anesthetic and surgical adverse events, otorrhea, blockage of the tube lumen, granulation tissue, premature extrusion, TT displacement into the middle ear, persistent perforation of the tympanic membrane, myringosclerosis, tympanic membrane atrophy, atelectasis and retraction pockets, worsened hearing thresholds, and other reported adverse events (plausibly related to TT). Studies reporting only postoperative otorrhea (during the 30 days after surgery )was excluded, as this outcome is likely confounded by the preoperative state of the middle ear.

Outcomes for KQ 4 (water precautions) included final health and patient-centered outcomes related to child and parental quality of life and intermediate outcomes related to the incidence and duration of otorrhea.

Outcomes evaluated relating to KQ 5 (treatment of otorrhea) included global and otitis-specific child and parental quality of life, duration of otorrhea, and need for removal of TT. Postoperative otorrhea was not an outcome of interest.

## Timing

We included studies with any duration of followup.

## Setting

Studies performed in both primary and specialty care settings were included.

## Study Design

We evaluated published, peer-reviewed studies only. Conference abstracts were excluded. For KQs 1 and 2, we included randomized comparative trials and nonrandomized comparative studies, prospective and retrospective, where treatment was assigned on a per patient basis. Studies with per ear assignment were excluded (e.g. TT placed by design in one ear only).

For KQ 3, we included prospective surgical studies enrolling at least 50 subjects (including arms of RCTs or NRCSs with 50 or more patients) and population based retrospective single-group studies (registry studies) with ≥1000 subjects.

# Evidence Identification

We conducted literature searches of all studies in MEDLINE®, both the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, EMBASE®, and CINAHL® (from inception) to identify primary research studies meeting our criteria. We used the search strategies in Appendix A. The last search was run on May 19, 2016. The TEP was asked to provide citations of potentially relevant articles. Additionally, we perused the reference lists of published clinical practice guidelines, relevant narrative and systematic reviews, and examined Scientific Information Packages from manufacturers. Existing systematic reviews were used primarily as sources of studies; we extracted and incorporated all studies de novo, and did not summarize or incorporate existing systematic reviews, per se.

We searched Devices@FDA.gov at www.accessdata.fda.gov/scripts/cdrh/devicesatfda/ for the classification product code "ETD" (TT). This returned 109 records, all of which are deemed to be substantially equivalent to previous devices (indicating there are no new data that the FDA considered) or have original approvals that predate the electronic records and require either contacting the manufacturer for information or requesting it from the FDA. We also searched the Clinicaltrials.gov Web site and the WHO International Clinical Trials Registry Platform for relevant study records. All records identified were screened for eligibility using the same criteria as was used for articles identified through literature searches.

At the start of citation screening, we implemented a training session, in which all researchers screened the same articles and conflicts were discussed. We iteratively continued training until agreement was reached regarding the nuances of the eligibility criteria for screening. All citations found by literature searches, including from sources other than electronic databases (e.g., TEP, existing systematic reviews) were independently screened by two researchers. Conflicts were resolved by discussion until a group consensus was reached. All screening was done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/).

# Data Extraction and Data Management

Each study was extracted by one methodologist. The extractions were reviewed and confirmed by at least one other methodologist. Any disagreements were resolved by discussion among the team members. Data was extracted into customized forms in the Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov). Upon completion of the review, the SRDR database will be made accessible to the general public with capacity to read, download, and comment on data. The basic elements and design of these forms is similar to those we have used for other comparative effectiveness reviews and includes elements that address population characteristics; descriptions of the interventions, exposures, and comparators analyzed; outcome

definitions; effect modifiers; enrolled and analyzed sample sizes; study design features; funding source; results; and risk of bias questions.

## Assessment of Methodological Risk of Bias of Individual Studies

We assessed the methodological quality of each study based on predefined criteria. For RCTs, we used the Cochrane risk of bias tool,[24] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used relevant questions from the Newcastle Ottawa Scale.[25] The methodological attributes of studies and comments on study execution and outcome measurement that pertain to specific outcomes within a study were considered when determining the overall strength of evidence for conclusions related to those outcomes, as is standard practice.

## Data Synthesis

All included studies were summarized in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, and results.

We analyzed different study designs separately. We compared and contrasted populations, exposures, and results across study designs. We examined any differences in findings between observational and intervention studies. We evaluated the risk of bias factors as possible explanations for any heterogeneity.

Specific methods and metrics (summary measures) meta-analyzed were chosen based on available outcomes. We conducted quantitative analysis for outcomes that have at least five studies reporting results that could be combined in a meta-analysis. When available, these were summarized as odds ratios of categorical outcomes and net change of continuous outcomes (e.g., mean hearing threshold).

For KQ 4, we conducted direct pairwise random effects meta-analyses of nonrandomized comparative studies that were sufficiently similar in population, interventions (water restriction vs. ear protection), and outcomes. The two randomized comparative trials were not combined in a meta-analysis on the basis of clinical heterogeneity (suggestion of higher baseline risk), as well as methodological heterogeneity. Rather, each was individually reported. We used typical models that assume that study-specific latent treatment effects are normally distributed across studies,[26] and estimated them by maximizing the restricted likelihood in a generalized linear mixed model, using the R[27] package *metafor*.[28]

For KQs 1 and 5, we performed network meta-analysis of clinical outcomes to compare treatment alternatives. We conducted network meta-analyses in the Bayesian framework, using the R *gemtc* package.[29, 30] A network meta-analysis is an extension of pairwise meta-analyses that simultaneously combines direct (when interventions are compared head-to-head) and indirect (when interventions are compared through other reference interventions) evidence. Combining the direct and indirect evidence not only improves precision of estimates, but also provides estimates for all pairwise comparisons, including those missing from the direct evidence. The key assumption of the network meta-analysis is that of consistency of direct and indirect effects. Consistency is likely to hold when the distribution of effect modifiers is (equivalently, patient characteristics are) similar across trials. If this assumption is violated, there may be inconsistency between the direct evidence and indirect evidence of treatment comparisons.

For network meta-analyses, we used a hierarchical model with a within-study level and a between-studies level that models responses at the arm level and nests arms within studies. We ran two sets of analyses, one assuming consistency of treatment effects and one examining this assumption. The models are shown in Appendix I. Briefly, the analysis assuming consistency parameterizes treatment effects as linear combinations of $T$-1 parameters, where $T$ is the number of treatments in the network. Treatment effects are assumed to be normally distributed across studies with a common variance, i.e., are homoscedastic random effects. We used weakly informative default priors on study-level mean treatment effects and on between-study means and variances. Priors on the means were uniform distributions, with standard errors 15 times larger than the observed scatter of study effect estimates. We put uniform priors on the standard deviation of between-studies treatment effects, with support determined from the observed scatter of treatment effects.

Estimation was done with MCMC via the JAGS sampler,[31] using initial values drawn randomly from the marginal distributions of the priors of respective parameters. We fit four MCMC chains. After a burn in of 5000 iterations, we monitored convergence of random effects means and variances automatically, by checking every 10000 iterations whether the Gelman Rubin diagnostic was less than 1.05 with 95% probability for all monitored parameters. After convergence was reached, an extra 10000 iterations were run. All models converged quickly, within 10000 iterations. Model fit was assessed by comparing the posterior mean of the residual deviance to the number of data points.[32] The ratio of residual deviance to number of data points ranged from 0.97 to 1.06, suggesting adequate model fit.

For each analysis, we empirically assessed if the network meta-analysis consistency assumption was violated by comparing the direct and indirect evidence using a node-splitting approach. We separately parameterized the direct and indirect effects, and compared the estimates of the two.[33, 34] These analyses were not suggestive of inconsistency, but in small networks, like the ones in this report, they can be underpowered. The split-node analysis is the statistically preferred version of naive analyses that compare direct and indirect estimates in a network. Formal model description, details of inconsistency analysis and illustrative trace and density plots are shown in Appendix I.

Results are presented in terms of means and corresponding 95% credible intervals (CrI). We also estimated the probability that a treatment is the most effective, second most effective, and so on, based on the results of the network meta-analyses.

Statistical heterogeneity was explored qualitatively. Because of the relatively small number of studies, and the little variability in characteristics, meta-regression analyses were not performed. Instead, we did subgroup analyses for the study characteristics of interest described in the corresponding KQ. Because these subgroup analyses did not change conclusions, they are not reported in detail.

## Grading the Strength of Evidence

We graded the strength of evidence (SOE) as per the AHRQ methods guide on assessing the strength of evidence.[35] We assessed the strength of evidence for each outcome. Following the standard AHRQ approach, for each intervention and comparison of intervention and for each outcome, we assessed the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the KQs, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the

overall findings across studies. Based on these assessments, we assigned a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect.

## Assessing Applicability

We assessed the direct applicability within and across studies with reference to children with specific comorbidities (Down syndrome, cleft palate, etc.), and whether interventions and comparators are used in current practice.

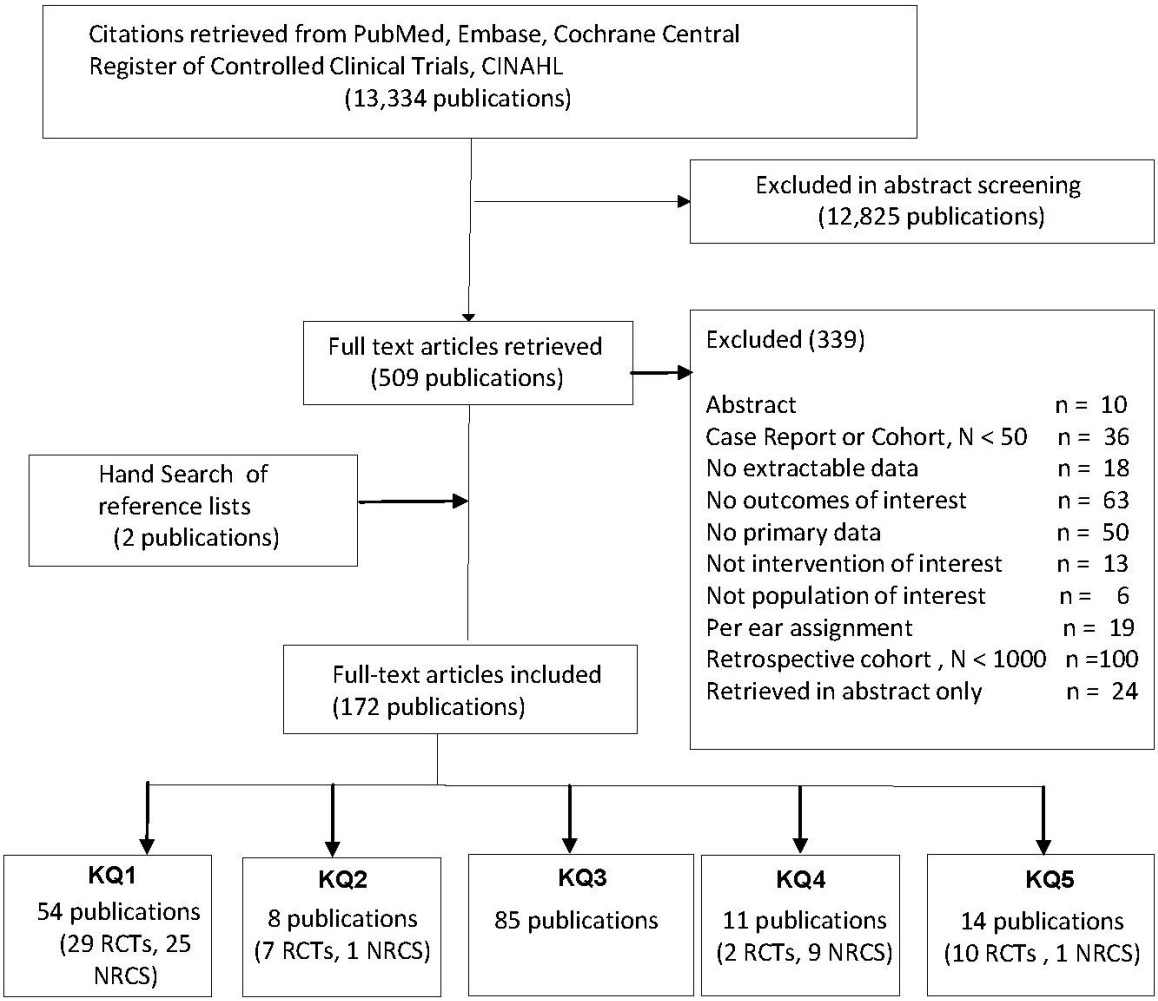
# Results

The literature searches yielded 13,334 citations (Figure 4). We identified 510 of these as potentially relevant full-text studies. These were retrieved for further evaluation. Overall, 339 full text articles did not meet eligibility criteria (see Appendix B for a list of rejected articles along with reasons for rejection); two additional publications were identified through a hand search of reference lists. . Searching the U.S. Food and Drug Administration (FDA) database, clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform did not yield any trials with results that were not already included in the report.

A total of 173 articles are included in this report. Searching the FDA database, clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform did not yield any trials with results that were not already included in the report.

As shown in Figure 4, the majority of included publications (n = 85) related to KQ 3. These included prospective surgical case series that followed 50 or more children after TT placement or large (≥ 1000 subject) registry-based retrospective cohorts. There are a relative paucity of studies available for the other the main effectiveness KQs.

**Figure 4. Literature flow diagram**




CINAHL = Cumulative Index to Nursing and Allied Health Literature; KQ = Key Question; NRCS = nonrandomized comparative trial; RCT = randomized controlled trial; some publications reported data from the same study. The KQ3 publications included 70 cohorts, 12 NRCSs and 3 RCTs from which the cohort most closely matching usual care was extracted. Detailed reasons for exclusion of studies reviewed in full text but not considered further are presented in Appendix B.

# Key Question 1

For children with chronic otitis media with effusion, what is the effectiveness of tympanostomy tubes (TT), compared to watchful waiting, on resolution of middle ear effusion, hearing and vestibular outcomes, quality of life, and other patient-centered outcomes?

a) What factors (such as age, age of onset, duration of effusion, comorbidities, and sociodemographic risk factors) predict which children are likely to benefit most from the intervention?
b) Does obtaining a hearing test help identify which children are more likely to benefit from the intervention?

## Eligible Studies

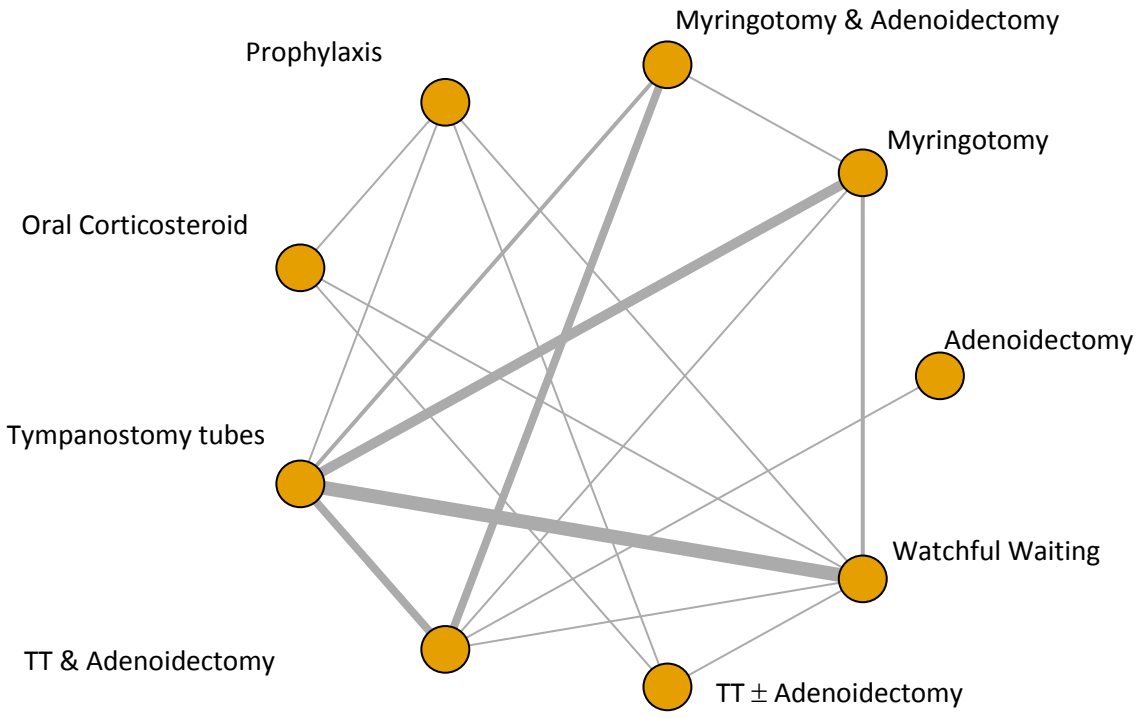
We identified 54 publications. Of these, there were 29 papers reporting 16 RCTs.[4, 36-63]There were 24 publications reporting 24 NRCSs that assessed the effectiveness of TT in children with chronic middle ear effusion.[64-87]

## Description of Randomized Trials

Among the 16 RCTs (Table 1), a majority enrolled children in the preschool and early school ages (mean age of enrolled children ranged from 1.6 to 5.4 years). Sample sizes ranged between 23 and 491. Most trials enrolled a majority of boys. The proportion of male children ranged from 48 to 82 percent. Most studies enrolled children with persistent middle ear effusion in one or both ears for periods of 2 to 6 months. Two studies included at least some patients with recurrent AOM with or without persistent middle ear effusion.[36, 49] Most studies were conducted in the United States and Europe. The majority completed enrollment more than a decade ago. Reporting of age of onset, duration of effusion, and sociodemographic risk factors was sparse. All RCTs excluded children with major comorbidities (e.g. Down syndrome and cleft palate). For details, see Appendixes C-E.

As illustrated in Figure 5, and detailed in Table 1, the RCTs compare multiple interventions: TT, TT with adenoidectomy, myringotomy with adenoidectomy, myringtomy alone, adenoidectomy alone, oral corticosteroid treatment, antibiotic prophylaxis, and watchful waiting.

**Figure 5. Evidence graph for the 16 RCTs**




Evidence graph for the 16 RCTs (10 comparing pairs, 4 comparing triplets, and 2 comparing quadruplets of treatments) identified in the systematic review. Of the 28 possible comparisons that are possible, 16 were examined in the RCTs. The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

TT= tympanostomy tubes; RCTs= Randomized Control Trials

**Table 1. Summary of randomized controlled trials (RCTs)**

| Study Year PMID Country | Inclusion Criteria | Age (years) | Enrollment period | Comparators (N) | Hearing (measurement time in months) | MEE (followup in months) |
|---|---|---|---|---|---|---|
| Bernard 1991 1861917 Canada[36] | MEE > 3 months in at least one ear | 2.5 to 7 | NR | Sulfisoxazole (65) vs. TT (60) | Mean HL (0,2,4,6,12,18) | NR |
| Casselbrant 2009 19819563 1997-2005 U.S.[37] | bilateral MEE >= 3 mo, unilateral MEE >= 6 mo | 2.0 to 3.9 | 1997-2005 | TT (32) vs. TT & adenoidectomy (32) vs Myringotomy & Adenoidectomy (34) | Study entry only | Percent time with MEE (18, 36) |
| Chaudhuri 2006 23120310 India[38] | Unclear | 0 to 12 | NR | Antibiotic prophylaxis (25) vs. Oral steroid (25) vs. Placebo (25) vs. TT +/- adenoidectomy (25) | | Composite cure (appearance, audiometry, tympanography) |
| Gates 1987 3683478 U.S.[88] | suspected SOM with MEE persisting >= 2 months | 4 to 8 | 4/1980-6/1984 | TT (129) vs. Myringotomy (107) vs. vs. TT & Adenoidectomy (125) vs. Myringotomy & Adenoidectomy (130) | Time with abnormal hearing & time with HL >= 20 dB | Percent time with effusion & time to 1st recurrence, proportion of exams with effusion |
| Mandel 1989 2789777a U.S.[44] | MEE >= 2 mo | 7 mo to 12 | 09/1979-09/1984 | TT (30) vs. Myringotomy (29) vs Control (29) | HL (0, 1,2) | Percent time with effusion (12, 24, 36) |
| Mandel 1989 2789777b U.S.[44] | MEE >= 2 mo | 7 mo to 12 | 09/1979-09/1984 | TT (11) vs. Myringotomy (12) | | |
| Mandel 1992 1565550 U.S.[45] | MEE >= 2 mo | 7 mo to 12 | 11/1981-06/1987 | TT (37) vs. Myringotomy (39) vs. Watchful waiting (4-6 months) (35) | HL (0,1,2,4) | Percent time with effusion (12, 36) |
| Maw 1999 10459904 UK[40, 46, 63] | bilateral OME & HL > = 20 dB | NR | 4/1991-12/1992 | TT (92) vs. Watchful waiting (90) | HL (0, 9) | Number with at least one middle ear without fluid |
| MRC Multicentre Otitis Media Study Group 2012 (TARGET) 12680834 UK [4, 47, 48] | bilateral OME & better ear HL >= 20 dB for 3 mo | 3.25 to 6.75 | 4/1994-1/1998 | TT (126) vs. TT & adenoidectomy (128) vs. Watchful waiting (122) | HL (0,3,6,9,12,15,18,21,24) | |
| Nguyen 2004 15126745 Canada[49] | recurrent OM with > 3 episodes in 6 mo or 4 in 12 mo, | 1.5 to 18 | 01/1998-01/2003 | TT (16) vs. TT & adenoidectomy (18) | Included in composite outcome | Included in composite outcome |

| | | | | | | |
|---|---|---|---|---|---|---|
| | persistent OME > 3 months, or HL > 30 dB | | | | | |
| Paradise 2001 11309632 U.S.[43, 50-52, 54] | bilateral MEE >= 3 mo, unilateral MEE >= 135 days) | < 3 | 6/1991-12/1995 | TT (216) vs. Watchful Waiting (213) | NR | Percent time with effusion (6,12,18,24) |
| Popova 2010 20399511 Bulgaria[55] | bilateral MEE >= 3 mo & HL > 20 dB | 3 to 7 | 2007-2009 | TT (42) vs. Myringotomy AND Adenoidectomy (36) | HL (0,1,6,12) | Number with recurrence |
| Rach 1991 2070526 Netherlands[56] | bilateral OME >= 6 mo | > 2 | NR | TT (22) vs. Watchful waiting (for 9 months then tubes if needed) (21) | NR | NR |
| Rovers 2000 10969126 Netherlands[41, 42, 57-60] | bilateral persistent OME 4-6 months | > 9 mo | 1/1996-4/1997 | TT (93) vs. Watchful waiting (94) | HL (0,6,12) | Percent with bilateral OME (3,6,9,12) |
| Velopic 2001 21397957 Croatia[61] | unilateral or bilateral OME >= 3 mo | 2 to 12 | 2004-2009 | TT (56) vs. TT & adenoidectomy | Average and frequency specific air bone gap (0, 6+) | Resolution of effusion at 6+ months postoperative. |
| Vlastos 2011 21205368 Greece[62] | sleep-disordered breathing & bilateral OME | 3 to 7 | 5/2007-5/2008 | TT & Adenoidectomy (25) vs. Myringotomy & Adenoidectomy (27) | HL (0,6,12) | |

TT: Tympanostomy tubes, HL: Hearing thresholds (time in months), OME: Otitis Media with effusion, MEE: Middle ear effusion, NR: not reported, mo: months

## Risk of Bias: RCTs

Overall, RCTs that compared TT and nonsurgical arms had high risk of bias, due to lack of blinding of participants and care providers (blinding is not feasible given the intervention). With the exception of Maw 1999[46] and Gates 1987,[88] trials had unclear (did not report) or had high risk of bias for lack of blinding of outcome assessors. The details of random sequence generation were unclear in the majority of studies (unclear risk of bias). Randomization sequence generation was adequately described in four RCTs.[4, 52, 62, 88] The Rach 1991 RCT reported that randomized allocation was performed only for the first 5 of 43 children entering the trial; each subsequent child was allocated to the treatment group that would lead to the smallest imbalance. While this allocation scheme is reminiscent of "minimization"-based randomized allocation schemes, the RCT was judged to have a high risk of confounding bias.[56] All studies had at least some incomplete outcome data for some subjects. The proportion of subjects with missing data increased in studies with longer term followup. The TARGET study employed missing data imputation to limit attrition bias.[4] Most studies reported an intention to treat analysis. However, in many studies, there was a high rate of crossover to surgical interventions (TT, adenoidectomy, or both).

## Description of Nonrandomized Comparative Studies

Of the 25 NRCSs,[64-87] 9 compared TT with watchful waiting or medical treatment and 2 compared TT with myringotomy. Outcomes evaluated included hearing levels, persistence of middle ear effusion and composite outcomes (cure, recurrence). These studies are summarized in Table 2. For futher details, see Appendices C-E.

Six studies evaluated comparisons of children with cleft palate who had early vs. delayed vs. medical treatment of chronic OME and reported outcomes related to language development, hearing levels, persistence of middle ear effusion. One study compared TT with medical treatment in children with primary ciliary dyskinesia and evaluated hearing levels, persistence of middle ear effusion and need for further surgery.

Eight studies compared TT with TT & adenoidectomy, adenoidectomy alone or adenoidectomy & myringotomy.

**Table 2. Summary of nonrandomized comparative studies (NRCSs)**

| Study, Year, PMID, Country | Enrollment period | Comparators (N) | Special populations | Covariate adjusted | Outcome(s) |
|---|---|---|---|---|---|
| Coyte 2001 11309633 Canada[72] | 1992-1997 | TT (10602) & adenoidectomy vs. TT (26714) | | Yes | Rate of rehospitalization; reinsertion of TT |
| De Beer 2004 15224825 Netherlands[74] | 2001 | TT (51) vs. OME without TT (132) vs. control (174) | | Yes | Hearing levels at 18 years |
| Forquer 1982 6184891 U.S.[67] | NR | TT (177) vs. medical treatment & delayed TT (170) vs. medical treatment (153) | | No | Hearing level; Middle ear effusion |
| Grievink 1993 8246466 Netherlands[70] | 9/1990-2/1991 | TT (37) vs. OME (151) vs. control (82) | | Yes | Language ability |
| Hu 2015 26429601 U.S.[85] | 2014 | TT (12) vs. TT & adenoidectomy or adenotonsillectomy (8) | | No | Hearing level |
| Hubbard 1985 4039792 U.S.[66] | 1/1979 | Early TT (24) vs. late TT (24) | Cleft palate | No | Hearing level |
| Kadhim 2007 | 1981-2004 | TT (36532) vs. TT & | | Yes | Need for further surgery |

| Study, Year, PMID, Country | Enrollment period | Comparators (N) | Special populations | Covariate adjusted | Outcome(s) |
|---|---|---|---|---|---|
| 17279052 Australia[76] | | adenoidectomy (7534) | | | |
| Kobayashi 2012 22386274 Japan[79] | 1996-1999 | Early TT (82) vs. late TT (bilateral: 6 mo, unilateral: 3 mo) (100) | Cleft palate | No | Language development |
| Kuşcu 2015 26545930 Turkey[86] | 2008-2013 | early TT (67) vs. late TT (22) vs. no TT (65) | Cleft palate | No | Hearing level, otoscopic findings |
| Li 2015 26281253 China[84] | 2002 - 2012 | TT (248) vs. Myringotomy (276) | Cleft palate | No | Cure, Recurrence |
| Li 2015 26281253 China[84] | 2003 - 2012 | TT (78) vs. Myringotomy (168) | Adenoidal hypertrophy | No | Cure, Recurrence |
| Marshak 1980 6778336 Israel[68] | NR | TT (29) vs. myringotomy & adenoidectomy (29) | | No | Middle ear effusion |
| Motta 2006 17465378 Italy[77] | 1/1/2001-12/31/2001 | TT & adenoidectomy (34) vs. adenoidectomy (40) | | No | Middle ear effusion |
| Niclasen 2016 27063746 Denmark[87] | 2001-2002 | 4+ episodes of OM (569) vs. 4+ episodes of OM& TT (999) | | Yes | Behavioral and Learning Difficulties |
| Peters 1994 8195687 Netherlands[69] | 9/1990-2/1991 | . | | Yes | Educational attainment, Reading & Spelling |
| Reiter 2009 19929085 Germany[78] | NR | TT & palate cleft repair (50) vs. palate cleft repair (66) | Cleft palate | No | Hearing level |
| Robson 1992 1431515 UK[65] | 1976-1988 | TT (38) vs. control (32) | Cleft palate | No | Hearing level; Middle ear effusion |
| Schilder 1997 9372253 UK[71] | 1990 | TT (56) vs. control (102) | | Yes | Hearing levels; Language & Educational achievement |
| Stenstrom 2005 16330739 Canada[75] | 1985-1989 | TT (38) vs. sulfisoxazole (27) | | No | Long term hearing thresholds |
| Tian 2015 26103659 China[83] | 1/2001-6/2013 | TT & Adenoidectomy (40 ears) vs. Myringotomy & Adenoidectomy (58 ears) | | No | Composite Outcome (symptoms, otoscopy, hearing level, tympanography) |
| Wolter 2012 22883987 Canada[80] | 1991-2009 | TT (26) vs. medical treatment (18) | Primary ciliary dyskinesia | No | Hearing level; Middle ear effusion; Need for further surgery |
| Xu 2003 12930655 China[73] | 9/1997-5/2000 | TT & palate cleft repair (31) vs. palate cleft repair (31) | Cleft palate | No | Hearing level |
| Yagi 1977 321716 Sudan[64] | NR | TT & myringotomy & adenoidectomy (100) vs. adenoidectomy (100) | | No | Middle ear effusion |
| Yousaf 2012 23855103 Pakistan[81] | 6/2008-12/2011 | TT (44) vs. myringotomy (26) | | No | Middle ear effusion |
| Youssef 2013 24265883 Egypt[82] | 3/2007-1/2009 | TT & myringotomy +/- adenoidectomy (86) vs. laser myringotomy +/- adenoidectomy (86) | | No | Middle ear effusion |

TT: Tympanostomy tubes, NR: not reported, mo: months

## Risk of Bias: Nonrandomized Comparative Studies

Only five studies used matching or multivariable regression methods to adjust for potential confounders (e.g. baseline severity of middle ear disease). See Appendix F for detailed risk of bias assessments. Generally, the studies that did not adjust for confounding are at high risk of bias.

## Outcomes: Nonrandomized Comparative Studies

The outcomes of NRCSs that evaluated behavioral, language and educational outcomes are summarized in Table 10.

The Coyte 2001 report analyzed hospital discharge records and found that treatment with TT and adenoidectomy compared with TT alone was associated with a reduction in the likelihood of reinsertion of TT (RR 0.5 [95% CI: 0.5-0.6]) and the likelihood of readmission for conditions related otitis media (RR 0.5 [95% CI: 0.5-0.6]), with greatest benefit in children three years of age or older.[72]

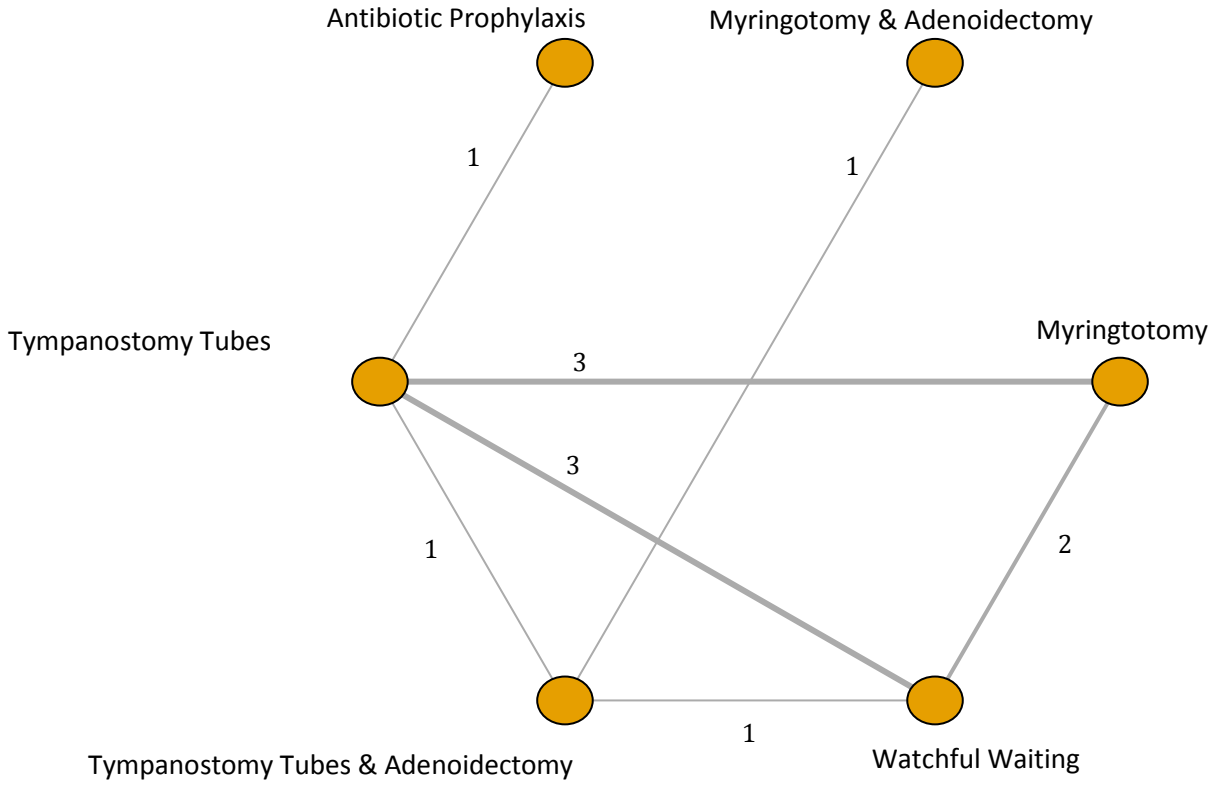
Schilder 1997 compared hearing levels and mean duration of otitis media with effusion (OME) at seven to eight years between children treated with TT at two to four years of age, with a (retrospectively) matched group of children who were not treated surgically. Pure tone average hearing levels measured at 0.5 to 4kHz were 11.4 and 8.1 dB (P=0.19) for treated and control ears, respectively. Similarly, mean OME percentages were not significantly different between groups ($P \leq 0.08$).[71]

## Hearing Outcomes: RCTs

Hearing thresholds (in dB) were reported by arm in 10 RCTs at various time points, allowing estimation of comparative effects between interventions. Pure tone average (typically averaged over 500, 100, 2000, and 4000 Hz) hearing thresholds were extracted. Hearing thresholds were variably reported as: averaged over both ears, best and worst ear, and right and left ear. When multiple averages were reported, we extracted for analysis the worst ear and the right ear. Six RCTs reported hearing thresholds at 1 to 3 months (classified as "early").[4, 36, 44, 45, 55] Five RCTs reported hearing thresholds at 12 to 24 months (classified as "late").[4, 36, 55, 58, 62] The remaining 6 RCTs did not report information in enough detail to include in quantitative analyses and are described separately. The Mandel 1989 RCT stratified children by preintervention hearing thresholds.[44] Patients with no significant hearing loss (≤ 20 dB bilaterally or ≤ 40 dB unilaterally) were randomized to watchful waiting, myringtomy, or TT. The 23 patients with significant hearing loss were randomized to myringotomy or TT only. We have included these two groups as separate RCTs in the meta-analysis.

Figure 6 shows the topology of the network for early hearing thresholds at 1 to 3 months. TT were the most common comparator, being compared in head-to-head trials with four interventions (all except for myringotomy with adenoidectomy). TT, TT with adenoidectomy, myringotomy, and watchful waiting have each been compared with at least two other interventions. By contrast antibiotic prophylaxis is compared only with TT and in only one trial, and myringotomy with adenoidectomy is compared only with TT with adenoidectomy, again only in one trial.

**Figure 6. Network graph for early (1-3 months) comparisons for hearing thresholds**




The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

Table 3 shows the combined direct and indirect data from the network meta-analysis for early hearing thresholds for all possible comparisons between the treatments. Bearing in mind that a difference in hearing thresholds of 10 dB is likely clinically important, it appears that interventions that ventilate the middle ear (TT and TT and adenoidectomy) improved hearing thresholds by -9.1 dB and -10.3 dB respectively, compared to watchful waiting, with 95% credible intervals that exclude a null effect in the 1- to 3-month time frame.

**Table 3. Differences in early hearing thresholds (in dB, 1-3 months)**

| | | | | | |
|---|---|---|---|---|---|
| **TT** | -1.2 (-9.8, 7.2) | 6.8 (0.3, 12.2) | -1.4 (-14.0, 11.1) | 9.1 (-0.4, 18.5) | 9.1 (3.2, 14.5) |
| 1.2 (-7.2, 9.8) | **TT + Adenoidectomy** | 8.0 (-2.1, 17.2) | -0.2 (-9.4, 9.0) | 10.3 (-2.4, 23.1) | 10.3 (1.6, 18.6) |
| -6.8 (-12.2, -0.3) | -8.0 (-17.2, 2.1) | **Myringotomy** | -8.2 (-21.2, 5.9) | 2.3 (-8.3, 14.0) | 2.3 (-4.0, 9.2) |
| 1.4 (-11.1, 14.0) | 0.2 (-9.0, 9.4) | 8.2 (-5.9, 21.2) | **Myringotomy + Adenoidectomy** | 10.5 (-5.1, 26.3) | 10.5 (-2.4, 22.9) |
| -9.1 (-18.5, 0.4) | -10.3 (-23.1, 2.4) | -2.3 (-14.0, 8.3) | -10.5 (-26.3, 5.1) | **Antibiotic prophylaxis** | 0.0 (-11.3, 10.7) |
| -9.1 (-14.5, -3.2) | -10.3 (-18.6, -1.6) | -2.3 (-9.2, 4.0) | -10.5 (-22.9, 2.4) | -0.0 (-10.7, 11.3) | **Watchful waiting** |

Differences in hearing thresholds (dB) and 95% Credible Intervals in early (at 1-3 months) hearing thresholds among the 6 treatments in **Figure 6.** Each cell contains the difference of the comparison of the intervention in the corresponding row versus the intervention in the corresponding column. Negative numbers imply better outcomes for the first.

Table 4 lists the probabilities derived from the network meta-analysis that an intervention is the first, second, etc., most effective with respect to early hearing thresholds. Table 5 aggregates these probabilities and lists the probability that an intervention is among either among the three most effect or the three least effective. TT placement has a 97 percent probability of being the most effective intervention, followed by TT and adenoidectomy (96%) and myringotomy and adenoidectomy (91%). Watchful waiting has high probability (99%) of being one of three least effective interventions, together with antibiotic prophylaxis and myringotomy alone.

**Table 4. Probabilities (percent) that an intervention ranks as the *i-th* most effective with respect to early hearing thresholds**

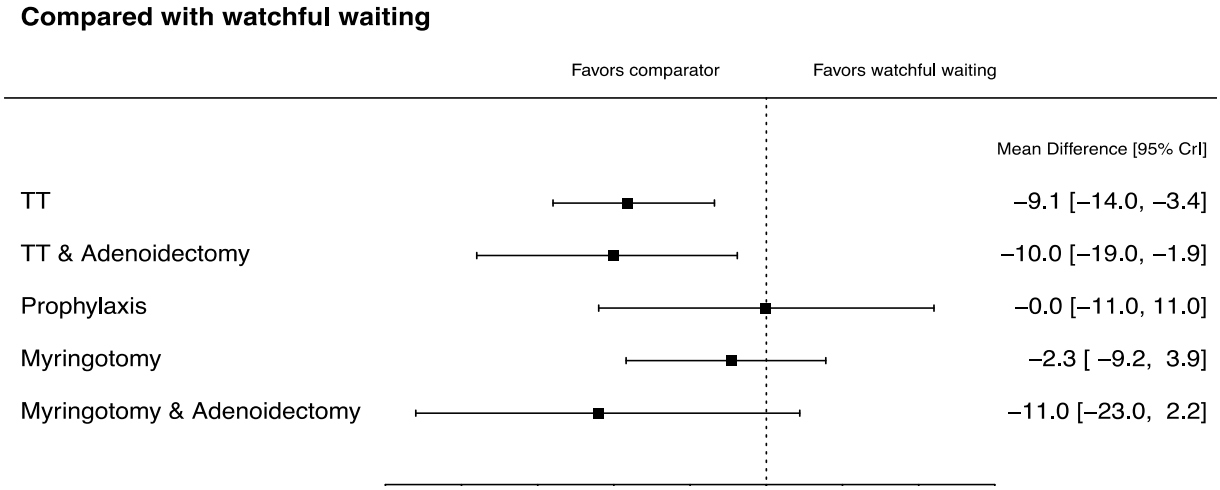
| Intervention | 1st | 2nd | 3rd | 4th | 5th | 6th |
|---|---|---|---|---|---|---|
| TT | 19 | 22 | 56 | 2 | 0 | 0 |
| TT + Adenoidectomy | 32 | 49 | 15 | 3 | 1 | 0 |
| Myringotomy | 1 | 2 | 5 | 59 | 24 | 9 |
| Myringotomy + Adenoidectomy | 47 | 24 | 20 | 4 | 2 | 2 |
| Antibiotic prophylaxis | 1 | 2 | 3 | 19 | 28 | 46 |
| Watchful waiting | 0 | 0 | 1 | 12 | 44 | 42 |

**Table 5. Probabilities (percent) that an intervention is among the three most effective with respect to early hearing thresholds**

| Intervention | Probability (%) of being among the 3 most effective interventions | Probability (%) of being among the 3 least effective interventions |
|---|---|---|
| TT | 97 | 3 |
| TT + Adenoidectomy | 96 | 4 |
| Myringotomy | 8 | 92 |
| Myringotomy + Adenoidectomy | 91 | 9 |
| Antibiotic prophylaxis | 6 | 94 |
| Watchful waiting | 1 | 99 |

As illustrated in Figure 7, when compared with watchful waiting at 1 to 3 months followup, mean hearing thresholds improved (decreased) by average of 9.1 dB following TT and by 10 dB following TT with adenoidectomy. Credible intervals for these effects exclude zero. The credible intervals for comparisons between watchful waiting and myringotomy alone, myringotomy with adenoidectomy, and oral antibiotic prophylaxis were wide, but did not exclude a null effect.

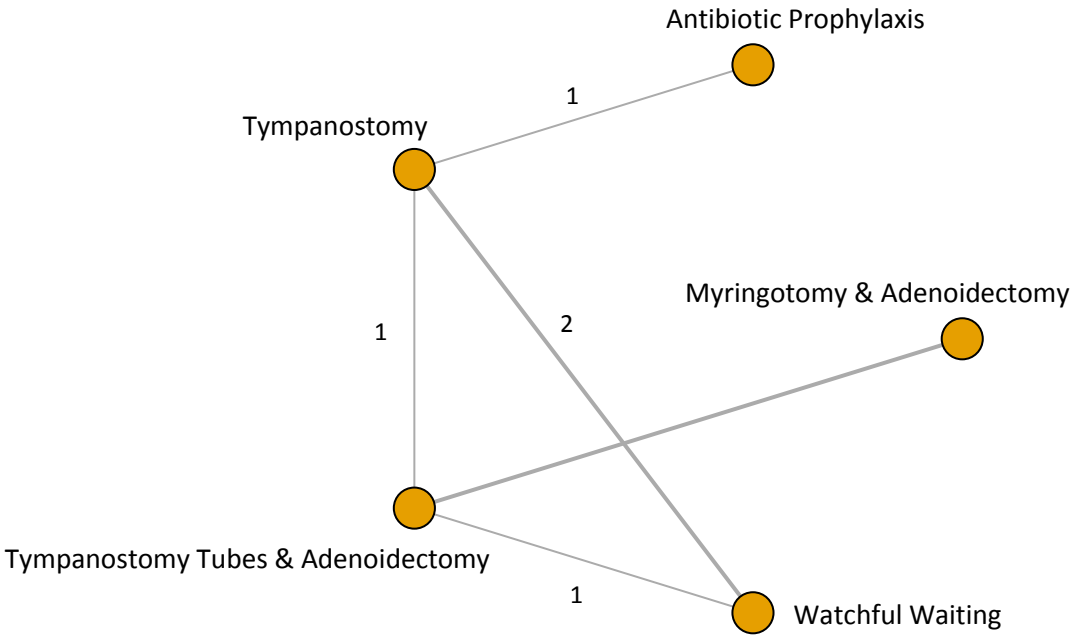
**Figure 7. Early (1 to 3 months) decrease (improvement) in mean hearing thresholds compared with watchful waiting**




CrI= Credibility Interval; TT=Tympanostomy Tubes

Figure 8 shows the topology of the network for late (12 to 24 month) hearing thresholds.

**Figure 8. Network diagram of late (12-24 months) comparisons for hearing thresholds**




The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

Table 6 shows combined direct and indirect data from the network meta-analysis for late hearing thresholds for all possible comparisons between the treatments. Bearing in mind that a difference in hearing thresholds of 10 dB is likely clinically important, none of the point estimates for improvement in hearing loss are of this magnitude, and credible intervals are wide and include the null effect. However, there is a trend suggesting that interventions including adenoidectomy (TT with adenoidectomy) may be more effective than watchful waiting.

**Table 6. Differences in late hearing thresholds (in dB, 1-3 months)**

| | | | | |
|---|---|---|---|---|
| **Myringtomy & Adenoidectomy** | 4.6 (-3.9, 12.0) | 4.3 (-2.4, 9.9) | 0.5 (-4.1, 4.3) | 4.3(-2.1, 10.2) |
| -4.6 (-12.0, 3.9) | **Prophylaxis** | -0.3 (-5.4, 4.7) | -4.2 (-10.7, 2.8) | -0.32 (-6.2, 6.2) |
| -4.3 (-9.9, 2.4) | 0.3 (-4.7, 5.4) | **TT** | -3.8 (-8.2, 0.8) | 0.01 (-3.3, 3.9) |
| -0.5 (-4.3, 4.1) | 4.1 (-2.8, 10.7) | 3.8 (-0.8, 8.2) | **TT & Adenoidectomy** | 3.8 (-0.6, 8.5) |
| -4.3 (-10.2, 2.1) | 0.32 (-6.2, 6.2) | 0.0 (-3.9, 3.3) | -3.8 (-8.5 0.6) | **Watchful waiting** |

Differences in hearing thresholds (dB) and 95% Credible Intervals in early (at 1-3 months) hearing thresholds among the 5 treatments in Figure 8. Each cell contains the difference of the comparison of the intervention in the corresponding row versus the intervention in the corresponding column. Negative numbers imply better outcomes for the first.

Table 7 lists the probabilities derived from the network meta-analysis that an intervention is the first and second most effective with respect to early hearing thresholds. Table 8 aggregates these probabilities and lists the probability that an intervention is among either the three most effect or the three least effective. At 12 to 24 months, interventions that include adenoidectomy (TT & Adenoidectomy and Myringotomy & Adenoidectomy) have the highest probability of being most effective, whereas watchful waiting, TT alone, and antibiotic prophylaxis all have probability of 90 percent or greater of being least effective.

**Table 7. Probabilities percent) that an intervention ranks as the *i-th* most effective with respect to late hearing thresholds**

| Intervention | 1st | 2nd | 3rd | 4th | 5th |
|---|---|---|---|---|---|
| TT | 1 | 4 | 27 | 48 | 21 |
| TT + Adenoidectomy | 33 | 59 | 5 | 2 | 1 |
| Myringotomy + Adenoidectomy | 59 | 29 | 6 | 3 | 3 |
| Antibiotic prophylaxis | 6 | 5 | 26 | 18 | 46 |
| Watchful waiting | 1 | 3 | 37 | 29 | 30 |

TT= Tympanostomy tube

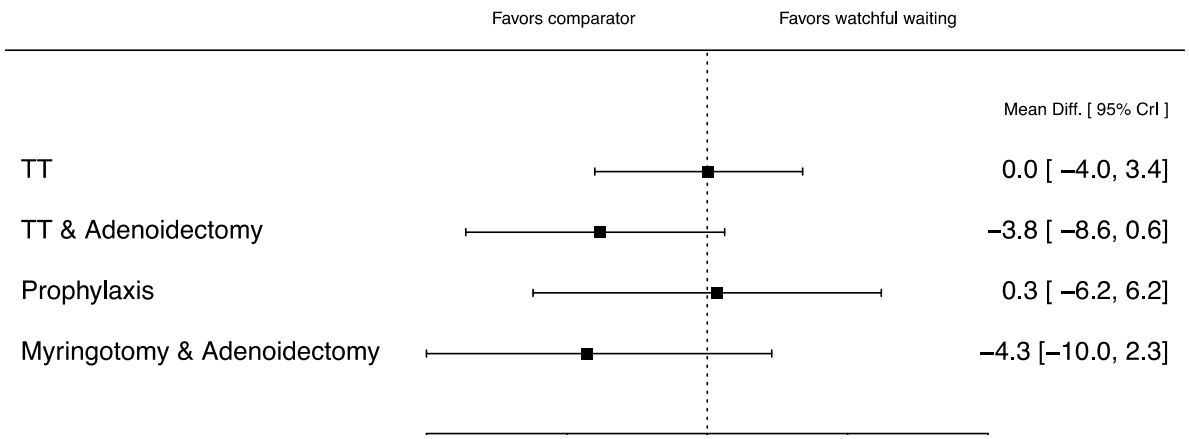
**Table 8. Probabilities (percent) that an intervention is among the two most effective with respect to late hearing thresholds**

| Intervention | Probability (%) of being among the 3 most effective interventions | Probability (%) of being among the 3 least effective interventions |
|---|---|---|
| TT | 5 | 95 |
| TT & Adenoidectomy | 92 | 8 |
| Myringotomy & Adenoidectomy | 88 | 12 |
| Antibiotic prophylaxis | 10 | 90 |
| Watchful waiting | 4 | 96 |

TT= Tympanostomy tube

As shown in Figure 9, by 12 to 24 months, the mean difference in hearing thresholds for TT alone, compared to watchful waiting is now centered on zero. The point estimates suggest that interventions that include adenoidectomy (TT with adenoidectomy and myringotomy with adenoidectomy) are more likely to be effective at 12 to 24 months, although 95% credible intervals do not exclude a zero mean difference.

**Figure 9. Late (12-24 months) decrease (improvement) in mean hearing thresholds compared with watchful waiting**




TT= Tympanostomy tube; CrI= Credibility Interval

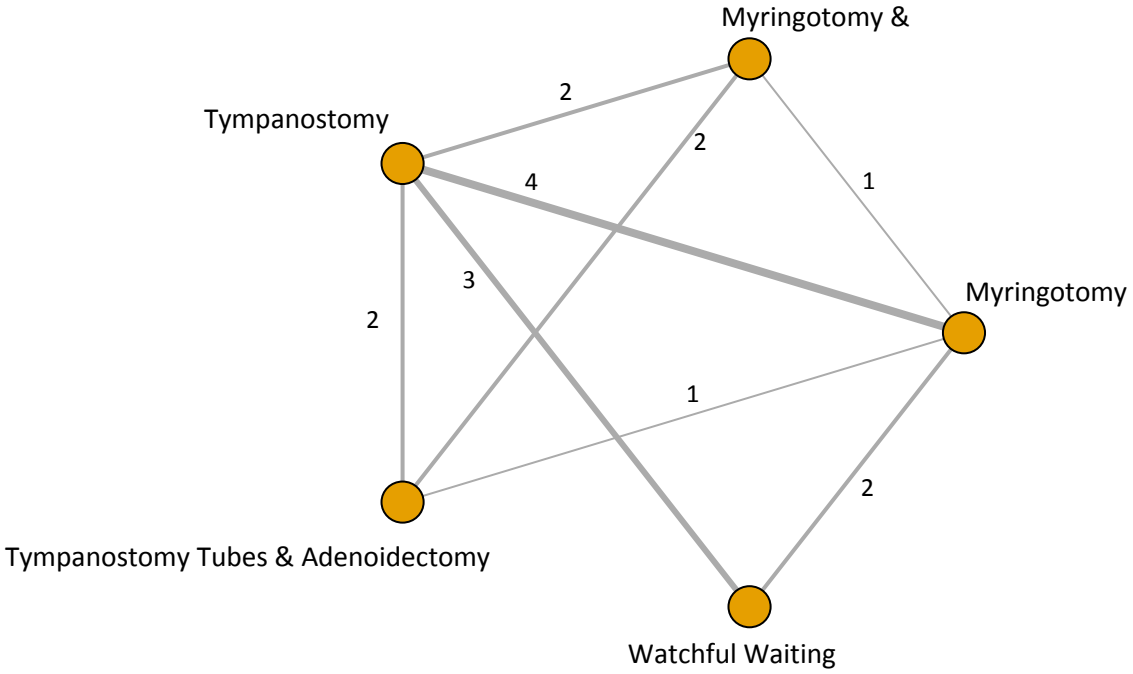
The results for the studies that reported measuring hearing thresholds, but did not report mean hearing thresholds needed for inclusion in the network meta-analysis are summarized below. In the MRC Multicentre Otitis Media Study Group 2004 report outcomes of a speech-in-noise automated toy test (SiN ATT), the authors hypothesized that a measure of understanding of speech in noisy situations may tap the disability experienced by children with OME. This study allocated children to receive TT, with or without adenoidectomy, or to medical management only and included 47 of 68 children also enrolled in the TARGET trial. They reported a significant treatment by baseline SiN ATT interaction (P=0.17), and concluded that children with poor

baseline SiN ATT are those most likely to benefit from surgery.[48] Chaudhuri 2006 reported a comparison of hearing thresholds between groups of children randomized to various medical treatments, placebo, or TT with or without adenoidectomy.[38] D'Eredità 2006 reported that hearing thresholds were normal at one year in both arms of a study comparing laser myringotomy to myringtomy with TT tubes in children, aged 2 to 6 years.[39] Gates 1985 reported in a trial of children 4 to 8 years of age (54 week followup) that those randomized to myringotomy alone experienced 16 weeks of abnormal hearing (pure-tone average of 20 dB or greater) compared to 11 weeks in those who received TT (P = 0.001). Gates 1987 reported that children treated with adenoidectomy, TT, and adenoidectomy had normal hearing (< 20 dB) in the better ear 90 to 93 percent of the time, as compared with 81 percent of the time (P < 0.001) in group treated with myringotomy alone.[89] Paradise 2001 reported measuring hearing thresholds, but did not report the results for the comparison of hearing thresholds.[52] Velopic 2011 found no postoperative (after more than six months) differences in average pure tone audiometry or resolution of middle ear effusion between children treated with TT & adenoidectomy and those treated with adenoidectomy alone. Average air bone gap at 2000 Hz was lower in the TT & adenoidectomy group (P=0.03).[61]

## Duration of Effusion

Six RCTs [37, 44, 45, 52, 88] reported the mean proportion of time with middle ear effusion. By multiplying this proportion by followup time in weeks, we estimate comparative effectiveness of interventions expressed as a mean difference in duration of effusion. Figure 10 shows the topology of the network for comparisons of the duration of middle ear effusion. Three trials directly compare TT and watchful waiting. The other comparators, which contribute indirect evidence, are myringotomy, myringtomy with adenoidectomy, TT and adenoidectomy.

**Figure 10. Network graph for duration of middle ear effusion**

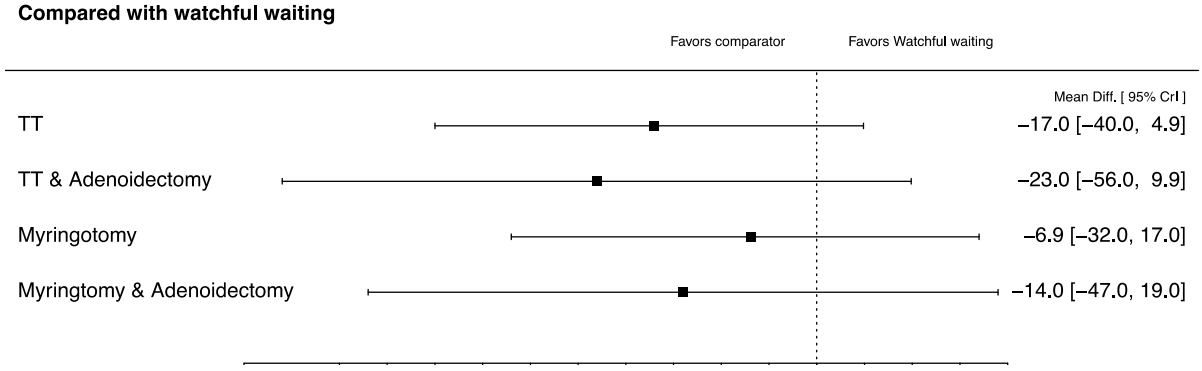



The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

Figure 11 shows a trend toward greater effectiveness for TT with adenoidectomy than TT alone. However, credible intervals are wide and cannot exclude a null effect for all interventions.

**Figure 11. Decrease (improvement) in mean duration of middle ear effusion compared with watchful waiting**




TT= Tympanostomy tube, CrI= Credibility Interval

As summarized in Table 9, TT and adenoidectomy and TT alone have moderately high probability (79% and 62%, respectively) of being the most effective interventions to decrease mean duration of middle ear effusion. Conversely, watchful waiting has a 94 percent probability of being among the three least effective interventions.

**Table 9. Probabilities (percent) that an intervention is among the two most effective with respect to duration of MEE**

| Intervention | Probability (%) of being among the 2 most effective interventions | Probability (%) of being among the 3 least effective interventions |
|---|---|---|
| TT | 62 | 38 |
| TT + Adenoidectomy | 79 | 21 |
| Myringotomy + Adenoidectomy | 12 | 88 |
| Antibiotic prophylaxis | 41 | 59 |
| Watchful waiting | 6 | 94 |

TT= Tympanostomy tube; MEE= Middle Ear Effusion

## Quality of Life and Patient-Centered Outcomes

Nine studies (5 RCTs, 4 NRCSs, and one that combined both designs) in 13 papers reported on 134 quality of life and patient-centered outcomes in 1665 children over multiple time points and arms. These studies reported only 14 outcomes with significant results (see Table 10).[40, 46, 50-54, 56, 58, 62, 69-71, 87] The results varied in magnitude and direction, even across subscales of the same test.

Five studies reported on 43 different IQ and other cognitive outcomes. Of these, five had significant results. Paradise found that children who were not eligible for randomization into a RCT for tubes because their otitis media was below the threshold had a significantly better result in the spelling subtest of the of the Woodcock-Johnson III Tests of Achievement, but not on any other subtest at ages 9 to 11. However, they found that the group included in the trial and randomized to early intervention with tubes had a better outcome on overall functioning in the Impairment Rating Scales, also at 9 to 11 years of age.[54] Peters 1994 found that after almost eight years, kids who had received TT in a nonrandomized study did significantly better on teacher's evaluation of their narrative writing skills, though not their reading or math scores.[69] Similarly, Hall 2009 found that at age 4.5 children who had been randomized to early surgery had better writing (adjusted OR 3.74, 95%CI 1.51 to 9.27) and language (adjusted OR 3.45, 95% CI 1.42 to 8.39) scores at school entry, though not better math or reading scores.[40]

Seven of the eight studies reported on 51 verbal outcomes, of which six were found to have significant differences. Paradise found a significant difference in nonword repetition at 4 years of age between children randomized to early versus delayed tympanostomy, and at 6 years of age among children randomized to early versus delayed tympanostomy, those who refused randomization, and those who were not deemed eligible due to lack of severity of OME. At both time points, the delayed treatment group performed slightly better (mean difference at 3 years -3.4, 95% CI -6.2 to -0.7; mean difference at 4 years -2, 95% CI -4.1 to -0.1). In grade 4, they found that those not eligible performed significantly better than both study arms on an oral reading fluency test, though those results were not replicated at any other time point. The not eligible group had significantly worse outcomes compared to the early treatment and randomization consult withheld groups on the Children's Version of the Hearing in Noise Test at 9 to 11 years old.[50-54] In a small study of 27 children, Schilder 1997 found a significant difference in two language measure outcomes, but not on the three others. In word forms production, the tubes group performed significantly better (mean difference 26.4, SD 0.92), as well as in the auditory discrimination measure (mean difference 0.08, SD 0.03).[71]

Four of the nine studies reported on 35 behavioral outcomes, of which three had significant findings. Paradise found that the early surgery group performed better on the Child Behavior Checklist total problems subscale (largest mean difference 2; 95% CI 0.1 to 4.8) than the other groups at ages 9 to 11. At the same age, the early intervention group performed better on the Disruptive Behavior Disorders Rating Scale, impulsivity and overactivity factor subscale (largest mean difference 2; 95% CI 0.1 to 4.8)[54] Niclasen reported a NRCS of performance on the Strengths and Difficulties Questionnaire (multiple subscales), parent and teacher version. They concluded that their findings suggest and association between 4 or more episodes of early otitis media treated with TT and behavioral and learning difficulties later in childhood.[87] However, they do not report statistical tests of the contrasts between treated and untreated children.

Only two studies reported on quality of life outcomes: Paradise reported on measures of parental stress at various ages,[50-54] and Vlastos 2011 reported on pediatric health related quality

of life.[62] Neither found any significant differences. Full details for all outcomes are in Appendix G.

**Table 10. Cognitive, verbal, behavioral, and quality of life outcomes**

| Study, year Design (N) | Outcomes: number reported (number statistically significant*) | | | |
|---|---|---|---|---|
| | Cognitive | Verbal | Behavioral | Quality of Life |
| Rach 1991 RCT (43)[56] | | 2 (0) | | |
| Niclasen 2016 NRCS (1568)[87] | 3(nr) | | 12 (nr) | |
| Rovers 2000 RCT (187)[58] | | 2 (0) | | |
| Hall 2009 RCT (136)[40] | 10 (2) | 6 (0) | 6 (1) | |
| Maw 1999 RCT (127)[46] | | 4 (0) | 2 (0) | |
| Vlastos 2011 RCT (45)[62] | | | | 1 (0) |
| Paradise, 2001, 2003, 2004, 2005, 2007 RCT/NRCS (402/729)[50-54] | 15 (2) | 18 (4) | 14 (2) | 4 (0) |
| Peters 1994 NRCS (188)[69] | 15 (1) | 5 (0) | | |
| Grievink 1993 NRCS (183)[70] | 1 (0) | 9 (0) | | |
| Schidler 1997 NRCS (27)[71] | | 5 (2) | | |

* No statistically significant effect of intervention on outcome (in either direction) reported †No statistical comparison reported.

RCT= Randomized Control Trial; NRCS= Nonrandomized Comparative Study, NR= Not Reported

# Key Question 2

For children with recurrent acute otitis media, what is the effectiveness of tympanostomy tubes (TT), compared to watchful waiting with episodic or prophylactic antibiotic therapy, on the frequency and severity of otitis media, quality of life, and other patient-centered outcomes?

## Description of Comparative Studies

We identified 8 publications, reporting on 7 RCTs[90-96] and 2 NRCSs.[8, 93] A total 1049 patients were randomized. The Mattila 2003 paper described two groups, an RCT which randomly allocated treatment in 137 patients, and a NRCS in which parental choice determined treatment in169 patients.[93] Grindler 2014, reported a cross-sectional comparison of quality of life outcomes in 1208 patients.[8]

### Comparators

Three RCTs[90-92] compared TT placement with daily oral antibiotic prophylaxis. Two of these studies included a comparison with placebo,[90, 91] and Kujala 2012 compared TT placement with no treatment.[95] The effectiveness of TT alone vs TT with adenoidectomy was evaluable in three studies.[93-95]

### Population Characteristics

Inclusion criteria were similar across studies, all required patients to have had three or more episodes of AOM in the preceding 6 months, or (in three studies) 4 or more episodes in past 12 to 18 months.

Studies varied on whether they required the presence or absence of middle ear effusion. Gonzalez 1986, El Sayed 1996, Mattila 2003 and Hammaren-Malmi 2005 did not exclude patients with otitis media with effusion.[90, 92-94] Conversely, Kujala 2012 and Casselbrant 1992 required patients to be free of middle ear effusion at time of assessment for surgery. [91, 95] For study details, see Appendixes C-E.

### Risk of Bias

The methodological and reporting quality of the included studies are generally of concern. In the RCTs of patients with recurrent AOM, randomization and allocation concealment were appropriately implemented in only one study.[95] Comparison groups were dissimilar or the comparability was unclear in most studies.[90, 92, 93] Blinding was partially implemented in only one study.[91] Randomization, group similarity and blinding could not be assessed in Hammarén-Malmi 2005.[94]

The cross-sectional NRCS was rated as high for risk of confounding bias (lack of adjustment for potential confounders and potential for selection bias).[8]

# Outcomes

## Randomized Comparative Studies

### Frequency and Severity of Recurrent Acute Otitis Media

We did not quantitatively pool the results, primarily because of the small number of studies and substantial heterogeneity in reported outcomes. The majority of studies were done prior to widespread use of the conjugate pneumococcal vaccine, in an era where antibiotic resistance was less common and prophylactic oral antibiotic therapy was more commonly used in clinical practice. Results are summarized by comparator below.

### TT Versus Placebo or No Treatment

Gonzalez 1986 reported on two related outcomes: the number of children with no further episodes of acute otitis media and the number of ear infections per child during the 6 month followup period (attack rate). In the placebo group, three of 20 children had no further episodes of AOM, compared to 12 of 22 in the TT group (p=0.01). The placebo group had an attack rate of 2.0 compared to the TT group, which had an attack rate of 0.86 (p=0.006).

Casselbrant 1992 also reported the number of new episodes per group divided by the total number of child years of followup. In the placebo group, this rate was 1.08 versus 1.02 in the TT group (p=0.25). In the placebo group, 40 percent had no further episodes of AOM, compared to 35 percent in the TT group. However, TT placement significantly decreased the percentage of time with AOM compared to placebo ($P$<0.001).

Kujala 2012 reported failure rate (defined as at least two episodes of AOM in 2 months, three in 6 months or persistent effusion lasting at least 2 months), percent of children with no recurrent AOM, cumulative number of AOM episodes, and one year incidence rates. There was an absolute difference in the proportion of failures of -13 percent (95% CI -25 to – 01, P = 0.04), between the TT and control groups. Thus 7.7 children would need to be treated with TT to prevent one additional failure. The one-year incidence rate (infections per child per year) was 0.55 (95% CI -0.93 to -0.17) lower in the TT group compared to the control group.[95]

### TT Versus Antibiotic Prophylaxis

In the Gonzalez 1986 RCT, 54.5 percent of children in the TT group and 24 percent in the sulfisoxazole prophylaxis group had no recurrent AOM (P = 0.02). The attack rate was 0.86 infections per child in the TT group and 1.4 in prophylaxis group (P = 0.08).[90]

Casselbrant 1992 reported a rate of 0.6 episodes of recurrent AOM per child-year children treated with Amoxicillin and a rate of 1.02 in their TT group (P = 0.001).[91]

El-Sayed found no difference in the treatment outcomes of children treated with trimethoprim/sulfamethoxazole compared to children treated with TT (P = 0.37).[92]

### TT Versus TT and Adenoidectomy

An RCT by Mattila 2003 found no difference in cumulative hazard of recurrent AOM or in efficacy, defined as one minus the adjusted relative risk in randomized and nonrandomized comparisons of children who underwent TT with adenoidectomy compared with TT alone.[93]

In the Kujala 2012 study, there was no significant difference in the TT with adenoidectomy group compared to the TT only group in the number of failures (absolute difference −5%, 95%

CI −16 to 6, P = 0.37), in the time to failure (P = 0.29) or to the first AOM (P = 0.6), or in the proportion of children with no AOM episodes (absolute difference 1%, CI −13 to 15, P =1.0).[95]

A subsequent 2005 RCT, which enrolled 217 children, 162 of whom had recurrent AOM, again found no differences in the mean number of otitis media episodes overall or in the subgroup of children with recurrent AOM at enrollment.[94]

### Quality of Life Outcomes

Although Kujala 2012 found that insertion of TT tubes, without or without adenoidectomy, significantly reduced the risk of recurrent AOM, a subsequent publication from the same trial examining quality of life outcomes at study entry, 4 months, and 12 months (assessed using the Otitis Media-6 questionnaire) found no differences in overall ear-related quality of life between surgically treated groups and no surgery groups, nor did they find any differences in the subscales of caregiver concern, emotional distress, physical suffering, activity limitations, hearing loss, or speech impairment.[96]

## Nonrandomized Comparative Studies

A cross sectional study by Grindler et al. reported both disease specific quality of life outcomes utilizing OM-6 score, and health related quality of life using the PedsWL Infant Impact Module in 1208 patients. The OM-6 score was higher (reflecting worse otitis specific quality of life) in children in otolaryngology practices who had been recommended to undergo TT placement than in children with prior TT placement.[8]

# Key Question 2a

What factors (such as age, age of onset, number of recurrences, presence of persistent middle ear effusion, comorbidities, sociodemographic risk factors, history of complications of acute otitis media, antibiotic allergy or intolerance) predict which children are likely to benefit from the intervention?

There are no prospective planned comparisons evaluating whether the presence of middle ear effusion (at time of surgical evaluation) modifies the effectiveness of TT placement for recurrent AOM. Gonzalez 1986 report a retrospective subgroup comparison based on the presence or absence of middle ear effusion at initial evaluation and conclude that the attack rate, as well as the number of patients who had no further bouts of AOM, was significantly better ($p < 0.05$) in those children without middle ear effusion. However, this group consisted of only 22 patients.[90] Two studies specifically excluded patients with middle ear effusion at time of surgical evaluation.[91,95]

Casselbrant 1992 analyzed data with a multivariable Poisson model and concluded that TT reduced the number of episodes of AOM/otorrhea only in those subjects whose episodes of AOM occurred year-round. In their model, younger age and white race were significantly associated with higher rates of recurrent AOM, but treatment by age and treatment by race interactions were not found.[91]

# Key Question 3

## What adverse events, surgical complications, and sequelae are associated with inserting tympanostomy tubes (TT) in children with either chronic otitis media with effusion or recurrent acute otitis media?

We extracted descriptive data on the occurrence of 11 adverse events from 85 prospective surgical studies enrolling at least 50 subjects (including arms of RCTs or NRCSs with 50 or more patients) and population-based retrospective single-group studies (registry studies) with at least 1000 subjects. Adverse events were also extracted from a treatment arm (if it included at least 50 patients) 10 RCTs and NRCSs identified for KQs 1 and 2. The adverse events extracted included perioperative complications, otorrhea, tube blockage, granulation tissue formation, premature extrusion, displacement of the TT into the middle ear space, persistent perforation, myringosclerosis, presence of atrophy, atelectasis or retraction, cholesteatoma, and long-term hearing loss. We did not consider other adverse events, such as antibiotic resistance, gastrointestinal side effects of antibiotics, or pain related to ear drops.

Table 11 provides a highly summarized summary of number of publications (some publications reported several cohorts summarized separately) that reported numbers of patients (or ears) for each adverse event. We do not estimate the frequency of adverse events in a population, rather a descriptive summary of observed median and range of estimates in studies.

**Table 11. Adverse events associated with TT placement**

| Adverse Event | N publications | Patients: Median Percent [25%, 75th%] | Ears: Median Percent (25%, 75th%) |
|---|---|---|---|
| Perioperative Complications | 4[95, 97-99] | NA | NA |
| Otorrhea | 39[17, 36, 42, 88, 97, 100-133] | 20.6 [13.1, 47.3] | 10.4 [9.1, 28.2] |
| Tube Blockage | 18[97, 99, 103, 123, 127, 130-142] | 9.0 [ 2.6, 10.7] | 4.0 [2.8, 17.1] |
| Granulation Tissue | 12[36, 106, 109, 110, 118, 127, 130-132, 134, 136, 143] | 3.3 [ 2.9, 5.7] | 3.9 [1.8, 5.7] |
| Premature Extrusion | 18[112, 115, 118, 123, 125, 127, 129, 130, 136, 140, 144-151] | 13.3 [ 7.1,47.9] | 4.1 [1.6, 14.0] |
| TT Displacement into middle ear | 8[127, 130, 134, 135, 143, 145, 152, 153] | NA | 0.8 [0.7, 0.9] |
| Persistent Perforation | 48[36, 44, 52, 61, 74, 91, 100, 101, 103, 105, 107, 108, 110, 116-118, 121, 122, 127, 129-131, 133-136, 138, 143-145, 147, 148, 150, 152-166] | 2.7 [1.8, 6.7] | 2.9 [ 2.0, 5.3 ] |
| Myringosclerosis | 22[36, 52, 61, 74, 122, 130-132, 134, 135, 148, 150, 152, 155, 157, 163, 167-172] | 33.5 [5.0, 38.0] | 17.1 [6.8, 43.9] |
| Atrophy, Atelectasis or Retraction | 22[52, 61, 100, 121, 122, 130, 131, 133, 136, 148, 149, 153, 155, 157, 161, 163, 166, 168, 170, 173-175] | 13.9 [7.5, 25.9] | 14.4 [ 5.0, 32.8] |
| Cholesteatoma | 24[88, 100, 108, 115, 122, 127, 131-134, 136, 143, 145-147, | 0.9 [0.2, 1.8] | 0.7 [ 0.1 ,3.2 ] |

| Adverse Event | N publications | Patients: Median Percent [25%, 75th%] | Ears: Median Percent (25%, 75th%) |
|---|---|---|---|
| | [155, 162, 167, 168, 173, 176-179] | | |
| Hearing Loss | 10 [99, 112, 114, 123, 129, 135, 148, 156, 167, 170] | 8.0 [ 1.2, 19.2] | NA |

NA: Not calculated when number of patients (ears) < 5.

TT=Tympanostomy Tubes

See **Appendix H** for an evidence map and study specific details. In general, the study specific definitions of adverse events were poorly reported and/or highly variable between studies. Not all cohorts followed all patients until extrusion of the tube, nor was followup complete in all studies.

**Perioperative** adverse events were described in 4 studies.[95, 97-99] Of these, three studies[95, 97, 99] reported surgical adverse events including ear canal abrasion, tympanic membrane tear and hemorrhage. The 2002 report by Hoffman[98], reported perioperative events in 0.81% of 3198 patients. Isaacson, 2008 report no operative deaths in a prospective series of 10,000 tube insertions.[99]

**Otorrhea** was reported in 39 publications. Otorrhea is particularly complex to characterize, as it may differ with respect to frequency, duration, volume, character (e.g. purulent vs. clear) and associated signs and symptoms (such as pain, fever or odor). Studies had different durations of followup, and used multiple categorical definitions (e.g. at least one episode or more than 3 episodes).

**Tube blockage** was reported in 18 publications. The median percentage of patients with TT blockage was 6.7% across studies. Duration of followup ranged from 2 weeks postoperative to time of extrusion or removal. In most cases, it was not possible to determine if occlusion was temporary or permanent.

**Granulation Tissue** was reported as an adverse event in 12 publications. In most cases studies did not report the clinical impact or symptoms associated with this finding.

**Premature Extrusion** was reported in 18 studies. Studies often either did not define what time interval was considered premature. The interquartile range for percent of premature extrusion was wide, likely due in large part to highly variable definitions.

**TT displacement into the middle ear**, reported in 9 studies.

**Persistent Perforation** of the tympanic membrane after TT extrusion or removal was reported in 49 publications in a median of 2.7 percent of patients. The majority of studies did not report the duration, associated symptoms or whether these were surgically repaired.

**Myringosclerosis**, reported in 22 studies, and **Atrophy, Atelectasis or Retraction** (also reported in 22 studies) were common, but definitions were variable and often poorly described.

**Cholesteatoma** was reported in 25 studies and **Hearing Loss** in 10 studies.

## Key Question 4

### Do water precautions reduce the incidence of tympanostomy tube otorrhea or affect quality of life?

## Description of Comparative Studies

We identified 11 publications which reported 2 RCTs[180, 181] and 9 NRCSs[182-190]

### RCTs

The RCTs are briefly summarized in Table 12. In the Goldstein 2005 study[180] children in the "ear plugs group" were instructed to wear ear plugs when bathing, showering and washing hair. The "no precautions" group was allowed to swim or bathe without ear plugs. Parents were given a calendar to record all swimming and bathing activities. A subgroup of children with 125 or more instances of water exposure was reported. The Parker 1994[181] RCT assigned children to a nonswimming group and a swimming group (without earplugs or other precautions).

**Table 12. RCTs: Water precautions — one or more episodes of otorrhea**

| Study PMID Enrollment dates Country (Design) | Followup time | Intervention | Population | n/N (%) | Odds ratio (95% CI) |
|---|---|---|---|---|---|
| Goldstein 2005 15689760 7/1996-6/1999 U.S.[180] | 1 year | Ear plugs | All Participants | 42/90 (46.7) | 0.68 (0.37 – 1.25) |
| | | No precautions | All Participants | 46/82 (56.1) | [reference] |
| | | Ear plugs | Children who each had ≥ 125 instances of water exposure | 29/39 (74.3) | 2.69 (0.95 – 7.64) |
| | | No precautions | Children who each had ≥ 125 instances of water exposure | 14/27 (51.8) | [reference] |
| Parker 1994 8024107 12/1989-2/1991 U.S.[181] | 1 year | Nonswimming | All Participants | 18/30 (60.0) | 0.71 (0.29 – 1.76) |
| | | Ear plugs† | All Participants | 13/15 (86.7) | 3.10 (0.64 – 15.04) |
| | | No precautions | All Participants | 42/62 (67.7) | [reference] |

†Randomized to the nonswimming group, but self-selected to swim using ear precautions (e.g., ear plugs, wax, cotton with petroleum jelly) – considered an nonrandomized comparative studyin the meta-analysis.

RCT=Randomized Control Trial; CI= Confidence Interval

## NRCS

In two of the 9 NRCSs, otorrhea was reported only as episodes-per-ear (not per patient) in children who chose to swim versus those who chose not to swim. Both studies report similar proportions of ears with otorrhea in swimmers and nonswimmers (6.4% vs. 6.9%[188]) and 23% vs. 18%[190]) and are not considered further.

The remaining 7 NRCSs (shown in Table 13) compared two alternate forms of water precaution (ear plugs or prohibition of swimming) versus no precautions (children allowed to swim without ear protection). Children permitted to swim were often instructed to avoid of high risk activities (e.g., diving, underwater swimming). See Table 13 and Appendixes C-E for study details.

**Table 13. NRCSs: Water precautions—one or moreepisodes of otorrhea**

| | | | | | |
|---|---|---|---|---|---|
| Becker 1987 3586818 4/1985-9/1985 U.S. (NRCS)[182] | ≥ 2 months | Nonswimming | All Participants | 9/30 (30) | 2.31 (0.67 – 7.94) |
| | | Ear plugs | All Participants | 7/23 (30.4) | 2.36 (0.64 – 8.70) |
| | | No precautions | All Participants | 5/32(15.6) | [reference] |
| Cohen 1994 8289048 1990-1992 Israel[183] | 2.5 years | Nonswimming | All Participants | 2/20 (10.0) | 1.11 (0.14 – 8.72) |
| | | No precautions | All Participants | 2/22 ( 9.1) | [reference] |
| el Silimy 1986 3780019 [No dates] UK[184] | 6 months | Nonswimming | All Participants | 14/41 (34.1) | 2.07 (0.78 – 5.50) |
| | | No precautions | All Participants | 9/45 (20.0) | [reference] |
| Francois1992 1485779 [No dates] France [185] | 3-4 months | Nonswimming | All Participants | 21/68 (30.1) | 2.89 (1.43 – 5.86) |
| | | No precautions | All Participants | 19/142 (13.3) | [reference] |

| | | | | | |
|---|---|---|---|---|---|
| Kaufmann 1999 10546304 1/1996-1/1997 Switzerland[186] | ≥ 3 months | Ear plugs | All Participants | 4/16 (25.0) | 0.59 (0.16 – 2.11) |
| | | No precautions | All Participants | 17/47 (36.2) | [reference] |
| Salata 1996 8607955 [No dates] U.S. [187] | 1.5 years | Nonswimming | All Participants | 7/116 (6.0) | 0.34 ( 0.14 – 0.82) |
| | | Ear plugs | All Participants | 12/44 (27.3) | 1.92 (0.88 – 4.42) |
| | | Ear drops | All Participants | 23/101 (22.8) | 1.55 (0.81 – 2.98) |
| | | No precautions | All Participants | 22/138 (15.9) | [reference] |
| Smelt 1984 653821 [No dates] UK[189] | ≥ 2 months | Nonswimming | All Participants | 6/40 (15.0) | 2.35 (0.55 – 10.12) |
| | | No precautions | All Participants | 3/43 ( 7.0) | [reference] |

95% Confidence intervals that exclude a null effect are shown in **bold**

# Risk of Bias

The Goldstein 2005 RCT was rated high risk of bias for allocation concealment and blinding of participants (investigators were blinded), but otherwise risk of bias was low or unclear. The Parker 1994 RCT was rated as high risk of bias for random sequence generation (use of social security numbers), blinding of participants, incomplete outcome data (only 105 of 212 available for followup), lack of an intention-to-treat analysis. (15/45 assigned to nonswimming group self-selected to swim and are analyzed as an NRCS), and compliance bias. All of the NRCSs had high risk of selection biases since patient assignment was based on parent and/or patient choice.

# Outcomes

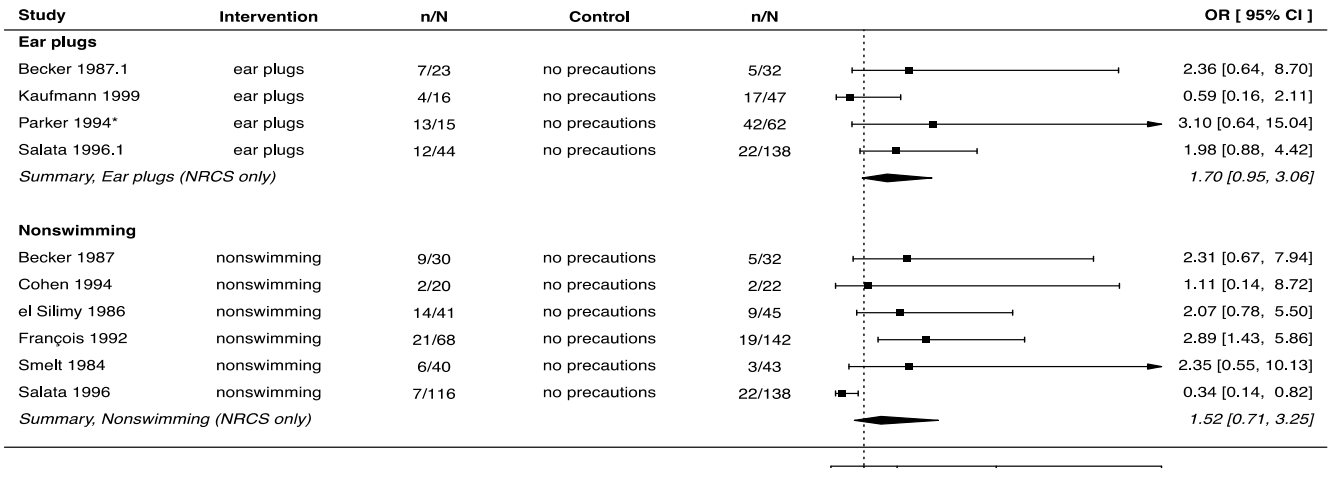
Goldstein 2005 reported a slightly lower adjusted rate of otorrhea randomly assigned to use ear plugs (0.07 episodes/month in intervention group versus 0.10 episodes/month in the control group, P=0.05).

The summary odds ratio reported by Goldstein was 0.68 (95% CI 0.37 to 1.25). Parker 1994 reported a summary odds ratio of 0.71 (95% CI 0.29 to 1.76)

Figure 12 summarizes our random effects meta-analysis of NRCSs, with separate summary estimates for each of the two forms of water protection (ear plugs and avoidance of swimming). The summary odds ratio comparing ear plugs versus no precautions of having one or more episodes of otorrhea was 1.7 (95% CI 0.95 to 3.06). The odds ratio for nonswimming compared to no precautions was 1.52 (95% CI 0.71 to 3.25). It is notable that event rates in the RCTs are generally higher in both control and intervention arms, compared with lower event rates in the NRCSs, possibly reflecting better ascertainment of episodes of otorrhea in the RCTs.

Overall, aside from the small reduction in mean number of episodes of otorrhea found in Goldstein 2005, the available evidence suggests that ear plugs or avoidance of swimming does not reduce the risk of swimming-related otorrhea.

**Figure 12. NRCSs only, children with one or more episodes of otorrhea**




OR = Odds ratio (values greater than 1 favor 'no precautions' arms; values less than 1 favor the intervention (ear plugs or nonswimming); NRCS=Nonrandomized Comparative Study; CI= Confidence Interval

# Key Question 5

## In children with tympanostomy tube otorrhea, what is the comparative effectiveness of topical antibiotic drops versus systemic antibiotics or watchful waiting on duration of otorrhea, quality of life, or need for tube removal?

We identified 14 publications,[19, 139, 142, 190-200] representing 11 studies (10 RCTs and 1 NRCS), with a total of 1811 patients analyzed (1405 in RCTs and 406 in the NRCS) that assessed the effectiveness of various interventions to treat TT otorrhea. The results and arm details of these studies are given in Table 14. For full study details, see Appendixes C-E.

# Risk of Bias

Risk of bias was low for random sequence generation and allocation concealment. However, 8 of 11 studies had high risk of bias due to open label design, which precluded blinding of personnel and care providers.

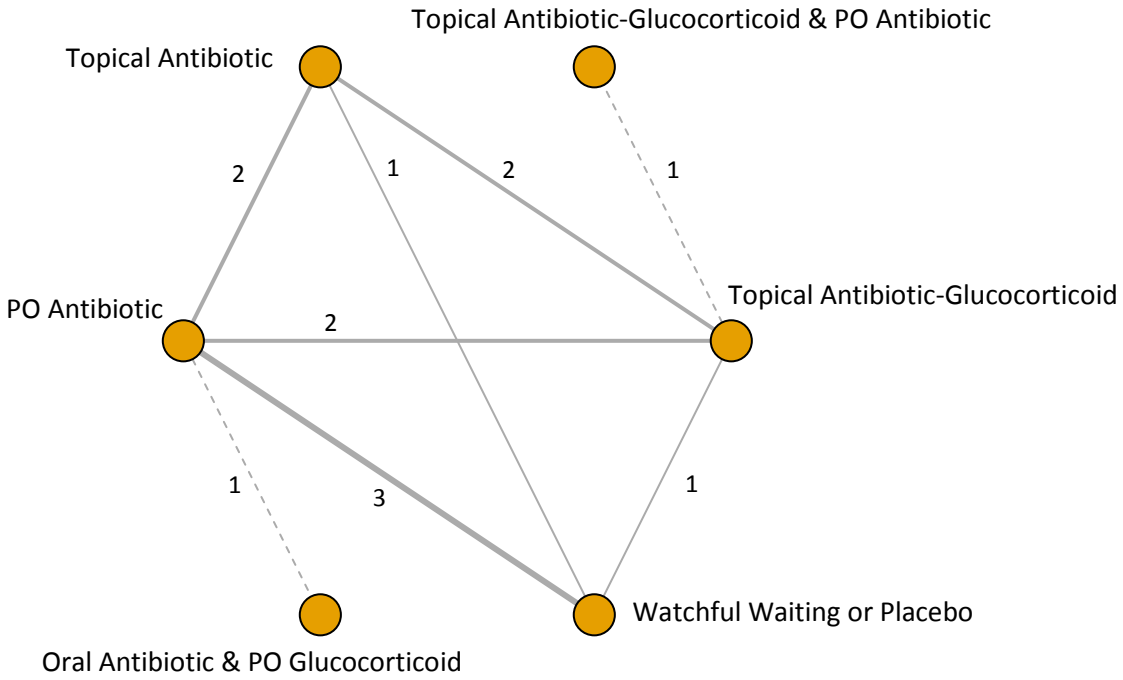
**Table 14. Effectiveness of various interventions to treat TT otorrhea**

| Study Year, PMID, Enrollment Period, Country | Intervention Details | Responders | N |
|---|---|---|---|
| Dohar 1999 10326811 U.S.[194] | ofloxacin eardrops | 119 | 141 |
| | unclear - historical practice | 140 | 218 |
| | unclear - current practice | 33 | 47 |
| Dohar 2006 16880248 5/2003-5/2004 U.S. & Finland[142] NRCS | ciprofloxacin/dexamethasone ear drops | 33 | 39 |
| | oral amoxicillin–clavulanate | 24 | 41 |
| Goldblatt 1998 10190709 U.S. | ofloxacin eardrops | 107 | 140 |
| | oral amoxicillin–clavulanate | 101 | 146 |
| Granath 2008 18565598 -2/1998-12/2002 Sweden[197] | hydrocortisone + oxytetracycline + polymyxine | 12 | 15 |
| | hydrocortisone + oxytetracycline + polymyxine & oral amoxacillin +/- clavulinate | 19 | 22 |
| Heslop 2010 20979100 5/2003-5/2007 Chile[198] | ciprofloxacin ear drops | 17 | 22 |
| | oral amoxicillin | 6 | 20 |
| | saline rinse | 12 | 26 |
| Roland 2003 14660913 3/2000-2/2001 U.S. [196] | ciprofloxacin/dexamethasone ear drops | 72 | 87 |
| | ciprofloxacin ear drops | 72 | 80 |
| Roland 2004 14702493 U.S.[139, 191, 201] | ciprofloxacin/dexamethasone ear drops | 174 | 207 |
| | ofloxacin eardrops | 153 | 216 |
| Ruohola 1999 10190921 03/1996-05/1997 Denmark[193] | oral amoxicillin & oral prednisolone | 22 | 23 |
| | oral amoxicillin | 24 | 27 |
| Ruohola 2003 12728089 09/1998-06/1999 Finland [195] | oral amoxicillin–clavulanate | 28 | 34 |
| | oral placebo | 13 | 32 |
| Strachan 2000 10865480 UK[202] | neomycin/polymyxin B/hydrocortisone (drops) | 24 | 29 |
| | neomycin/dexamethasone | 19 | 29 |
| van Dongen 2014 24552319 6/2009-5/2012 Netherlands [19, 199] | hydrocortisone–bacitracin–colistin eardrops | 72 | 76 |
| | oral amoxicillin–clavulanate | 43 | 77 |
| | initial observation | 34 | 75 |

TT= Tympanostomy Tubes; NRCS= Nonrandomized Comparative Study

The studies reported multiple comparisons, summarized in Figure 13, including oral antibiotics (amoxicillin and amoxicillin/clavulinate), various antibiotic drops, and various antibiotic-glucocorticoid drops, oral corticosteroids, and combinations. Treatment arms grouped in the watchful waiting/placebo category included watchful waiting,[199] oral placebo[195] and topical saline wash.[198]

**Figure 13. Network of treatment comparisons (RCTs)**




Two studies are not shown in network graph: 1) Dohar 1999 (undefined comparators. 2) Roland 2004 (comparison of two topical antibiotic-glucocorticoid treatments). Studies with the treatment arms show as dotted lines do not contribute indirect information, and are excluded from the network meta-analysis. The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

PO= Oral; RCT= Randomized Control Trial

# Outcomes

## Clinical Cure

Eleven studies reported the number of clinically cured patients in each arm, often at multiple timepoints. All studies reported additional intermediate outcomes (e.g., cessation, improvement, or duration of otorrhea). For the meta-analysis, we chose the time designated by each of these studies as the test of cure (range 7 to 20 days after initiation of treatment).

Four studies were excluded from the network meta-analysis. In two studies, this related to the intervention. Dohar 1999[194] NRCS reported clinical cure in 84.6 percent of 143 patients treated with topical ofloxacin in compared to a 64.2 percent in a historical practice group (n=218) and a

70 percent clinical cure rate in a concurrent practice group (n=47). However, the specific treatments used in the historical practice group and concurrent practice group were not reported. The second excluded study, Strachan 2000 [202], compared an antibiotic-glucocorticoid topical drop containing neomycin sulfate, polymyxin B sulfate and hydrocortisone with a topical spray formulation containing neomycin sulfate and dexamethasone. They concluded that topical treatment with a nonpressurized ear spray was easier to use and caused less discomfort than ear drops. However, they found no overall difference in number of patients cured..

Two studies[193, 197] compared dual interventions (i.e. topical antibiotic-glucocorticoid and oral antibiotic, oral antibiotic and oral glucocorticoid) and were not included in the network meta-analysis, as they contributed no indirect evidence for the comparisons of primary interest.

The pairwise comparative effects of interventions are shown in Table 15. Treatment strategies that include topical antibiotic-glucocorticoid drops predominate over oral antibiotics and watchful waiting or placebo. Treatment strategies that include topical antibiotic-glucocorticoid drops predominate over oral antibiotics and watchful waiting or placebo.

**Table 15. Network meta-analysis of interventions for otorrhea**

| | | | |
|---|---|---|---|
| **Topical Antibiotic-Glucocorticoid** | -0.49 (-2.03, 1.08) | -1.68 (-3.32, -0.16) | -2.46 (-4.4, -0.6) |
| 0.49 (-1.08, 2.03) | **Topical Antibiotic** | -1.19 (-2.82, 0.31) | -1.97 (-3.94, -0.14) |
| 1.68 (0.16, 3.32) | 1.19 (-0.31, 2.82) | **Oral Antibiotic** | -0.78 (-2.33, 0.78) |
| 2.46 (0.6, 4.4) | 1.97 (0.14, 3.94) | 0.78 (-0.78, 2.33) | **WW or Placebo** |

Ab-GC: Antibiotic-glucocorticoid. Differences in Log Odds Ratios with 95% Credible Intervals for clinical cure of otorrhea among the 4 treatments in Figure 13. Each cell contains the odds ratio for the comparison of the intervention in the corresponding row versus the intervention in the corresponding column.

WW= Watchful Waiting

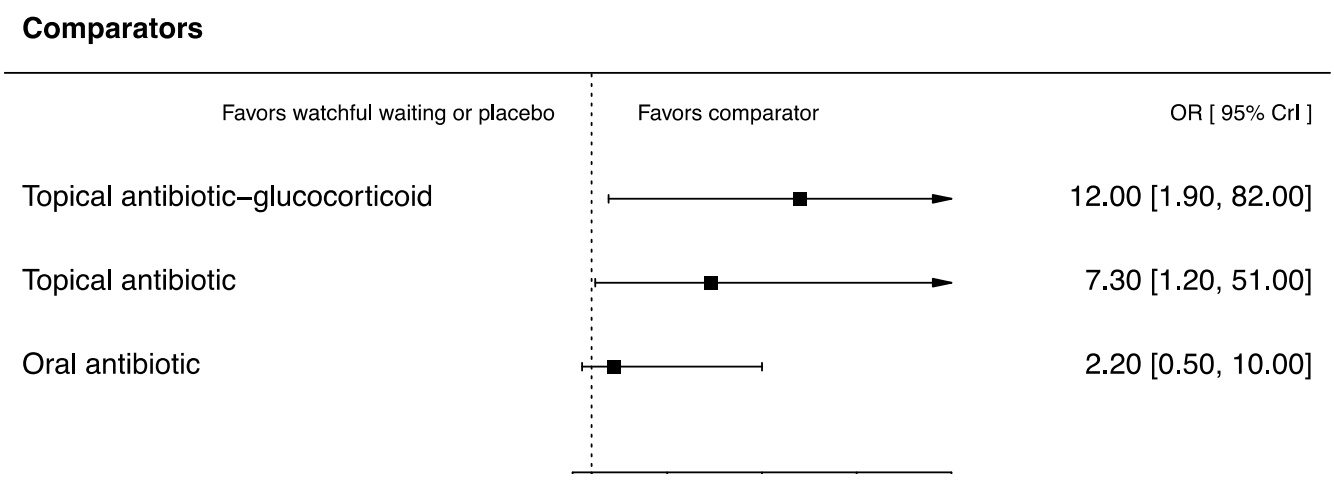
Table 16 lists the probabilities derived from the network meta-analysis that a particular intervention is ranks first to fourth most effective. The probability rankings suggest: 1) treatment strategies that include topical antibiotic drops predominate treatment with oral antibiotics and 2) all active treatments are more effective than watchful waiting/placebo.

**Table 16. Probabilities (%) that an intervention ranks as the *i-th* most effective with respect to clinical resolution of otorrhea**

| Intervention | 1st | 2nd | 3rd | 4th |
|---|---|---|---|---|
| Topical Antibiotic-Glucocorticoid | 77 | 21 | 1 | 0 |
| Topical Antibiotic | 22 | 73 | 5 | 1 |
| Oral antibiotic | 1 | 5 | 83 | 12 |
| Watchful waiting/placebo | 0 | 1 | 12 | 87 |

Figure 14 illustrates the relative effectiveness of each intervention compared to watchful waiting or placebo. Treatment with either topical antibiotic-glucocorticoid or topical antibiotic are superior to watchful waiting/placebo.

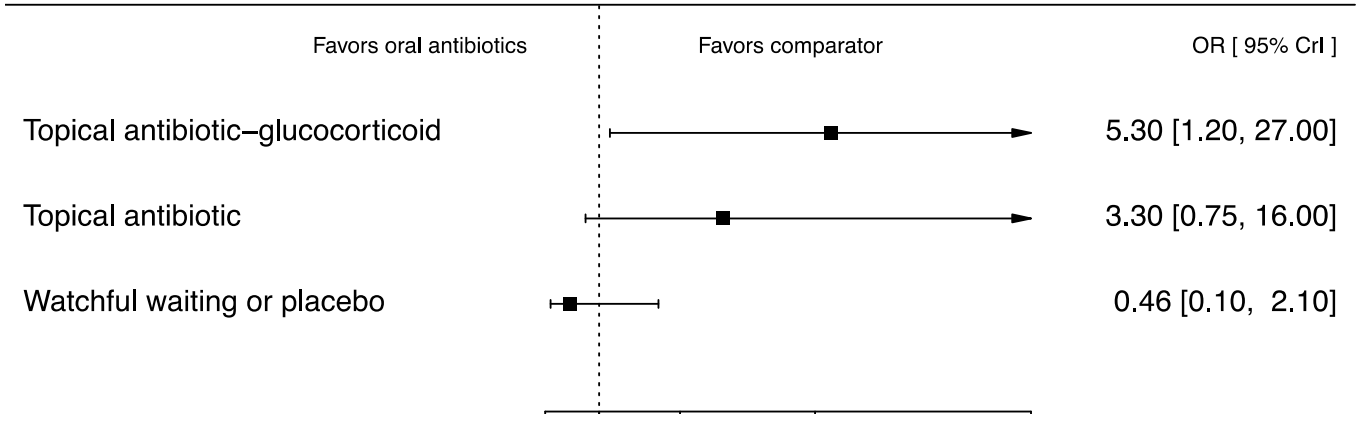
**Figure 14. Relative effectiveness of various interventions compared to watchful waiting or placebo**




CrI= Credibility Interval; OR= Odds Ratio

Figure 15 illustrates the relative effectiveness of each intervention compared to oral antibiotics. Treatment with topical antibiotic-glucocorticoid is superior to oral antibiotics. The relative effectiveness of topical antibiotic (without glucocorticoid) compared to oral antibiotics suggests greater effectiveness, but the credible interval includes one.

**Figure 15. Relative effectiveness of interventions compared to oral antibiotics**




CrI= Credibility Interval; OR= Odds Ratio

## Quality of Life

A single study (summarized in Table 17) reports quality of life outcomes related to our comparative effectiveness questions. Van Dongen 2014 evaluated quality of life in 230 children with otorrhea who received either watchful waiting, oral antibiotics, or antibiotic-glucocorticoid drops for 7 days.[199] At baseline, the generic and disease-specific health-related quality-of-life scores indicated good quality of life and were similar across the groups. At 2 weeks of followup, the change in the generic health-related quality-of-life scores did not differ significantly among the study groups. The changes in the disease-specific health-related quality-of-life scores at 2 weeks were small but consistently favored ear drops. The minimal clinically important difference for the generic Quality of Life instrument used in Van Dongen 2014 (CHQ-PF28) is not clear. Using as reference the range of the score, which is between 1 and 35 with higher values implying better quality of life, the 95% confidence intervals for the within group differences are judged to be large; thus it is possible that the Van Dongen 2014 trial results cannot exclude clinically important differences.

**Table 17. Quality of life outcomes**

| Author | Outcome | Timepoint | Arm | N analyzed | Baseline median (range) | Within Arm Median Difference (range) | P value |
|---|---|---|---|---|---|---|---|
| van Dongen 2014 24552319 25896832 6/2009-5/2012 Netherlands [19, 199, 200] | Quality of life (CHQ-PF28, lower scores indicate better QOL) | 2 weeks | watchful waiting | 77 | 14 (5, 33) | 0.5 (-15, 26) | NS |
| | | | oral antibiotic | 77 | 15.5 (6, 28) | 1 (-11, 18) | NS |
| | | | antibiotic-glucocorticoid drops | 76 | 15.5 (6, 29) | -1 (-14, 11) | NS |

QoL= Quality of Life, NS= not signficant

# Discussion

## Overall Summary and Strength of Evidence

Our systematic review of 172 publications focused on five Key Questions (KQ), which evaluate the evidence for the effectiveness of tympanostomy tubes (TT) in children with chronic middle ear effusion and recurrent acute otitis media, the adverse events (harms) associated with this procedure, the need for water precautions in children with TT, and the treatment of TT otorrhea.

## Key Question 1

In children with chronic otitis media with effusion, 32 publications reported results of 22 RCTs. Hearing thresholds were obtained in 16 RCTs, and in 10 trials they were reported by arm at various time points.

TT placement (compared to watchful waiting) resulted in improved average hearing thresholds 1 to 3 months after surgery. During this period, when the majority of tubes are functioning, mean hearing thresholds decreased by an average of 9.1 dB (95% CrI -14 to -3.4). A similar improvement was seen for children treated with TT and adenoidectomy (10 dB [95% CrI -19 to -1.9]) improvement. No significant change in hearing thresholds was noted after treatment with myringotomy alone or with oral antibiotic prophylaxis.

By 1 to 2 years, when most tubes have extruded, hearing thresholds are no longer different, likely reflecting the favorable natural history of spontaneous resolution of middle ear effusion in most children. There was a trend suggesting improved thresholds in children undergoing adenoidectomy, but credible intervals are wide and include the null effect.

The IPD by Boonacker et. al., which relied on a *post hoc* composite outcome, concluded that adenoidectomy is most beneficial in children four years or older with persistent otitis media with effusion. In this group at 12 months, 51% of those who had adenoidectomy failed, whereas 70% of those who did not have adenoidectomy failed (Risk Difference 19%: 95% Cl 12% - 26%; NNT = 6). No significant benefit of adenoidectomy was found in children less than 4 years old.[2]

Data were very sparse with respect to which factors might predict those children more likely to benefit from TT. The individual patient data meta-analysis (IPD) reported by Rovers et. al. focused on interactions between treatment and baseline characteristics. They found significant interactions between daycare attendance in children 3 years or younger, and in children over 4 years of age with a hearing level of 25 dB or greater in both ears, and concluded that TT might be used in young children attending day-care; or in older children with a hearing level of 25 dB or baseline hearing level persisting for at least 12 weeks. They noted that average hearing level at baseline did not obviously modify the effect estimate.[203]

Quality of life and other patient-centered outcomes (cognitive, language, and behavioral) were reported in eight studies (five RCTs, three NRCSs, and one that combined both designs) in 12 papers. These studies reported on 119 quality of life and patient-centered outcomes in 1665 children over multiple time points and interventions. These studies reported only 14 outcomes with significant results. In general, the results were not significant and varied in magnitude and direction, even across subscales of the same test.

Overall, the evidence suggests that TT placement results in improved average hearing thresholds during early followup of 1 to 3 months after surgery. However, these improvements are not sustained at 1 to 2 years. There is limited evidence regarding quality of life outcomes, but

neither of the two studies that evaluated parental stress and health related quality of life found significant improvements in surgically treated children. Evidence for improved cognitive, language, or behavioral outcomes after TT compared to watchful waiting is similarly lacking.

## Key Question 2

In children with recurrent acute otitis media, seven publications reported results of six RCTs. We were unable to provide pooled results due to the small number of studies, multiple interventions, and heterogeneity in reported outcomes. The limited available evidence suggests that TT placement decreases the number of further episodes and the overall number of episodes of recurrent AOM.

Although Kujala 2012 found that insertion of TT, without or without adenoidectomy, significantly reduced the risk of recurrent AOM, a subsequent publication of quality of life outcomes from this trial found no differences in overall ear-related quality of life between surgically treated groups and no-surgery groups, nor did they find any differences in the subscales of caregiver concern, emotional distress, physical suffering, activity limitations, hearing loss, or speech impairment.[96]

Very little evidence from RCTs is available to evaluate factors that identify children most likely to benefit from TT placement. A post hoc subgroup (n=22) comparison in one study concluded that patients with middle ear effusion at the time of surgical evaluation had improved outcomes.[90] The other two studies specifically excluded patients with middle ear effusion.[91, 95]

Three RCTs consistently found no difference in recurrent episodes of AOM when comparing TT versus TT and adenoidectomy. However, the Boonaker 2014 IPD meta-analysis concluded that children less than 2 years old years with recurrent AOM had a greater chance of clinical improvement. In this younger group at 12 months, 16% of those who had adenoidectomy failed, whereas 27% of those who did not have adenoidectomy failed [RD 12%, 95% Cl: 6% to 18%; NNT = 9].[2]

## Key Question 3

In general, study specific definitions of adverse events were incompletely reported or highly variable between studies. Not all cohorts followed all patients until extrusion of the tube, nor was followup complete in all studies. Several adverse event categories have very wide interquartile ranges (e.g. otorrhea, premature extrusion, and myringosclerosis). This is likely because of highly variable definitions. For example, in some studies, counts of patients with at least one episode of otorrhea were included, while other studies included only patients with purulent ear discharge. Otorrhea is particularly complex to characterize, as it may with respect to frequency, duration, volume, character, and associated symptoms. Other adverse events, such as hearing loss and cholesteatoma, are likely confounded by the severity of preexisting and ongoing middle ear disease.

## Key Question 4

We identified nine studies, two RCTs and seven NRCSs that evaluate physical ear protection (e.g. ear plugs) or water restriction (e.g. no swimming or head immersion while bathing) in children after TT placement. A single RCT reported a slightly lower adjusted rate of otorrhea in children assigned to wear ear plugs. The unadjusted odds ratio of having one or more episodes of otorrhea was not significantly different (OR 0.68, 95% CI 0.37 to 1.25). A second RCT, with

high risk of bias, found a nonsignificant difference in the odds ratio in nonswimmers versus swimmers (OR 0.71, 95% CI 0.29 to 1.76). Separate meta-analysis of NRCSs with evaluated ear protection and nonswimming tend to favor no precautions and swimming, but their confidence intervals do not exclude a null effect. In addition, the included NRCSs have high risk of confounding and other biases.

# Key Question 5

Seven studies were included in a network meta-analysis of the comparative effectiveness of various treatments for TT otorrhea. The common outcome evaluated was clinical cure, defined as absence of otorrhea after completion of treatment.

The odds of clinical cure were 12-fold (95% CrI: 1.9 – 82) higher [NNT 2.2 (assuming a baseline rate 0.45)][a] for antibiotic-glucocorticoid drops, compared to watchful waiting/placebo. Similarly, the odds of clinical cure were 7.3-fold (95% CrI: 1.2 – 51) higher [NNT 2.5 (assuming a baseline rate of 0.45)][b] for topical antibiotic drops (compared to watchful waiting/placebo).

Compared to oral antibiotics, treatment with topical-glucocorticoid drops demonstrated higher effectiveness, odds ratio 5.3 (95% CrI: 1.2 to 27) [NNT 3.2 (assuming a baseline rate 0.56)].[c] The odds ratio for topical antibiotic drops was 3.3 (95% CrI: 0.74 – 16)[NNT 5 (assuming a baseline rate of 0.69)][d], although the credible interval includes 1.

[a] As seen in: van Dongen TM, van der Heijden GJ, Venekamp RP, et al. A trial of treatment for acute otorrhea in children with tympanostomy tubes. N Engl J Med. 2014 Feb 20;370(8):723-33. doi: 10.1056/NEJMoa1301630. PMID: 24552319. (34 of 75 in watchful waiting arm)

[b] As seen in: Heslop A, Lildholdt T, Gammelgaard N, et al. Topical ciprofloxacin is superior to topical saline and systemic antibiotics in the treatment of tympanostomy tube otorrhea in children: the results of a randomized clinical trial. Laryngoscope. 2010 Dec;120(12):2516-20. doi: 10.1002/lary.21015. PMID: 20979100. (12/26 cured in saline rinse (placebo) arm)

[c] As seen in: van Dongen TM, van der Heijden GJ, Venekamp RP, et al. A trial of treatment for acute otorrhea in children with tympanostomy tubes. N Engl J Med. 2014 Feb 20;370(8):723-33. doi: 10.1056/NEJMoa1301630. PMID: 24552319. (43 of 77 cured in oral antibiotic arm)

[d] As seen in: Goldblatt EL, Dohar J, Nozza RJ, et al. Topical ofloxacin versus systemic amoxicillin/clavulanate in purulent otorrhea in children with tympanostomy tubes. Int J Pediatr Otorhinolaryngol. 1998 Nov 15;46(1-2):91-101. PMID: 10190709. (101 of 146 cured in oral antibiotic arm)

An overall summary of main conclusions with an assessment of the strength of evidence is summarized in Table 18.

**Table 18. Strength of evidence assessment**

| Key Question or Population | Outcome | Comparison | Risk of Bias for the evidence-base | Consistency | Precision | Directness | Overall Rating | Key Findings and Comments |
|---|---|---|---|---|---|---|---|---|
| *Key Question 1* | | | | | | | | |
| Effectiveness of TT in children with chronic MEE | Improvement (decrease) in mean hearing level 1-3 months | TT vs. Watchful waiting | Moderate to high | Consistent | Somewhat imprecise | Mix of direct and indirect from network MA | Moderate | 6 RCT Effective: -9.1 dB (CrI: -14.5, -3.2) |
| | | TT & | Moderate | Consistent | Somewhat | Mix of | Moderate | 6 RCT |

| Key Question or Population | Outcome | Comparison | Risk of Bias for the evidence-base | Consistency | Precision | Directness | Overall Rating | Key Findings and Comments |
|---|---|---|---|---|---|---|---|---|
| | | Adenoidectomy vs. Watchful waiting | to high | | imprecise | direct and indirect from network MA | | Effective: -10.3 dB (CrI: -18.6, -1.6) |
| | Improvement (decrease) in mean hearing level (12-24 months) | TT vs. Watchful waiting | Moderate to high | Consistent | Mostly precise | Mix of direct and indirect from network MA | Moderate | 5 RCT Not effective: 0.03 dB (CrI: -3.9, 3.3) |
| | | TT & Adenoidectomy vs. Watchful waiting | Moderate to high | Consistent | Imprecise | Mix of direct and indirect from network MA | Insufficient | 5 RCT Possibly effective: -3.8 dB (CrI: -8.5, 0.62 |
| | Decrease in mean duration of time with middle ear effusion | TT vs. Watchful waiting | Moderate to high | Consistent | Imprecise | Mix of direct and indirect from network MA | Insufficient | 6 RCT Possibly effective: -17 weeks (CrI: -40.0, 4.9) |
| | | TT & Adenoidectomy vs. Watchful waiting | Moderate to high | Consistent | Imprecise | Mix of direct and indirect from network MA | Insufficient | 6 RCT Possibly effective: -23 weeks (CrI: -56.0, 9.9) |
| | Quality of life and patient – centered outcomes | TT vs Watchful waiting | Low to moderate | Consistent | Imprecise | Direct | Low | 5 RCTs, 3 NRCSs Not effective Multiple outcomes No quantitative synthesis done |
| | Hearing test as a modifier of effectiveness | | Moderate to high | Unknown | Imprecise | Direct | Insufficient | No quantitative synthesis done |
| | Other patient factors which modify effectiveness of TT | | Moderate to high | Unknown | Imprecise | Direct | Insufficient | No quantitative synthesis Sparse reporting of potential predictors |
| Separately for populations at | various | | High | Inconsistent | Imprecise | Direct | Insufficient | No RCTs 6 NRCSs |

| Key Question or Population | Outcome | Comparison | Risk of Bias for the evidence-base | Consistency | Precision | Directness | Overall Rating | Key Findings and Comments |
|---|---|---|---|---|---|---|---|---|
| high risk (e.g. cleft palate, Down syndrome) | | | | | | | | |
| *Key Question 2* | | | | | | | | |
| Tympanostomy tubes in children with recurrent AOM | | TT vs. Watchful waiting | High | Consistent | Imprecise | Direct | Low | 6 RCTs (1049 patients)<br>No quantitative synthesis<br>Magnitude of clinically important effects unclear |
| | | TT vs. TT & Adenoidectomy | Moderate to high | Consistent | Imprecise | Direct | Low | 3 RCTs<br>No quantitative synthesis |
| | Quality of Life | TT vs. Watchful waiting | Moderate | NA | Imprecise | Direct | Low | 1 RCT |
| | Factors which identify children most likely to benefit | TT vs. Watchful waiting | High | Unknown | Imprecise | Indirect | Insufficient | |
| *Key Question 4* | | | | | | | | |
| Ear plugs or water restrictions in children with TT | Average rate of otorrhea | Ear plugs vs. no precautions | Moderate | NA | Imprecise | Direct | Low | Possibly effective<br>Single RCT<br>Magnitude of clinically important effects unclear |
| | | Nonswimming vs. no precautions | High | NA | Imprecise | Direct | Low | No effect<br>Single RCT |
| | Risk of one or more episodes of otorrhea | Ear plugs vs. no precautions | High | Consistent | Imprecise | Direct | Low | Not effective<br>4 NRCSs<br>OR 1.7 (CrI: 0.9, 3.1) |
| | | Nonswimming vs. no precautions | High | Mostly consistent | Imprecise | Direct | Low | Not effective<br>6 NRCSs<br>OR 1.52 (CrI: 0.7, 3.2) |
| *Key Question 5* | | | | | | | | |
| Treatment of TT otorrhea | | Topical antibiotic- | Moderate | Consistent | Somewhat imprecise | Mix of direct | Moderate | Network MA of 7 |

| Key Question or Population | Outcome | Comparison | Risk of Bias for the evidence-base | Consistency | Precision | Directness | Overall Rating | Key Findings and Comments |
|---|---|---|---|---|---|---|---|---|
| | | glucocorticoid drops vs. watchful waiting | | | | and indirect from network MA | | studies Effective: OR 12.0 (CrI: 1.9, 82.0) |
| | | Topical antibiotic drops vs watchful waiting | Moderate | Consistent | Somewhat imprecise | Mix of direct and indirect from network MA | Moderate | Network MA of 7 studies Effective: OR 7.2 (CrI: 1.2, 51.0) |
| | | Topical antibiotic-glucocorticoid drops vs. oral antibiotics | Moderate | Consistent | Somewhat imprecise | Mix of direct and indirect from network MA | Moderate | Network MA of 10 studies Effective: OR 5.3 (CrI: 1.2, 27.0) |
| | | Topical antibiotic vs. oral antibiotics | Moderate | Consistent | Imprecise | Mix of direct and indirect from network MA | Insufficient | Network MA of 10 studies OR 3.3 (CrI: 0.75, 16.0) |
| | Quality of Life | | Moderate | NA | Imprecise | Direct | Insufficient | Single RCT |

CrI= Credibility Interval; MA = meta-analysis; OR = odds ratio; dB = decibel, MEE= middle ear effusion; TT=Tympanostomy Tubes; MEE= Middle Ear Effusion; RCT= Randomized Control Trial, NRCS=Nonrandomized Comparative Study

# Limitations

The available evidence base is composed of studies that evaluate multiple interventions. Several of these, such as myringotomy alone and oral antibiotic prophylaxis, are rarely used in current practice. Thus, the direct evidence relating to the comparisons of interest must rely on a smaller subset of studies or be augmented with indirect evidence from network meta-analysis.

Many of these trials were performed prior to widespread use of conjugate pneumococcal vaccines and in an era where antibiotic resistance was less common. It is unclear whether these or other factors affect the relative (current vs. historical) benefits of TT placement for recurrent AOM.

With the exception of two trials [36, 49] that included children with chronic MEE or recurrent AOM, most enrolled predominately children with chronic MEE. The degree to which patients in clinical practice may have both chronic MEE and recurrent AOM is unclear.

In general, individual studies did not explore treatment effect heterogeneity across subgroups of children by age, sex, clinical history, or sociodemographic factors. Further, we were not able to conduct meaningful subgroup analyses across studies, because most trials used similar inclusion criteria, and thus were not highly variable in terms of the proportions of age, sex,

clinical indications, or other baseline characteristics, and because reporting of information on sociodemographic risk factors was sparse and inconsistent.

The generalizability of results to infants and young toddlers and to school age children is also uncertain, given that children in these age groups are underrepresented in available trials.

With the exception of a few NRCSs, patients with cleft palate and Down syndrome have been systematically excluded from comparative trials, limiting the applicability of the evidence for these and other similar subgroups, who experience a higher burden of middle ear disease. Similarly, patients at increased risk of developmental or behavioral sequelae from middle ear disease have not been included (or at least identified) in trials to date.

Across RCTs included in KQs 1 and 2, there was universal lack of blinding of participants, and in many cases of outcome assessors, suggesting a higher risk for ascertainment (measurement) bias, especially for subjective, patient-reported outcomes. Given the intervention in question, placement of a tube in a visible anatomic structure, blinding of participants is not easily accomplished. In addition many studies are at risk for attrition bias, due to dropouts and incomplete followup.

Our meta-analysis of hearing levels used average pure tone hearing levels (typically reported as an average over frequencies of 500, 1000, 2000 and 4000 Hz). This simple measurement is likely insufficient to fully elucidate the complex relationships between hearing and speech perception and development in children.

Assessment of the effectiveness of TT in children with recurrent acute otitis media is particularly challenging, since an episode of AOM in control children (with intact tympanic membrane) results in otalgia and inflammatory changes, whereas children with a functioning TT may present with varying degrees of otorrhea. Bacterial cultures performed in the setting of research may assist in differentiating infections due to organisms associated with AOM from superinfections or colonization with other organisms (e.g. *Staphylococcus* or *Pseudomonas* species). Intermediate, outcomes which rely on simple counts or rates of otorrhea, fail to account for the variable character of otorrhea with respect to duration, character, and patient impact. For example, otorrhea may be transient (of little to no concern), recurrent (of more concern, but usually readily managed), or chronic (of considerable concern and difficult to manage).

Our network meta-analysis of the effectiveness of treatments for otorrhea combines trials of fluoroquinolones with other non FDA approved preparations. This presumes equivalent effectiveness and does not consider variable side effects, such as ototoxicity, which may be associated with some agents.

## Future Research Recommendations

Current indications for TT placement largely reflect the inclusion criteria used in clinical trials. Well-validated prognostic models are urgently needed to further stratify the risk of individual children with regard to persistence of middle ear effusion or recurrent AOM.

Pragmatic trials are needed, particularly in children with recurrent AOM, but also in children with chronic MEE or some combination of both. There should be an emphasis on exploring treatment effect heterogeneity, i.e. differential effects of interventions in populations at different risk levels for outcomes of interest. Of specific interest is information on the effects of interventions among higher risk groups, such as patients with cleft palate, Down syndrome, and children with neurodevelopmental disorders.

Since TTs are no longer effective after extrusion, future trials should record per-ear and per-patient outcomes conditional on whether the TT has been extruded and conduct appropriate

analyses to estimate the causal effects of TTs among children who still have TTs in place. An analogous observation is that, in trials comparing nonsurgical and surgical interventions, interpretation of findings by intention to treat analyses are often complicated by the high cross-over rates from nonsurgical interventions, such as watchful waiting to surgical ones such as TTs.

Outcome assessment in children with recurrent acute otitis media is challenging, since an episode of AOM in children with an intact tympanic membrane results in otalgia and inflammatory changes, whereas children with a functioning TT exhibit otorrhea. Reliance on outcomes based on simple counts or rates of otorrhea fail to account for the variable character of otorrhea, which can be transient (of little to no concern), recurrent (of more concern, but usually readily managed), or chronic (of considerable concern and difficult to manage). Future trials would benefit from standardization and consistent definition of adverse events. In some cases, e.g. premature extrusion, one author's premature extrusion may be another's time extrusion, depending on the duration of anticipated need.[204]

Bacteriologic evaluations performed in the research setting may assist in differentiating otorrhea resulting from infection with organisms associated with AOM (e.g. *Streptoccus pneumoniae*, nontypable *Haemophilus influenza*) from superinfections with organisms associated with chronic otorrhea (e.g. *Staphylococcus aureus* and *Pseudomonas aeruginosa*).[205]

## Conclusions

Overall, the evidence suggests that TT placed in children with persistent middle-ear effusion result in short term improvements in hearing compared to watchful waiting. However, there is no evidence of a sustained benefit.

Our network meta-analysis of hearing thresholds suggests the possibility of a more sustained improvement in hearing thresholds in at least some children who undergo adenoidectomy and TT placement. A nuanced understanding of which children may benefit from adenoidectomy is limited by the small evidence base and our use of aggregate data.

The evidence suggests that TT did not improve cognition, behavior, or quality of life. However, the evidence if sparse, and prevents any definitive conclusions. The results apply to otherwise healthy children without baseline disorders or delays in language, cognition, or and provide little guidance for the treatment of children who may be at increased risk for speech, language, or learning problems because of baseline sensory, physical, cognitive or behavioral factors.

Children with recurrent AOM may have fewer episodes after TT placement, but the evidence base is severely limited. It is unclear whether quality of life outcomes are improved. The benefits of TT placement must be weighed against a variety of adverse events associated with TT placement.

In children in whom TT have been placed, there is no compelling evidence for the need to either avoid swimming or bathing or use ear plugs or bathing caps

Should otorrhea develop, the available evidence supports treatment of TT otorrhea with a topical antibiotic or antibiotic-glucocorticoid drop.

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# Appendix A. Literature Search

## MEDLINE (5/19/16, 6553 Citations)

((otitis) OR (“glue ear”) OR "Otitis Media with Effusion"[Mesh] OR "Otitis Media, Suppurative"[Mesh] OR "Ear, Middle/secretion"[Mesh] OR (middle and ear and (effusion* or infect* or inflame* or disease*)) OR ((OME OR SOM or AOM) AND (otitis OR ear)) OR ((mucoid* AND middle AND ear) OR (mucous AND middle AND ear) OR (seromuc* AND middle AND ear)))
AND
(tympanostomy OR grommet* OR ((ear or “pressure equalization” or PE or myringotomy or ventilating or ventilation) and (tube or tubes)) OR “Otitis Media with Effusion/surgery”[mesh] OR "Middle Ear Ventilation"[Mesh] OR ((middle AND (ear OR tympanic)) AND (tube or tubes)) OR "Otologic Surgical Procedures"[Mesh] OR T-tube or tabulation)

## COCHRANE (5/19/16, 393 Citations)

((otitis) OR (“glue ear”) OR [mh “Otitis Media with Effusion”] OR [mh “Otitis Media, Suppurative”] OR [mh “Ear, Middle/secretion”] OR (middle and ear and (effusion* or infect* or inflame* or disease*)) OR ((OME OR SOM or AOM) AND (otitis OR ear)) OR ((mucoid* AND middle AND ear) OR (mucous AND middle AND ear) OR (seromuc* AND middle AND ear)))
AND
(tympanostomy OR grommet* OR ((ear or “pressure equalization” or PE or myringotomy or ventilating or ventilation) and (tube or tubes)) OR [mh “Otitis Media with Effusion/surgery”] OR [mh "Middle Ear Ventilation"] OR ((middle AND (ear OR tympanic)) AND (tube or tubes)) OR [mh “Otologic Surgical Procedures"] OR T-tube or tabulation)

## CINAHL (5/19/16, 852 Citations)

((MH "Otitis") OR (MH "Otitis Media with Effusion") OR (MH "Otitis Media") OR otitis OR (“glue ear”) OR (MH "Ear, Middle") OR (middle and ear and (effusion* or infect* or inflame* or disease*)) OR ((OME OR SOM or AOM) AND (otitis OR ear)) OR ((mucoid* AND middle AND ear) OR (mucous AND middle AND ear) OR (seromuc* AND middle AND ear)))
AND
(tympanostomy or myringotomy OR (MH "Middle Ear Ventilation") OR grommet* OR ((ear or “pressure equalization” or PE or myringotomy or ventilating or ventilation) and (tube or tubes)) OR ((middle AND (ear OR tympanic)) AND (tube or tubes)) OR (MH "Ear Surgery") OR T-tube or tabulation)

## EMBASE (5/19/16, 5556 Citations)

(otitis OR 'otitis media'/exp OR glue ear OR (middle and ear and (effusion* or infect* or inflame* or disease*)) OR ((OME OR SOM or AOM) AND (otitis OR ear)) OR ((mucoid* AND middle AND ear) OR (mucous AND middle AND ear) OR (seromuc* AND middle AND ear)))
AND
(tympanostomy OR 'tympanostomy tube'/exp OR 'myringotomy'/exp OR 'middle ear ventilation'/exp OR grommet* OR ((ear or “pressure equalization” or PE or myringotomy or ventilating or ventilation) and (tube or tubes)) OR ((middle AND (ear OR tympanic)) AND (tube or tubes)) OR T-tube or tabulation)

# Appendix B. Excluded Studies

**Table B1. Excluded studies**

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | Diacova S. and Desvignes V. and Chiaburu A. and Chirtoca D. and Parii S. | Tympanostomy and adenoidectomy for treatment of otitis media in children | Archives of Disease in Childhood (2012) 97 SUPPL. 2 (A453). Date of Publication: October 2012 | Abstract |
| | Cheng L. and Chen S. and Cheng J. | Does tube type matter in posttympanostomy tube otorrhea? | Otolaryngology - Head and Neck Surgery (United States) (2014) 151:1 SUPPL. 1 (P147). Date of Publication: September 2014 | Abstract |
| | Chen S. and Cheng L. and Chen T. and Cheng J. and Cheng R. and Cheng D. | A review of 2399 ears for postmyringotomy tube otorrhea | Otolaryngology - Head and Neck Surgery (United States) (2012) 147 SUPPL. 2 (P130-P131). Date of Publication: August 2012 | Abstract |
| | Wang M.-C. | Ventilation tube insertions for pediatric otitis media with effusion: With adenoidectomy or not | Otolaryngology - Head and Neck Surgery (2011) 145 SUPPL. 2 (114). Date of Publication: August 2011 | Abstract |
| | Russell C. and Black O. and Dutt D. and Ray A. and Devlin M. and Wynne D. | Are ventilation tubes (grommets) in cleft children truly associated with increased complication rates? Results of a nested case control study of cleft and non-cleft children | British Journal of Oral and Maxillofacial Surgery (2012) 50 SUPPL. 1 (S2-S3). Date of Publication: June 2012 | Abstract |
| | Sidell D.R. and Hunter L. and Lin L. and Arjmand E.M. | Risk factors for hearing loss in the setting of pressure equalization tube placement in children | Otolaryngology - Head and Neck Surgery (United States) (2013) 149:2 SUPPL. 1 (P122). Date of Publication: September 2013 | Abstract |
| | Black O. and Dutt D. and Russell C. and Devlin M. and Ray A. and Wynne D. | Ventilation tubes in cleft children carry no higher risk of complication than their use in non cleft children: Results of a nested case control study | Clinical Otolaryngology (2012) 37 SUPPL. 1 (181-182). Date of Publication: July 2012 | Abstract |
| | Wolter N.E. and Dell S. and James A.L. and Campisi P. | Middle ear ventilation in children with primary ciliary dyskinesia | Otolaryngology - Head and Neck Surgery (2011) 145 SUPPL. 2 (111). Date of Publication: August 2011 | Abstract |
| | Diacova S. and Ababii I. and Maniuc M. and Danilov L. and Ababii P. and Diacova O. and McDonald T.J. | Modified surgery in children with persistent and recurrent otitis media | Archives of Disease in Childhood (2014) 99 SUPPL. 2 (A137). Date of Publication: October 2014 | Abstract |
| | Sobin, L. B. and Imbery, T. E. and Tatum, S. A. and Nicholas, B. D. and Koester, L. | Long-term otologic outcomes in patients with cleft palates | | Abstract |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 5567839 | J K Graham | Serous otitis media: complication of polyethylene tube insertion | Eye, ear, nose & throat monthly | Case report |
| 12610892 | Pulec J.L. and Deguine C. | Long-term ventilating tube with tympanosclerosis | Ear, Nose and Throat Journal (2003) 82:1 (8). Date of Publication: 1 Jan 2003 | Case report |
| 11011482 | Pulec J.L. and Deguine C. | Long-term ventilating tube with tympanosclerosis | Ear, Nose and Throat Journal (2000) 79:9 (680). Date of Publication: 2000 | Case report |
| 13157738 | Armstrong B.W. | A new treatment for chronic secretory otitis media | Archives of otolaryngology (1954) 59:6 (653-654). Date of Publication: 1954 | Case report |
| 5081036 | Gulzow J. | Observations during long-term drainage of the middle ear in chronic catarrh of the eustachian tube | Zeitschrift fur Laryngologie, Rhinologie, Otologie und ihre Grenzgebiete (1972) 51:10 (665-670). Date of Publication: Oct 1972 | Case report |
| 10624048 | Deguine C. and Pulec J.L. | Grommet ventilation myringostomy with cholesteatoma | Ear, Nose and Throat Journal (1999) 78:12 (884). Date of Publication: 1999 | Case report |
| 18357935 | Abbarah T. and Abbarah M.A. | Migration of T-tubes to the middle ear | Ear, Nose and Throat Journal (2008) 87:1. Date of Publication: January 2008 | Case report |
| 16406076 | Riccardo D'Eredita and Udayan K Shah | Contact diode laser myringotomy for medium-duration middle ear ventilation in children | International journal of pediatric otorhinolaryngology | Cohort, N < 50 |
| 3218926 | C C Lau and K K Loh and N Kunaratnam | Middle ear diseases in cleft palate patients in Singapore | Annals of the Academy of Medicine, Singapore | Cohort, N < 50 |
| 5778864 | J H Per-Lee | Experiences with a "permanent" wide flange middle ear ventilation tube | The Laryngoscope | Cohort, N < 50 |
| 17440366 | Mohamed E Hassan and Sherif Askar | Does palatal muscle reconstruction affect the functional outcome of cleft palate surgery? | Plastic and reconstructive surgery | Cohort, N < 50 |
| 9041283 | M N Orlin and S K Effgen and S D Handler | Effect of otitis media with effusion on gross motor ability in preschool-aged children: preliminary findings | Pediatrics | Cohort, N < 50 |
| 7619414 | R W Force and M C Hart and S A Plummer and D A Powell and M C Nahata | Topical ciprofloxacin for otorrhea after tympanostomy tube placement | Archives of otolaryngology--head & neck surgery | Cohort, N < 50 |
| 6023618 | W L Draper | Secretory otitis media in children: a study of 540 children | The Laryngoscope | Cohort, N < 50 |
| 8504893 | M Selikowitz | Short-term efficacy of tympanostomy tubes for secretory otitis media in children with Down syndrome | Developmental medicine and child neurology | Cohort, N < 50 |
| 8551144 | D P Martin-Hirsch and C J Woodhead and C E Vize | Long-term ventilation of the middle ear using a tympanotomy technique | The Journal of laryngology and otology | Cohort, N < 50 |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 10504021 | Y Iino and Y Imamura and S Harigai and Y Tanaka | Efficacy of tympanostomy tube insertion for otitis media with effusion in children with Down syndrome | International journal of pediatric otorhinolaryngology | Cohort, N < 50 |
| 3444993 | B Pérez Piñero and D López Aguado and M E Campos Bañales | [Tympanosclerosis and the ventilation tube] | Revue de laryngologie - otologie - rhinologie | Cohort, N < 50 |
| 7818639 | J G Gilbert | Swimming and grommets: a prospective survey | The New Zealand medical journal | Cohort, N < 50 |
| 7861292 | S Harigai | [Longitudinal studies in hearing-impaired children with Down's syndrome] | Nihon Jibiinkoka Gakkai kaiho | Cohort, N < 50 |
| 14823225 | {CHAUVET} | [Consideration on the therapy of tubal otorrhea] | Gazette médicale de France | Cohort, N < 50 |
| 1742892 | P J Dawes and B J Bingham and R Rhys and M V Griffiths | Aspirating middle ear effusions when inserting ventilation tubes: does it influence post-operative otorrhoea, tube obstruction or the development of tympanosclerosis? | Clinical otolaryngology and allied sciences | Cohort, N < 50 |
| 19251534 | Mao-Che Wang and Chia-Yu Liu and An-Suey Shiao | Water penetration into middle ear through ventilation tubes in children while swimming | Journal of the Chinese Medical Association : JCMA | Cohort, N < 50 |
| 3418217 | C Watson and K S Mangat | A comparison of audiometric performance and complications of T tubes and Shepard grommets | The Journal of laryngology and otology | Cohort, N < 50 |
| 512469 | J Samuel and G Rosen and Y Vered | Use of middle ear ventilation tubes in recurrent acute otitis media | The Journal of laryngology and otology | Cohort, N < 50 |
| 2769837 | D McRae and D J Gatland and R Youngs and J Cook | Aspiration of middle ear effusions prior to grommet insertion an etiological factor in tympanosclerosis | The Journal of otolaryngology | Cohort, N < 50 |
| 3427802 | E Chevretton and B J Bingham and E Firman | The prevention of tympanic membrane perforation following the removal of long-term Paparella type II ventilation tubes | Clinical otolaryngology and allied sciences | Cohort, N < 50 |
| 3243014 | T H Lesser and K R Williams and D W Skinner | Tympanosclerosis, grommets and shear stresses | Clinical otolaryngology and allied sciences | Cohort, N < 50 |
| 4855092 | H L Wilson | The steel whisker tube in chronic secretory otitis media | Transactions - American Academy of Ophthalmology and Otolaryngology. American Academy of Ophthalmology and Otolaryngology | Cohort, N < 50 |
| 5550610 | N Shah | Use of grommets in 'glue' ears | The Journal of laryngology and otology | Cohort, N < 50 |
| 22796197 | Tuomas Klockars and Jorma Rautio | Early placement of ventilation tubes in cleft lip and palate patients: does palatal closure affect tube occlusion and short-term | International journal of pediatric otorhinolaryngology | Cohort, N < 50 |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | | outcome? | | |
| 1863436 | H C Pillsbury and J H Grose and J W Hall | Otitis media with effusion in children. Binaural hearing before and after corrective surgery | Archives of otolaryngology--head & neck surgery | Cohort, N < 50 |
| 14568787 | Joseph W Hall and John H Grose and Emily Buss and Madhu B Dev and Amelia F Drake and Harold C Pillsbury | The effect of otitis media with effusion on perceptual masking | Archives of otolaryngology--head & neck surgery | Cohort, N < 50 |
| 7190178 | Q Bailey | The Castelli membrane in the treatment of glue ear | The Journal of laryngology and otology | Cohort, N < 50 |
| 18072559 | Wei Li and Wei Shang and Ai-hua Yu and Xiao-heng Zhang and Yu-xin Liu and Xiu-ming Wan and Mu-yun Jia and Ning-yi Li | [Early treatment of middle ear disease in cleft palate infants] | Hua xi kou qiang yi xue za zhi = Huaxi kouqiang yixue zazhi = West China journal of stomatology | Cohort, N < 50 |
| 26949997 | Nihat Kılıç and Özgür Yörük and Songül Cömert Kılıç and Gülhan Çatal and Sezgin Kurt | Rapid maxillary expansion versus middle ear tube placement:Comparison of hearing improvements in children with resistance otitis media with effusion | Mar | Cohort, N < 50 |
| 2492178 | G A Gates and C A Avery and J C Cooper and T J Prihoda | Chronic secretory otitis media: effects of surgical management | The Annals of otology, rhinology & laryngology. Supplement | No extractable data |
| 4040338 | G A Gates and C Wachtendorf and E M Hearne and G R Holt | Treatment of chronic otitis media with effusion: results of tympanostomy tubes | American journal of otolaryngology | No extractable data |
| 3336263 | G A Gates and C A Avery and T J Prihoda | Effect of adenoidectomy upon children with chronic otitis media with effusion | The Laryngoscope | No extractable data |
| 11678951 | {Medical Research Council Multicentre Otitis Media Study Group} | Surgery for persistent otitis media with effusion: generalizability of results from the UK trial (TARGET). Trial of Alternative Regimens in Glue Ear Treatment | Clinical otolaryngology and allied sciences | No extractable data |
| 11434951 | M M Rovers and G A Zielhuis and K Bennett and M Haggard | Generalisability of clinical trials in otitis media with effusion | International journal of pediatric otorhinolaryngology | No extractable data |
| 18685496 | {MRC Multicentre Otitis Media Study Group} | An extension of the Jerger classification of tympanograms for ventilation tube patency--specification and evaluation of equivalent ear-canal volume criteria | Ear and hearing | No extractable data |
| 12363423 | A A Maheshwar and M A P Milling and M Kumar and M I Clayton and A Thomas | Use of hearing aids in the management of children with cleft palate | International journal of pediatric otorhinolaryngology | No extractable data |
| 25677370 | Joong Ho Ahn and Woo Seok Kang | Critical reassessment of the probability of | Acta oto-laryngologica | No extractable |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | and Ji Heui Kim and Kyung S Koh and Tae Hyun Yoon | receiving additional ventilation tube insertion for recurrent otitis media with effusion in children with a cleft palate | | data |
| 3818186 | H Hafner and I Anteby and H Pratt and M Goldsher and R Shenhav and H Z Joachims | Auditory brainstem evoked potentials in evaluating the efficacy of surgical ventilation of the middle ear | International journal of pediatric otorhinolaryngology | No extractable data |
| 10542923 | J D Hern and D A Jonathan | Insertion of ventilation tubes: does the site matter? | Clinical otolaryngology and allied sciences | No extractable data |
| 8741962 | L L Hunter and R H Margolis and J R Rykken and C T Le and K A Daly and G S Giebink | High frequency hearing loss associated with otitis media | Ear and hearing | No extractable data |
| 3818185 | I Anteby and H Hafner and H Pratt and N Uri | Auditory brainstem evoked potentials in evaluating the central effects of middle ear effusion | International journal of pediatric otorhinolaryngology | No extractable data |
| 6778358 | B Hussl and K Welzl-Mueller | Secretory otitis media and mastoid pneumatization | The Annals of otology, rhinology & laryngology. Supplement | No extractable data |
| 24243868 | Christina T Ryborg and Jens Søndergaard and Jørgen Lous and Anders Munck and Pia V Larsen and Janus L Thomsen | Quality of life in children with otitis media--a cohort study | Family practice | No extractable data |
| 11074114 | Y Rakover and K Keywan and G Rosen | Comparison of the incidence of cholesteatoma surgery before and after using ventilation tubes for secretory otitis media | International journal of pediatric otorhinolaryngology | No extractable data |
| 5795401 | Paradise J.L. and Bluestone C.D. and Felder H. | The universality of otitis media in 50 infants with cleft palate | Pediatrics (1969) 44:1 (463-471). Date of Publication: 1969 | No extractable data |
| | Morales D.S.R. and Testa J.R.G. and Guilherme A. and Fukuda Y. | Permanence time of 164 ventilation tympanic tubes in 82 cleft palate pacients | Revista Brasileira de Otorrinolaringologia (2001) 67:1 (22-27). Date of Publication: 2001 | No extractable data |
| 22531243 | Van Dongen T.M.A. and Schilder A.G.M. and Manders L.A. and Van Der Veen E.L. and Van Der Heijden G.J.M.G. | Good agreement between parents and physician in the assessment of ear discharge in children | Pediatric Infectious Disease Journal (2012) 31:8 (868-869). Date of Publication: August 2012 | No extractable data |
| 4666579 | King J.T. | Modified exploratory ulterior tympanotomy in chronic secretory otitis media in children | Trans. Amer. Acad. Ophthal. Otolaryng. (1972) 76:5 (1292-1295). Date of Publication: 1972 | No outcomes of interest |
| 25676152 | Christian Hamilton Heidemann and Henrik Hein Lauridsen and Anette Drøhse Kjeldsen and Christian Emil | Quality-of-Life Differences among Diagnostic Subgroups of Children Receiving Ventilating Tubes for Otitis | Oct | No outcomes of interest |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | Faber and Eva Charlotte Jung Johansen and Christian Godballe | Media | | |
| 12622537 | Mark Boston and Joe McCook and Bonnie Burke and Craig Derkay | Incidence of and risk factors for additional tympanostomy tube insertion in children | Archives of otolaryngology--head & neck surgery | No outcomes of interest |
| 8877207 | A R Maw and R Bawden and L O'Keefe and P Gurr | Does the type of middle ear aspirate have any prognostic significance in otitis media with effusion in children? | Clinical otolaryngology and allied sciences | No outcomes of interest |
| 21106257 | Richard M Rosenfeld and David W Jang and Konstantin Tarashansky | Tympanostomy tube outcomes in children at-risk and not at-risk for developmental delays | International journal of pediatric otorhinolaryngology | No outcomes of interest |
| 22183901 | Nathan S Alexander and Brian D Kulbersh and C Hope Heath and Renee A Desmond and Eric Caron and Audie L Woolley and Jimmy Scott Hill and W Peyton Shirley and Brian J Wiatrak | MRSA and non-MRSA otorrhea in children: a comparative study of clinical course | Archives of otolaryngology--head & neck surgery | No outcomes of interest |
| 12117333 | Michele Richards and Carla Giannoni | Quality-of-life outcomes after surgical intervention for otitis media | Archives of otolaryngology--head & neck surgery | No outcomes of interest |
| 12439177 | Rahmi Kiliç and Mustafa A Safak and Ali Ozdek and Hakan Göçmen and Dilek Kiliç and Erdal Samim | Effect of 23 valent pneumococcal polysaccharide and Haemophilus influenza conjugated vaccines on the clinical course of otitis media with effusion | The Laryngoscope | No outcomes of interest |
| 6539321 | O G Neumann and R Laszig | [Diagnosis and therapy of seromucous otitis. Experience with 2766 operations on children] | HNO | No outcomes of interest |
| 2254809 | M Suetake and T Kobayashi and T Takasaka and H Shinkawa | [Middle ear air volume and prognosis of secretory otitis media] | Nihon Jibiinkoka Gakkai kaiho | No outcomes of interest |
| 8260856 | T C Theoharides and S S Manolidis and H Vliagoftis and L S Manolidis | Treatment of secretory otitis media with local instillation of hydroxyzine | International archives of allergy and immunology | No outcomes of interest |
| 8026089 | A R Maw and R Bawden | Factors affecting resolution of otitis media with effusion in children | Clinical otolaryngology and allied sciences | No outcomes of interest |
| 24983459 | Mao-Che Wang and Ying-Piao Wang and Chia-Huei Chu and Tzong-Yang Tu and An-Suey Shiao and Pesus Chou | The protective effect of adenoidectomy on pediatric tympanostomy tube re-insertions: a population-based birth cohort study | PloS one | No outcomes of interest |
| 7218998 | B F Jaffe | Are water and tympanotomy tubes compatible? | The Laryngoscope | No outcomes of interest |
| 1787379 | A Golz and S T Westerman and L M | Effect of middle ear effusion on the | The Journal of laryngology and otology | No outcomes of |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | Gilbert and H Z Joachims and A Netzer | vestibular labyrinth | | interest |
| 3974389 | B F Lounsbury | Swimming unprotected with long-shafted middle ear ventilation tubes | The Laryngoscope | No outcomes of interest |
| 9596366 | A Golz and B Angel-Yeger and S Parush | Evaluation of balance disturbances in children with middle ear effusion | International journal of pediatric otorhinolaryngology | No outcomes of interest |
| 17645949 | Yan Chow and David A M Wabnitz and John Ling | Quality of life outcomes after ventilating tube insertion for otitis media in an Australian population | International journal of pediatric otorhinolaryngology | No outcomes of interest |
| 20504840 | Petri S Mattila and Sari Hammarén-Malmi and Harri Saxen and Tarja Kaijalainen and Helena Käyhty and Jussi Tarkkanen | Adenoidectomy and nasopharyngeal carriage of Streptococcus pneumoniae in young children | Archives of disease in childhood | No outcomes of interest |
| 7193427 | H H Elverland and I W Mair and O K Haugeto and K E Schrøder | Influence of adenoid hypertrophy on secretory otitis media | The Annals of otology, rhinology, and laryngology | No outcomes of interest |
| 23917659 | Leticia Reis Borges and Jorge Rizzato Paschoal and Maria Francisca Colella-Santos | (Central) auditory processing: the impact of otitis media | Clinics (São Paulo, Brazil) | No outcomes of interest |
| | Donaldson J.A. | The role of artificial(bullet) eustaciiian tube in cleft palate patients | Cleft Palate Journal (1966) 3:1 (61-66). Date of Publication: 1966 | No outcomes of interest |
| 26218381 | Lauren A Hanes and Amanda Murphy and Jill E Hatchette and Raylene Delorey and Kenneth L Wilson and Paul Hong and Michael Bezuhly | Chronic Otitis Media with Effusion Is Associated with Increased Risk of Secondary Speech Surgery | Aug | No outcomes of interest |
| 2563465 | G A Zielhuis and G H Rach and P van den Broek | Screening for otitis media with effusion in preschool children | Lancet (London, England) | No outcomes of interest |
| 1571119 | G S Giebink and K Daly and D J Buran and M Satz and T Ayre | Predictors for postoperative otorrhea following tympanostomy tube insertion | Archives of otolaryngology--head & neck surgery | No outcomes of interest |
| 26454528 | P Niemi and J Numminen and M Rautiainen and M Helminen and H Vinkka-Puhakka and T Peltomäki | The effect of adenoidectomy on occlusal development and nasal cavity volume in children with recurrent middle ear infection | International journal of pediatric otorhinolaryngology | No outcomes of interest |
| 17403263 | S Sood and A Waddell | Accurate consent for insertion and later removal of grommets | The Journal of laryngology and otology | No outcomes of interest |
| 10208683 | C G Gourin and R N Hubbell | Otorrhea after insertion of silver oxide-impregnated silastic tympanostomy tubes | Archives of otolaryngology--head & neck surgery | No outcomes of interest |
| 17043261 | Erwin L van der Veen and Anne G M Schilder and Niels van Heerbeek | Predictors of chronic suppurative otitis media in children | Archives of otolaryngology--head & neck surgery | No outcomes of interest |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | and Monique Verhoeff and Gerhard A Zielhuis and Maroeska M Rovers | | | |
| 22835927 | Petri S Mattila and Sari Hammarén-Malmi and Harri Saxen and Tarja Kaijalainen and Helena Käyhty and Jussi Tarkkanen | Adenoidectomy in young children and serum IgG antibodies to pneumococcal surface protein A and choline binding protein A | International journal of pediatric otorhinolaryngology | No outcomes of interest |
| 14643475 | Joseph Dohar | Microbiology of otorrhea in children with tympanostomy tubes: implications for therapy | International journal of pediatric otorhinolaryngology | No outcomes of interest |
| 19131420 | P S Mattila and S Hammarén-Malmi and A S Pelkonen and L P Malmberg and M J Mäkelä and H Saxen and J Tarkkanen | Effect of adenoidectomy on respiratory function: a randomised prospective study | Archives of disease in childhood | No outcomes of interest |
| 3201954 | I Augustsson and C Nilsson and P Neander | Do we treat "the right" children with secretory otitis media at the ENT clinic? | Acta oto-laryngologica. Supplementum | No outcomes of interest |
| 25764097 | Thijs M A van Dongen and Roderick P Venekamp and Annemarie M J Wensing and Debby Bogaert and Elisabeth A M Sanders and Anne G M Schilder | Acute otorrhea in children with tympanostomy tubes: prevalence of bacteria and viruses in the post-pneumococcal conjugate vaccine era | The Pediatric infectious disease journal | No outcomes of interest |
| 9176804 | Y Rakover and K Keywan and G Rosen | Safety of topical ear drops containing ototoxic antibiotics | The Journal of otolaryngology | No outcomes of interest |
| 9288214 | H Valtonen and Y Qvarnberg and H Puhakka and J Nuutinen | Early post-tympanostomy otorrhea in children under 17 months of age | Acta oto-laryngologica | No outcomes of interest |
| 14740537 | Ivan Baljosević and Vladan Subarević and Nikola Mircetić and Jovana Jecmenica and Jovica Karanov and Zorica Vasiljević | [Suppurative middle ear infection as a complication after tympanostomy tube placement] | Medicinski pregled | No outcomes of interest |
| 3670236 | M Stura and G Ivani | [Insertion of trans-tympanic drainage in muco-gelatinous otitis in children] | Minerva pediatrica | No outcomes of interest |
| 17178938 | David M Poetker and D Richard Lindstrom and Nalin J Patel and Stephen F Conley and Valerie A Flanary and T Roxanne Link and Joseph E Kerschner | Ofloxacin otic drops vs neomycin-polymyxin B otic drops as prophylaxis against early postoperative tympanostomy tube otorrhea | Archives of otolaryngology--head & neck surgery | No outcomes of interest |
| 2128487 | K Roos and G Granström and G Karlsson and L Lind and S Olling and U Renvall | Ear discharge after insertion of transmyringeal tubes | International journal of pediatric otorhinolaryngology | No outcomes of interest |
| 12161732 | Gordon J Siegel and Rakesh K | Laser office ventilation of ears with | Otolaryngology--head and neck surgery : | No outcomes of |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | Chandra | insertion of tubes | official journal of American Academy of Otolaryngology-Head and Neck Surgery | interest |
| 5249846 | M S Robertson | Chronic secretoty otitis media: treatment with trans-tympanic indwelling polythene tubes | The New Zealand medical journal | No outcomes of interest |
| 8745020 | K A Daly and G S Giebink and B Lindgren and R H Margolis and D Westover and L L Hunter and C T Le and D Buran | Randomized trial of the efficacy of trimethoprim-sulfamethoxazole and prednisone in preventing post-tympanostomy tube morbidity | The Pediatric infectious disease journal | No outcomes of interest |
| 16172353 | Brechtje de Beer and Ad Snik and Anne G M Schilder and Kees Graamans and Gerhard A Zielhuis | The effect of otitis media in childhood on the development of middle ear admittance on reaching adulthood | Archives of otolaryngology--head & neck surgery | No outcomes of interest |
| 1479274 | M A Salam and C Wengraf | Glue under pressure: a bad prognostic sign for recurrence of otitis media with effusion | The Journal of laryngology and otology | No outcomes of interest |
| 23379112 | Min Huang and Sijun Zhao and Yun Li and Xiangyue Peng and Yuting Kuang and Songliang Long | [The effect of tympanostomy tube surgery in cleft palate children with secretory otitis media] | Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery | No outcomes of interest |
| 3713407 | G A Gates and C Avery and T J Prihoda and G R Holt | Post-tympanostomy otorrhea | The Laryngoscope | No outcomes of interest |
| 16510637 | Niels van Heerbeek and Masja Straetemans and Selma P Wiertsema and Koen J A O Ingels and Ger T Rijkers and Anne G M Schilder and Elisabeth A M Sanders and Gerhard A Zielhuis | Effect of combined pneumococcal conjugate and polysaccharide vaccination on recurrent otitis media with effusion | Pediatrics | No outcomes of interest |
| | Coates H. | Preventing and treating grommet tube otorrhoea | Medicine Today (2002) 3:10 (77-79). Date of Publication: 1 Oct 2002 | No outcomes of interest |
| | Coates H. and Sashikumar A. | A prospective clinical trial of antibiotic/steroid ear drops and incidence of infection following ventilation tube insertion | Journal of the Otolaryngological Society of Australia (1990) 6:4 (272-274). Date of Publication: 1990 | No outcomes of interest |
| | Becker C.G. and Da Silva A.L. and Guimaraes R.E.S. and Becker H.M.G. and Barra I.M. and Oliveira W.D. | Surgical treatment of otitis media with effusion: Ventilation tube versus topical application of mitomycin C | Revista Brasileira de Otorrinolaringologia (2003) 69:4 (513-519). Date of Publication: 2003 | No outcomes of interest |
| | Raja H. and Williams J. and Tzifa K. | Audiology following up grommets can improve efficiency and finances for ENT | Clinical Otolaryngology (2012) 37 SUPPL. 1 (176). Date of Publication: July 2012 | No outcomes of interest |
| 25554572 | Axel Håkansson and Rut Florentzson and Lisa Tuomi and Caterina Finizia | Transmyringeal ventilation tube treatment in children: hearing outcome after 10 years | Feb | No outcomes of interest |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 26985629 | Eric A Mair and Albert H Park and Debra Don and Jeffrey Koempel and Moraye Bear and Carl LeBel | Safety and Efficacy of Intratympanic Ciprofloxacin Otic Suspension in Children With Middle Ear Effusion Undergoing Tympanostomy Tube Placement: Two Randomized Clinical Trials | May | No outcomes of interest |
| 26611339 | Jacob W Zeiders and Charles A Syms and Mary T Mitskavich and David M Yen and Daniel T Harfe and Ryan D Shields and Brent J Lanier and Andrew R Gould and Jason Mouzakes and C Layton Elliott | Tympanostomy tube placement in awake, unrestrained pediatric patients: A prospective, multicenter study | Dec | No outcomes of interest |
| 26454528 | P Niemi and J Numminen and M Rautiainen and M Helminen and H Vinkka-Puhakka and T Peltomäki | The effect of adenoidectomy on occlusal development and nasal cavity volume in children with recurrent middle ear infection | Dec | No outcomes of interest |
| 11797262 | C R Cannon and W H Replogle | Otorrhea following Ultracil ear tube insertion | Journal of the Mississippi State Medical Association | No outcomes of interest |
| 3517534 | T J Balkany and I K Arenberg and R L Steenerson | Ventilation tube surgery and middle ear irrigation | The Laryngoscope | No outcomes of interest |
| 17049144 | Marisol Carignan and Dominique Dorion and Marie-France Stephenson and Michel Rouleau | First myringotomy with insertion of a modified Goode T-Tube: changing the perforation paradigm | The Journal of otolaryngology | No outcomes of interest |
| 21777983 | David M Gleinser and Hilda H Kriel and Shraddha Mukerji | The relationship between repeat tympanostomy tube insertion and adenoidectomy | International journal of pediatric otorhinolaryngology | No outcomes of interest |
| 7550814 | D A Clements and L Langdon and C Bland and E Walter | Influenza A vaccine decreases the incidence of otitis media in 6- to 30-month-old children in day care | Archives of pediatrics & adolescent medicine | No outcomes of interest |
|  | Elverland H.H. and Haugeto O.K. and Andersen L. | Adenoidectomy and secretory otitis media | Acta Oto-Laryngologica (1982) 94:Suppl. 386 (134-136). Date of Publication: 1982 | No outcomes of interest |
| 26545794 | Oumama El Ezzi and Georges Herzog and Martin Broome and Chantal Trichet-Zbinden and Judith Hohlfeld and Jacques Cherpillod and Anthony S de Buys Roessingh | Grommets and speech at three and six years in children born with total cleft or cleft palate | Dec | No outcomes of interest |
| 25598382 | Wan X. and Yang J. and Jia H. | Efficacy of surgery, recurrence factors and treatment strategies of otitis media with effusion in children | Zhonghua er bi yan hou tou jing wai ke za zhi = Chinese journal of otorhinolaryngology head and neck surgery (2014) 49:11 (964-967). Date of Publication: 1 Nov 2014 | No primary data |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 8656164 | A Adelman | Water precautions in children with tympanostomy tubes | The Journal of family practice | No primary data |
| 15851429 | M M Rovers and N Black and G G Browning and R Maw and G A Zielhuis and M P Haggard | Grommets in otitis media with effusion: an individual patient data meta-analysis | Archives of disease in childhood | No primary data |
| 6974210 | L J Hall | Chronic serous otitis media | The Journal of the Kentucky Medical Association | No primary data |
| 6357648 | T Lildholdt | Secretory otitis media. The significance of negative middle ear pressure and the results of a controlled study of ventilation tubes | Danish medical bulletin | No primary data |
| 11509152 | M B Stephens | Does delaying placement of tympanostomy tubes have an adverse effect on developmental outcomes in children with persistent middle ear effusions? | The Journal of family practice | No primary data |
| 1110316 | L W Pratt | The use of equalization tubes in nonsuppurative otits media | The Journal of the Maine Medical Association | No primary data |
| 8461735 | A F Bisset | Persistent glue ear in children | BMJ (Clinical research ed.) | No primary data |
| 16299942 | | Early tymp tubes do not improve outcomes after 3+ years | The Journal of family practice | No primary data |
| 7017311 | D E Gebhart | Tympanostomy tubes in the otitis media prone child | The Laryngoscope | No primary data |
| 24438691 | Chantal W B Boonacker and Maroeska M Rovers and George G Browning and Arno W Hoes and Anne G M Schilder and Martin J Burton | Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis | Health technology assessment (Winchester, England) | No primary data |
| 8404550 | C Deguine and J L Pulec | Long-term ventilation myringostomy | Ear, nose, & throat journal | No primary data |
| 567665 | M E Alberts | Ventilation of glue ears | Journal of the Iowa Medical Society | No primary data |
| 8482269 | M D Poole | Treatment of otorrhea associated with tubes or perforations | Ear, nose, & throat journal | No primary data |
| 24524194 | Chin-Lung Kuo and Yuan-Heng Tsao and An-Suey Shiao | Critical reassessment of the probability of receiving additional ventilation tube insertion for recurrent otitis media with effusion in children with cleft palate | Acta oto-laryngologica | No primary data |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 880099 | D W Johnson and R H Mathog and R H Maisel | Tympanostomy tube protection with ear plugs | Archives of otolaryngology (Chicago, Ill. : 1960) | No primary data |
| 3522165 | | The surgical management of glue ear | Drug and therapeutics bulletin | No primary data |
| 3743473 | I J Moore and G F Moore and A J Yonkers | Otitis media in the cleft palate patient | Ear, nose, & throat journal | No primary data |
| 1009868 | B K Devgan | Spoon-bobbin drain tube | Ear, nose, & throat journal | No primary data |
| 11115295 | C Giannoni | Swimming with tympanostomy tubes | Archives of otolaryngology--head & neck surgery | No primary data |
| 853006 | R Reck | A rare complication of use of the middle ear ventilation tube (PVC) | HNO | No primary data |
| 17537888 | Morten Lindbaek | Prompt insertion of tympanostomy tubes in infants and toddlers with persistent middle ear effusion did not improve developmental outcomes at 9-11 years of age | Evidence-based medicine | No primary data |
| 4079654 | V Cerkez | [Treatment of secretory otitis: medical or surgical therapy?] | Liječnički vjesnik | No primary data |
| 1416480 | A Clarós | [Otitis media. Surgical treatment] | Anales españoles de pediatría | No primary data |
| 8494594 | P Federspil | [Treatment of "suppurating ear" with intact middle ear tubes] | Laryngo- rhino- otologie | No primary data |
| 6778337 | J L Paradise and C D Bluestone and K D Rogers and F H Taylor | Efficacy of adenoidectomy in recurrent otitis media. Historical overview and preliminary results from a randomized, controlled trial | The Annals of otology, rhinology & laryngology. Supplement | No primary data |
| 12107957 | Jørgen Lous and Maj-Britt Glenn Lauritsen | [Inserted tympanostomy tube in prolonged secretory otitis has no effect on language development] | Ugeskrift for laeger | No primary data |
| 1161091 | R J van der Wal | [Swimming with perforated tympanic membrane?] | Nederlands tijdschrift voor geneeskunde | No primary data |
| 6576790 | N Fernández-Blasini | [Tonsils, adenoids and related problems: use and abuse of ventilation tubes] | Boletín de la Asociación Médica de Puerto Rico | No primary data |
| 1535965 | C Chavanne | [Surgical treatment of secretory otitis media in children] | Revue médicale de la Suisse romande | No primary data |
| | Poole M.D. | Bacterial resistance to quinolone otic drops is nearly zero | Ear, Nose and Throat Journal (2007) 86:11 SUPPL. 1 (13-14). Date of Publication: November 2007 | No primary data |
| 4819101 | Mawson S.R. | Middle ear effusions: therapy and clinical | Annals of Otology, Rhinology and | No primary |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | | results | Laryngology (1974) 83:11 sup (71-72). Date of Publication: 1974 | data |
| | Brown M.W. | Glue ear | South Australian Clinics (1975) 7:1 (69-71). Date of Publication: 1975 | No primary data |
| | Husson Y. and Troy C. | Tubal catarrh | Concours Medical (1975) 97:33 (5041-5048). Date of Publication: 1975 | No primary data |
| 11115297 | Brodsky L. | Swimming with tympanostomy tubes: The controversy continues | Archives of Otolaryngology - Head and Neck Surgery (2000) 126:12 ([d]1509). Date of Publication: 2000 | No primary data |
| 6077690 | Deutsch H.J. | Serous otitis media. An effective, practical approach to diagnosis and therapy of this most common cause of conductive loss of hearing in children | Penn. Med. (1967) 70:11 (53-55). Date of Publication: 1967 | No primary data |
| 5773899 | Cross J.P. | The expanding role of tympanostomy tubes | Virginia Med.Mth. (1969) 96:2 (387-393). Date of Publication: 1969 | No primary data |
| 1549417 | Landay S.E. and Schwartz R.H. | Recommendations for swimming for children with ear infection and/or associated complications | Pediatric Infectious Disease Journal (1992) 11:1 (58-59). Date of Publication: 1992 | No primary data |
| | Mees K. | The use of grommets in serous otitis media | Munchener Medizinische Wochenschrift (1982) 124:11 (39-44). Date of Publication: 1982 | No primary data |
| | Namyslowski G. and Gierek T. and Pilch J. and Iwanowski P. | Tarflen tubes for draining of tympanic cavity | Otolaryngologia Polska (1987) 41:5 ( 334-338). Date of Publication: 1987 | No primary data |
| | Dohar J.E. | Are topical quinolones safe for middle ear use in children? | Ear, Nose and Throat Journal (2006) 85:10 SUPPL. 1 (6-7). Date of Publication: October 2006 | No primary data |
| | Rovers M.M. and Krabbe P.F. and Straatman H. | Ventilation tubes did not improve quality of life in persistent otitis media with effusion | Evidence-Based Medicine (2001) 6:4 (121). Date of Publication: 2001 | No primary data |
| 8486102 | Pulec J.L. and Deguine C. | Secretory otitis media (Glue Ear) | Ear, Nose and Throat Journal (1993) 72:4 (254). Date of Publication: 1993 | No primary data |
| 25695362 | Chin-Lung Kuo | A critical appraisal of ventilation tube insertion in children with cleft palate | Feb | No primary data |
| 25677370 | Joong Ho Ahn and Woo Seok Kang and Ji Heui Kim and Kyung S Koh and Tae Hyun Yoon | Critical reassessment of the probability of receiving additional ventilation tube insertion for recurrent otitis media with effusion in children with a cleft palate | May | No primary data |
| 24524194 | Chin-Lung Kuo and Yuan-Heng Tsao and An-Suey Shiao | Critical reassessment of the probability of receiving additional ventilation tube | May | No primary data |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | | insertion for recurrent otitis media with effusion in children with cleft palate | | |
| | Outhoff, K. | Grommets | | No primary data |
| 26216610 | Del Mar, C. D. and Hoffmann, T. | Autoinflation: An effective nondrug intervention for glue ear | | No primary data |
| | Anonymous | Erratum to: Long term complications of ventilation tube insertion in children with otitis media with effusion: Vojnosanit Pregl 2015; 72(1): 40-43 | | No primary data |
| 1102070 | Alejandro Hoberman | Efficacy of Tympanostomy Tubes for Children With Recurrent Acute Otitis Media | | No primary data |
| 16480003 | Takeshi Yagi and Ken Hayashi and Hisayoshi Shikii and Yuko Miyamoto and Makoto Oda and Atsushi Shinkawa | [Effect of volume reduction surgery by radiofrequency for enlarged adenoid causing recurrent otitis media with effusion] | Nihon Jibiinkoka Gakkai kaiho | Not intervention of interest |
| 25215630 | Kavita Dedhia and Sukgi Choi and David H Chi | Management of refractory tympanostomy tube otorrhea with ear wicks | Mar | Not intervention of interest |
| 25873182 | Mirjana Kostić and Ksenija Ribarić Jankes and Robert Trotić and Mihael Ries and Branka Ledić and Vladimir Bedeković | Clinical and audiological findings in children with acute otitis media | Jul | Not intervention of interest |
| 26281252 | Wenrong Jiang and Tao He and Qian Zheng and Wei Zheng and Bing Shi and Chao Yang and Chenghao Li | [Integrated assessment of middle ear dysfunction in cleft palate patients and optimization of therapeutic schedule] | Hua xi kou qiang yi xue za zhi = Huaxi kouqiang yixue zazhi = West China journal of stomatology | Not intervention of interest |
| 6540371 | S J de Vries and R Wentges | [Ear drum grommets and swimming] | Nederlands tijdschrift voor geneeskunde | Not intervention of interest |
| 10406313 | O C Ilicali and N Keleş and K Değer and I Savaş | Relationship of passive cigarette smoking to otitis media | Archives of otolaryngology--head & neck surgery | Not intervention of interest |
| 9253394 | S M Marcus | Assessing non-consent bias with parallel randomized and nonrandomized clinical trials | Journal of clinical epidemiology | Not intervention of interest |
| 25873182 | Mirjana Kostić and Ksenija Ribarić Jankes and Robert Trotić and Mihael Ries and Branka Ledić and Vladimir Bedeković | Clinical and audiological findings in children with acute otitis media | Acta oto-laryngologica | Not intervention of interest |
| 3701198 | E Vartiainen and J Kärjä and S | Surgery of chronic otitis media in young | The Journal of laryngology and otology | Not intervention |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | Karjalainen | patients | | of interest |
| 962698 | M C Gydé | When the weeping stopped: an otologist views otorrhea and gentamicin | Archives of otolaryngology (Chicago, Ill. : 1960) | Not intervention of interest |
| 14551787 | Elbieta Hassmann and Boena Skotnicka and Maria Baczek and Małgorzata Piszcz | Laser myringotomy in otitis media with effusion: long-term follow-up | European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery | Not intervention of interest |
| 25274185 | A Qureishi and G Garas and A Mallick and D Parker | The psychosocial impact of hearing aids in children with otitis media with effusion | The Journal of laryngology and otology | Not intervention of interest |
| 21362577 | Chang Ho Lee and Chan Kee Yoo and Jong Eui Hong and Hong Joong Kim and Dae Geun Lim and Kwang Joong Kim | Resolved effusion on myringotomy: a study of dry tap without general anesthesia | International journal of pediatric otorhinolaryngology | Not intervention of interest |
| 20058316 | Katrina Spilsbury and Ian Miller and James B Semmens and Francis J Lannigan | Factors associated with developing cholesteatoma: a study of 45,980 children with middle ear disease | The Laryngoscope | Not population of interest |
| 19091429 | Yun Shan Phua and Lesley J Salkeld and Tristan M B de Chalain | Middle ear disease in children with cleft palate: protocols for management | International journal of pediatric otorhinolaryngology | Not population of interest |
| 4470582 | I S Thomson | Exudative otitis media, grommets and cholesteatoma | The Journal of laryngology and otology | Not population of interest |
| 7098686 | H Heumann and E Steinbach and R Seuffer | [A clinical and experimental study on precious metal ventilation tubes (author's transl)] | Laryngologie, Rhinologie, Otologie | Not population of interest |
| | Fujita A. and Kurata K. and Takahashi H. and Takagita S. | Clinical efficacy of clarithromycin treatment of refractory otitis media with effusion | Practica Otologica (1994) 87:9 (1287-1291). Date of Publication: 1994 | Not population of interest |
| 7642987 | H L Tay and R P Mills | Tympanic membrane atelectasis in childhood otitis media with effusion | The Journal of laryngology and otology | Not population of interest |
| 6380828 | C H Bulman and S J Brook and M G Berry | A prospective randomized trial of adenoidectomy vs grommet insertion in the treatment of glue ear | Clinical otolaryngology and allied sciences | Per ear assignment |
| 6598263 | T Lildholdt | Consequences of ventilation tube treatment | Acta oto-laryngologica. Supplementum | Per ear assignment |
| 2037414 | M J Cunningham and E H Harley | Preventing perioperative obstruction of tympanostomy tubes: a prospective trial of a simple method | International journal of pediatric otorhinolaryngology | Per ear assignment |
| 5070299 | D Kilby and S H Richards and G Hart | Grommets and glue ears: two-year results | The Journal of laryngology and otology | Per ear assignment |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 3389234 | A R Maw | Tonsils and adenoids. Their relation to secretory otitis media | Advances in oto-rhino-laryngology | Per ear assignment |
| 9199524 | M Gaihede and T Lildholdt and J Lunding | Sequelae of secretory otitis media: changes in middle ear biomechanics | Acta oto-laryngologica | Per ear assignment |
| 2394020 | A J Parker and A R Maw and J E Powell | Intra-tympanic membrane bleeding after grommet insertion and tympanosclerosis | Clinical otolaryngology and allied sciences | Per ear assignment |
| 3524910 | N Black and J Crowther and A Freeland | The effectiveness of adenoidectomy in the treatment of glue ear: a randomized controlled trial | Clinical otolaryngology and allied sciences | Per ear assignment |
| 21072756 | Paul Hong and Neil Smith and Liane B Johnson and Gerard Corsten | A randomized double-blind controlled trial of phosphorylcholine-coated tympanostomy tube versus standard tympanostomy tube in children with recurrent acute and chronic otitis media | The Laryngoscope | Per ear assignment |
| 2872514 | A R Maw and F Herod | Otoscopic, impedance, and audiometric findings in glue ear treated by adenoidectomy and tonsillectomy. A prospective randomised study | Lancet (London, England) | Per ear assignment |
| 2196954 | N A Black and C F Sanderson and A P Freeland and M P Vessey | A randomised controlled trial of surgery for glue ear | BMJ (Clinical research ed.) | Per ear assignment |
| 1919311 | A R Maw | Development of tympanosclerosis in children with otitis media with effusion and ventilation tubes | The Journal of laryngology and otology | Per ear assignment |
| 650647 | M J Brown and S H Richards and A G Ambegaokar | Grommets and glue ear: a five-year follow up of a controlled trial | Journal of the Royal Society of Medicine | Per ear assignment |
| 3348665 | H R Grant and R E Quiney and D M Mercer and S Lodge | Cleft palate and glue ear | Archives of disease in childhood | Per ear assignment |
| 3243009 | D W Skinner and T H Lesser and S H Richards | A 15 year follow-up of a controlled trial of the use of grommets in glue ear | Clinical otolaryngology and allied sciences | Per ear assignment |
| 16368152 | Uneri C. and Baglam T. and Yazici M. | The effect of Vitamin E treatment on the development of myringosclerosis after ventilation tube insertion | International Journal of Pediatric Otorhinolaryngology (2006) 70:6 (1045-1048). Date of Publication: June 2006 | Per ear assignment |
| 10912691 | Banerjee A.R. and Jennings C. and Marshall J.N. and Narula A.A. | The effect of topical adrenaline on the development of myringosclerosis after tympanostomy tube insertion | American Journal of Otology (2000) 21:4 (482-484). Date of Publication: July 2000 | Per ear assignment |
| 4925501 | Richards S.H. | Grommets and glue ears: A clinical trial | J.Laryng (1971) 85:1 (155-156). Date of Publication: 1971 | Per ear assignment |
| | Coates H. and Chai F. and Oates | The use of surface treated and silver oxide | Australian Journal of Otolaryngology (1998) | Per ear |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | J. | impregnated tympanostomy tubes in reducing post-operative otorrhoea | 3:1 (16-19). Date of Publication: Jan 1998 | assignment |
| 27063749 | Han Zhang and Yaser Alrajhi and Hamdy El-Hakim | Variables associated with repeated ventilation tube insertion in healthy non-syndromic children | May | Retrospective cohort N < 1000 |
| 456299 | M Kremer and L Podoshin and M Fradis | Treatment of serous otitis media with tympanic ventilation tubes | Ear, nose, & throat journal | Retrospective cohort N < 1000 |
| 16214225 | Ingrid Augustsson and Ingemar Engstrand | Hearing loss as a sequel of secretory and acute otitis media as reflected by audiometric screening of Swedish conscripts | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |
| 2845850 | M François and O Laccourreye and J N Margo and V Herman and P Narcy | [Short-term complications of transtympanic aerators] | Annales d'oto-laryngologie et de chirurgie cervico faciale : bulletin de la Société d'oto-laryngologie des hôpitaux de Paris | Retrospective cohort N < 1000 |
| 8470547 | E Manders and J Tyberghein | The effects of ventilation tube placement on hearing, speech, language, cognition and behaviour | Acta oto-rhino-laryngologica Belgica | Retrospective cohort N < 1000 |
| | Walker P. | Persistent perforation following spontaneous extrusion of ventilation tubes in children | Australian Journal of Otolaryngology (2003) 6:1 (18-23). Date of Publication: May 2003 | Retrospective cohort N < 1000 |
| | Somekawa Y. | Ear discharge following insertion of tympanostomy tube | Oto-Rhino-Laryngology Tokyo (1981) 24:6 (23-31+3). Date of Publication: 1981 | Retrospective cohort N < 1000 |
| 26443477 | Richard M Rosenfeld and Krishna Sury and Christopher Mascarinas | Office Insertion of Tympanostomy Tubes without Anesthesia in Young Children | Dec | Retrospective cohort N < 1000 |
| 12567079 | Ron B Mitchell and Ellen Call and James Kelly | Ear, nose and throat disorders in children with Down syndrome | The Laryngoscope | Retrospective cohort N < 1000 |
| 1451676 | S S Hussain | Extrusion rate of Shah and Shepard ventilation tubes in children | Ear, nose, & throat journal | Retrospective cohort N < 1000 |
| 16822553 | Fatma Homood Al Anazy | Iatrogenic cholesteatoma in children with OME in a training program | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |
| 12707661 | M Tayyar Kalcioglu and Yasar Cokkeser and Ahmet Kizilay and Orhan Ozturan | Follow-up of 366 ears after tympanostomy tube insertion: why is it draining? | Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery | Retrospective cohort N < 1000 |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 17970145 | Svetlana Diacova and Thomas J McDonald | A comparison of outcomes following tympanostomy tube placement or conservative measures for management of otitis media with effusion | Ear, nose, & throat journal | Retrospective cohort N < 1000 |
| 15373873 | D S Kim and P L A Moore and T J Rockley | Long-term Paparella II grommet use in the management of persistent childhood otitis media: a 5-year follow-up study | Clinical otolaryngology and allied sciences | Retrospective cohort N < 1000 |
| 6890608 | W M Luxford and J L Sheehy | Myringotomy and ventilation tubes: a report of 1,568 ears | The Laryngoscope | Retrospective cohort N < 1000 |
| 22518157 | Bilal Gani and A J Kinshuck and R Sharma | A review of hearing loss in cleft palate patients | International journal of otolaryngology | Retrospective cohort N < 1000 |
| 7242199 | J H Per-Lee | Long-term middle ear ventilation | The Laryngoscope | Retrospective cohort N < 1000 |
| 8436454 | K S Mangat and G A Morrison and T M Ganniwalla | T-tubes: a retrospective review of 1274 insertions over a 4-year period | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |
| 6874239 | J F Sederberg-Olsen and A E Sederberg-Olsen and A M Jensen | The prognostic significance of the air volume in the middle ear for the tendency to recurrence of secretory middle ear condition | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |
| 3835916 | Y Kawasaki and Y Sakamoto and Y Honmura and T Tatehara and K Miyagawa and Y Urao and J Kanzaki | Long-term results of ventilation tube for otitis media with effusion in children | Auris, nasus, larynx | Retrospective cohort N < 1000 |
| 9118577 | D Strachan and G Hope and M Hussain | Long-term follow-up of children inserted with T-tubes as a primary procedure for otitis media with effusion | Clinical otolaryngology and allied sciences | Retrospective cohort N < 1000 |
| 4809194 | Paradise J.L. and Bluestone C.D. | Early treatment of the universal otitis media of infants with cleft palate | Pediatrics (1974) 53:1 (48-54). Date of Publication: 1974 | Retrospective cohort N < 1000 |
| | Laurikainen E. and Suonpaa J. | Topical use of aminoglycoside ear drops in children with purulent draining ventilation tubes. A follow-up study | Acta Oto-Laryngologica (1984) 98:SUPPL. 412 (103-104). Date of Publication: 1984 | Retrospective cohort N < 1000 |
| | Kowata I. and Kobayashi S. and Onodera A. | Follow-up study of secretory otitis media in children | Otologia Fukuoka (1979) 25:SUPPL. 1 (153-157). Date of Publication: 1979 | Retrospective cohort N < 1000 |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | Ichihara T. and Haginomori S.-I. and Mori A. and Kanazawa A. and Nishikado A. and Kawata R. | Ventilation tube treatment in children with otitis media with effusion | Otolaryngology - Head and Neck Surgery (United States) (2012) 147 SUPPL. 2 (P225). Date of Publication: August 2012 | Retrospective cohort N < 1000 |
| | Boedts D. | Middle ear ventilation and tympanic membrane tube (Dutch) | Tijdschrift voor Geneeskunde (1975) 31:8 (395-397). Date of Publication: 1975 | Retrospective cohort N < 1000 |
| | Gristwood R. | Management of the draining ventilation tube in secretory otitis media | Australian Journal of Otolaryngology (1998) 3:2 (147-148). Date of Publication: 1998 | Retrospective cohort N < 1000 |
| | Meghji S. and Rea P. | Follow-up audit for grommets for persistent otitis media with effusion: Are we follow nice guidelines? | International Journal of Surgery (2013) 11:8 (637). Date of Publication: 2013 | Retrospective cohort N < 1000 |
| 3955712 | F Odehnal and A Tomecková | [Tympanic ventilation tubes in the so-called "glue ear"] | Ceskoslovenská otolaryngologie | Retrospective cohort N < 1000 |
| 4040160 | Y Somekawa and K Kobayashi and T Yamaguchi and K Shimoda and T Suzuki and A Kataura | [Long-term result of grommets in children with secretory otitis media] | Nihon Jibiinkoka Gakkai kaiho | Retrospective cohort N < 1000 |
| 12235880 | Hiroshi Ogawa | [Otitis media with effusion: a study of 346 cases in an outpatient clinic] | Nihon Jibiinkoka Gakkai kaiho | Retrospective cohort N < 1000 |
| 2594453 | M E Pichichero and L R Berghash and A S Hengerer | Anatomic and audiologic sequelae after tympanostomy tube insertion or prolonged antibiotic therapy for otitis media | The Pediatric infectious disease journal | Retrospective cohort N < 1000 |
| 3927225 | M R Klingensmith and M Strauss and G H Conner | A comparison of retention and complication rates of large-bore (Paparella II) and small-bore middle ear ventilating tubes | Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery | Retrospective cohort N < 1000 |
| 16813031 | Stanley Mui and Barry M Rasgon and Raymond L Hilsinger and Brent Lewis and Gretchen Lactao | Tympanostomy tubes for otitis media: quality-of-life improvement for children and parents | Ear, nose, & throat journal | Retrospective cohort N < 1000 |
| 5058477 | S R Mawson and P Fagan | Tympanic effusions in children. Long-term results of treatment by myringotomy, aspiration and indwelling tubes (grommets) | The Journal of laryngology and otology | Retrospective cohort N < 1000 |
| 4041175 | V Svane-Knudsen and T Lildholdt | Sequelae of ventilation tubes following tonsillectomy | Archives of oto-rhino-laryngology | Retrospective cohort N < 1000 |
| 2037413 | B H Matt and R P Miller and R M Meyers and J M Campbell and R T Cotton | Incidence of perforation with Goode T-tube | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 3698323 | J W Curley | Grommet insertion: some basic questions answered | Clinical otolaryngology and allied sciences | Retrospective cohort N < 1000 |
| 955999 | A E Kortekangas and E Virolainen | [Experiences with polyethylene ventilation tubes in children with recurrent middle ear inflammation (author's transl)] | HNO | Retrospective cohort N < 1000 |
| 2631910 | M T Dueñas Polo and J L Pardal Refoyo and A Ramos Macías and F Ruiz Martín and A Cañizo Alvarez | [Transtympanic ventilation tubes and serous otitis media. Study of 100 cases] | Acta otorrinolaringológica española | Retrospective cohort N < 1000 |
| 1867910 | J Vallés Fontanet and X Perramón Montoliu | [The clinical evolution of transtympanic ventilation tubes in serous otitis. A study of 123 cases] | Acta otorrinolaringológica española | Retrospective cohort N < 1000 |
| 6538920 | G Geyer | [The seromucous tympanum] | Laryngologie, Rhinologie, Otologie | Retrospective cohort N < 1000 |
| 7873230 | J A Jiménez Antolín and O Lasso Luis and E Muñoz Platón and M Rodríguez Francos and E Galdeano Granda | [Myringotomy and transtympanic ventilation tubes in secretory otitis media. A study of 108 children] | Acta otorrinolaringológica española | Retrospective cohort N < 1000 |
| 15583925 | V Gudziol and W J Mann | [Otological findings in adults with isolated cleft palate or cleft lip, jaw, and palate] | Mund-, Kiefer- und Gesichtschirurgie : MKG | Retrospective cohort N < 1000 |
| 3618986 | P Canals Ruiz and J L Peris Beaufills and F López Catalá and C Morera Pérez | [Secretory otitis media: surgical treatment and results] | Anales otorrinolaringológicos ibero-americanos | Retrospective cohort N < 1000 |
| 8991399 | J L Lacosta and M Zabaleta and I Erdozain | [The evolution of otitis media with effusion treated by transtympanic drainage] | Acta otorrinolaringológica española | Retrospective cohort N < 1000 |
| 8928639 | C Stenström and L Ingvarsson | Late effects on ear disease in otitis-prone children: a long-term follow-up study | Acta oto-laryngologica | Retrospective cohort N < 1000 |
| 26443477 | Richard M Rosenfeld and Krishna Sury and Christopher Mascarinas | Office Insertion of Tympanostomy Tubes without Anesthesia in Young Children | Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery | Retrospective cohort N < 1000 |
| 5074564 | N Stangeland | [Otosalpingitis--treatment with a polyethylene tube in the ear drum] | Tidsskrift for den Norske lægeforening : tidsskrift for praktisk medicin, ny række | Retrospective cohort N < 1000 |
| 7462026 | J E Hug and C R Pfaltz | [Short- or long-term middle ear ventilation? (author's transl)] | HNO | Retrospective cohort N < |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | | | | 1000 |
| 4636406 | C von Sydow | [Middle-ear drainage in otosalpingitis] | Läkartidningen | Retrospective cohort N < 1000 |
| 10853347 | M Fücsek and M Gábriel | [Long-term results of tube insertion in treating otitis media with effusion] | Orvosi hetilap | Retrospective cohort N < 1000 |
| 3604104 | K Haralampiev and B Kitanoski and B Ristić and M Jaćimović | [Surgical treatment of chronic secretory otitis using aeration-drainage tubes] | Vojnosanitetski pregled | Retrospective cohort N < 1000 |
| 7569388 | J P Dachy and I Evrard | | Revue de laryngologie - otologie - rhinologie | Retrospective cohort N < 1000 |
| 8191069 | F Devars and L Traissac | [Goode's transtympanic drains. Indications and complications] | Revue de laryngologie - otologie - rhinologie | Retrospective cohort N < 1000 |
| 16903334 | Beata Zielnik-Jurkiewicz and Olga Olszewska-Sosińska and Magdalena Rakowska | [Results of treatment with tympanostomy tubes in children with otitis media with effusion] | Otolaryngologia polska = The Polish otolaryngology | Retrospective cohort N < 1000 |
| 9518333 | B Zielnik-Jurkiewicz and J Gutkowska | [Effect of surgical treatment of otitis media with effusion on children. Personal experience] | Otolaryngologia polska = The Polish otolaryngology | Retrospective cohort N < 1000 |
| 156771 | M Wayoff and J P Kocher and C Chobaut and C Simon | [Long-term results of transtympanic drainage] | Journal français d'oto-rhino-laryngologie; audiophonologie, chirurgie maxillo-faciale | Retrospective cohort N < 1000 |
| 4039907 | M Klein | [Presentation and trial of a new medium-duration transtympanic ventilator] | Annales d'oto-laryngologie et de chirurgie cervico faciale : bulletin de la Société d'oto-laryngologie des hôpitaux de Paris | Retrospective cohort N < 1000 |
| 3705232 | J F Sederberg-Olsen and A E Sederberg-Olsen and A M Jensen | [Complications of grommets in specialist practice] | Ugeskrift for laeger | Retrospective cohort N < 1000 |
| 10337163 | S Chodynicki and B Lazarczyk | [The results of treatment of otitis media with suppuration in children by ventilation tubes] | Otolaryngologia polska = The Polish otolaryngology | Retrospective cohort N < 1000 |
| 25554572 | Axel Håkansson and Rut Florentzson and Lisa Tuomi and Caterina Finizia | Transmyringeal ventilation tube treatment in children: hearing outcome after 10 years | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |
| 21846926 | Inessa Fishman and Kevin J Sykes | Demographics and microbiology of | Otolaryngology--head and neck surgery : | Retrospective |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | and Rebecca Horvat and Rangaraj Selvarangan and Jason Newland and Julie L Wei | otorrhea through patent tubes failing ototopical and/or oral antibiotic therapy | official journal of American Academy of Otolaryngology-Head and Neck Surgery | cohort N < 1000 |
| 9119591 | T Saito and E Iwaki and Y Kohno and T Ohtsubo and I Noda and S Mori and T Yamamoto and Y Shibamori and H Saito | Prevention of persistent ear drum perforation after long-term ventilation tube treatment for otitis media with effusion in children | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |
| 16500457 | Frank Hill | The Triune, a new silicone tympanostomy tube | Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery | Retrospective cohort N < 1000 |
| 16230588 | James M Coticchia and Joseph E Dohar | Methicillin-resistant Staphylococcus aureus otorrhea after tympanostomy tube placement | Archives of otolaryngology--head & neck surgery | Retrospective cohort N < 1000 |
| 3835921 | N Yanagihara and T Yagi | Limitation of long term ventilation tube: in view of complications and hearing restoration | Auris, nasus, larynx | Retrospective cohort N < 1000 |
| 26115935 | Mallory B O'Niel and Laura D Cassidy and T Roxanne Link and Joseph E Kerschner | Tracking tympanostomy tube outcomes in pediatric patients with otitis media using an electronic database | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |
| 3835931 | M Sakai and A Shinkawa and S Saito and H Miyake | Late results of hearing in children treated with tympanostomy tube | Auris, nasus, larynx | Retrospective cohort N < 1000 |
| 4843116 | L A Hughes and F R Warder and W R Hudson | Complications of tympanostomy tubes | Archives of otolaryngology (Chicago, Ill. : 1960) | Retrospective cohort N < 1000 |
| 11564294 | Y Talmon and H Gadban and A Samet and P Gilbey and V Letichevsky | Medium-term middle ear ventilation with self-manufactured polyethylene T-tubes for the treatment of children with middle ear effusion | The Journal of laryngology and otology | Retrospective cohort N < 1000 |
| 9853658 | E Iwaki and T Saito and G Tsuda and C Sugimoto and Y Kimura and N Takahashi and K Fujita and H Sunaga and H Saito | Timing for removal of tympanic ventilation tube in children | Auris, nasus, larynx | Retrospective cohort N < 1000 |
| 6685748 | M Ben-Ami and G Rosen and T Shlezinger and S Konack and M Ben-Ami | Otitis media with effusion--complications after treatment | The Journal of laryngology and otology | Retrospective cohort N < 1000 |
| 6778333 | W Draf and P Schulz | Insertion of ventilation tubes into the medical ear: results and complications. A seven-year review | The Annals of otology, rhinology & laryngology. Supplement | Retrospective cohort N < 1000 |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 7192378 | J J Holt and S G Harner | Effects of large-bore middle ear ventilation tubes | Otolaryngology and head and neck surgery | Retrospective cohort N < 1000 |
| 11738691 | Oren Friedman and Ellen S Deutsch and James S Reilly and Steven P Cook | The feasibility of office-based laser-assisted tympanic membrane fenestration with tympanostomy tube insertion: the duPont Hospital experience | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |
| 8588632 | A G Schilder and G A Zielhuis and M P Haggard and P van den Broek | Long-term effects of otitis media with effusion: otomicroscopic findings | The American journal of otology | Retrospective cohort N < 1000 |
| 3915206 | T J Balkany and I K Arenberg and R L Steenerson | Middle ear irrigation during insertion of ventilation tubes | Auris, nasus, larynx | Retrospective cohort N < 1000 |
| 15829063 | Marie Ryding and Peter White and Olof Kalm | Course and long-term outcome of 'refractory' secretory otitis media | The Journal of laryngology and otology | Retrospective cohort N < 1000 |
| 12472518 | P Sheahan and A W Blayney and J N Sheahan and M J Earley | Sequelae of otitis media with effusion among children with cleft lip and/or cleft palate | Clinical otolaryngology and allied sciences | Retrospective cohort N < 1000 |
| 26043589 | Vladimir Djordjević and Bojana Bukurov and Nenad Arsović and Snežana Ješić and Jovica Milovanović and Vladimir Nešić | Long term complications of ventilation tube insertion in children with otitis media with effusion | Vojnosanitetski pregled | Retrospective cohort N < 1000 |
| 3835919 | M Suzuki and K Kodera | Long term follow-up of secretory otitis media in children: the effects of adenotonsillectomy with insertion of a ventilation tube | Auris, nasus, larynx | Retrospective cohort N < 1000 |
| 3189124 | L A Hughes and D Wight | Tympanostomy tubes: long-term effects | American family physician | Retrospective cohort N < 1000 |
| 969088 | D G Pappas | Triflanged tube for chronic serous otitis media | Transactions. Section on Otolaryngology. American Academy of Ophthalmology and Otolaryngology | Retrospective cohort N < 1000 |
| 18225626 | Arthur H Allen | Is i.v. access necessary for myringotomy with tubes? | Ear, nose, & throat journal | Retrospective cohort N < 1000 |
| 3427799 | R W Slack and J M Gardner and C Chatfield | Otorrhoea in children with middle ear ventilation tubes: a comparison of different types of tubes | Clinical otolaryngology and allied sciences | Retrospective cohort N < 1000 |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 6085804 | P Arcand and P Gauthier and G Bilodeau and G Chapados and A Abela and R Desjardins and P P Gagnon and A J Guerguerian | Post-myringotomy care: a prospective study | The Journal of otolaryngology | Retrospective cohort N < 1000 |
| 1011326 | T Palva and E Kokko | Middle ear effusions -- complications of disease and treatment | The Journal of otolaryngology | Retrospective cohort N < 1000 |
| 10994430 | G D Smyth and C C Patterson and S Hall | Tympanostomy tubes: do they significantly benefit the patient? | Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery | Retrospective cohort N < 1000 |
| 2589073 | J F Sederberg-Olsen and A E Sederberg-Olsen and A M Jensen | Late results of treatment with ventilation tubes for secretory otitis media in ENT practice | Acta oto-laryngologica | Retrospective cohort N < 1000 |
| 24735607 | Hye Ran Hong and Tae Su Kim and Jong Woo Chung | Long-term follow-up of otitis media with effusion in children: comparisons between a ventilation tube group and a non-ventilation tube group | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |
| 6682411 | G Pestalozza and G Cusmano and E Tessitore and A Bonelli | Transtympanic drains in the treatment of serous otitis in children; anatomical versus functional long term results | International journal of pediatric otorhinolaryngology | Retrospective cohort N < 1000 |
| 20359098 | Qi Gui and Zhinan Wang and Ping Chen | [Retaining time of tympanic ventilation tube and aural complications] | Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery | Retrospective cohort N < 1000 |
| 23002647 | Ningbo Wang and Enqin Zhang and Chunbo Lan and Wenwen Xiao and Jiabin Liu | [Clinical research of T tube implantation on children with chronic otitis media] | Lin chuang er bi yan hou tou jing wai ke za zhi = Journal of clinical otorhinolaryngology, head, and neck surgery | Retrospective cohort N < 1000 |
| 1874637 | J Mertens and B Schwenk | [Cholesteatoma and chronic tubal middle ear infection in children. A 10 year overview] | HNO | Retrospective cohort N < 1000 |
| 26281253 | Sen Li and Hong Zhang and Yun Wei and Xilei Zhang and Yingru Wu and Jiang Qian and Liang Shen and Zhengjian Zhang | [Clinical comparative study on the treatment characteristics of secretory otitis media between cleft and non-cleft palate patients] | Jun | Retrospective cohort N < 1000 |
| 9055175 | Hui Y. and Park A. and Crysdale W.S. and Forte V. | Ototoxicity from ototopical aminoglycosides | Journal of Otolaryngology (1997) 26:1 (53-56). Date of Publication: February 1997 | Retrospective cohort N < 1000 |
| 6821430 | Leopold D.A. and McCabe B.F. | Factors influencing tympanostomy tube function and extrusion: A study of 1,127 ears | Otolaryngology - Head and Neck Surgery (1980) 88:4 (447-454). Date of Publication: 1980 | Retrospective cohort N < 1000 |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| 26548470 | Gabriella Fekete-Szabó and Fekete Kiss and László Rovó | [Long-term follow-up after tympanostomy tube insertion in children with serous otitis media] | Nov | Retrospective cohort N < 1000 |
| 27067029 | Chii-Yuan Huang and Chuan-Song Wu and Chao-Hsiun Tang and Mao-Che Wang and Ting-Yu Kuo and Tzong-Yang Tu | Palatoplasty decreases the re-insertion rate of middle ear ventilation tube in cleft palate children - A population-based birth cohort study | Apr | Retrospective cohort N < 1000 |
| 6542693 | M Lucić | [Therapy of exudative chronic otitis using ventilating tubes. Results and consequences] | Srpski arhiv za celokupno lekarstvo | Reviewed in abstract only |
| 10377838 | S Sanković and R Dergenc | [Surgical treatment of secretory otitis media: persistent perforation as a rare complication] | Srpski arhiv za celokupno lekarstvo | Reviewed in abstract only |
| 22433702 | | [First experience with the use of tympanostomy for the management of acute otitis media in children] | Vestnik otorinolaringologii | Reviewed in abstract only |
| 21166142 | Elzbieta Hassmann-Poznańska and Artur Goździewski and Małgorzata Piszcz and Hanna Zajaczkiewicz and Bozena Skotnicka | [Influence of tympanic membrane changes on immittance and extended frequency audiometric findings] | Otolaryngologia polska = The Polish otolaryngology | Reviewed in abstract only |
| 7725152 | B Ristić and K Haralampiev and R Filipovski | [Complications in secretory otitis media treated with aeration-drainage tubes] | Srpski arhiv za celokupno lekarstvo | Reviewed in abstract only |
| | Viada J. and Carcamo F. and Carrillo L. | Evaluation of results with middle ear ventilation tubes in treatment of serous otitis | Revista de Otorrinolaringologia y Cirurgia de Cabeza y Cuello (1979) 39:2 (47-55). Date of Publication: 1979 | Reviewed in abstract only |
| | Sanchez T.G. and Ognibene R.Z. and Gondin M. and Bento R.F. | Audiometric findings after ear ventilation tubes extrusion | Revista Brasileira de Otorrinolaringologia (1992) 58:2 (99-102). Date of Publication: 1992 | Reviewed in abstract only |
| | Scherer H. | Transtympanic ventilation of the middle ear by means of tympanic drainage | Praxis Magazin Med. (1995) :3 (44+46). Date of Publication: 1995 | Reviewed in abstract only |
| | Suzuki M. | A long-term follow-up of secretory otitis media in children | Otolaryngology (1984) 56:7 (469-473). Date of Publication: 1984 | Reviewed in abstract only |
| | Neubauer R. and Slama K. | Experience with the use of a ventilation tube STIPULA in the treatment of otitis media chronica secretoria at the ENT department of the masaryk hospital in Usti nad Labem during a 17-year period | Otorinolaryngologie a Foniatrie (2003) 52:2 (65-70). Date of Publication: 2003 | Reviewed in abstract only |
| | Ohnishi T. | Comparative study of middle ear ventilating tubes | Otolaryngology (1980) 52:8 (575-581). Date of Publication: 1980 | Reviewed in abstract only |

| PMID | Author(s) | Title | Journal | Exclusion Reason |
|---|---|---|---|---|
| | Paquelin F. and Doncieux D. and Luboinski B. and Henin J.M. | Continuous transtympanic drainage in children with a non purulent cryptogenetic exudate of the middle ear | ANN.OTO-LARYNG. (1973) 90:9 (565-569). Date of Publication: 1973 | Reviewed in abstract only |
| | Yokoyama T. | Results of tympanostomy tube for children with secretory otitis media | Otolaryngology (1979) 51:9 (655-660). Date of Publication: 1979 | Reviewed in abstract only |
| | Prauzinska M. and Sroczynski J. and Pucher B. and Szydlowski J. | The effectiveness of ventilation tubes treatment in otitis media with effusion in children | Family Medicine and Primary Care Review (2014) 16:3 (277-278). Date of Publication: July-September 2014 | Reviewed in abstract only |
| | Rashid D. and Ahmad B. and Malik S.M. and Rahat Z.M. and Malik K.Z. | Otitis media with effusion-cost effective options | Journal of the College of Physicians and Surgeons Pakistan (2002) 12:5 (274-276). Date of Publication: 2002 | Reviewed in abstract only |
| | Attallah M.S. and Essa A.E. | Common complications following ventilation tube insertion | Indian Journal of Otology (1999) 5:1 (17-20). Date of Publication: 1999 | Reviewed in abstract only |
| | Yagi T. | The long-term result of middle far ventilation tube | Otolaryngology (1985) 57:6 (463-468). Date of Publication: 1985 | Reviewed in abstract only |
| | Bartonkova K. and Janecek D. and Lenert R. | Mean time of insertion of a pressure equalizing tube (PET) | Otorinolaryngologie a Foniatrie (2002) 51:3 (161-164). Date of Publication: 2002 | Reviewed in abstract only |
| | Slapak I. and Hornik P. and Machac J. and Machalova M. and Fryckova A. and Chrobok V. and Vokurka J. and Hybasek I. | Use of a ventilation tube and recurrent otitis media in child age | Otorinolaryngologie a Foniatrie (1999) 48:3 (143-146). Date of Publication: 1999 | Reviewed in abstract only |
| | Hatanaka E. | Results of treatment with large ventilating tubes and grommet tubes in children with middle ear effusion | Otolaryngology (1983) 55:11 (915-919). Date of Publication: 1983 | Reviewed in abstract only |
| | Pospiech L. and Rak J. and Jaworska M. and Klempous J. | Effects of surgical and pharmacological management of otitis media with effusion in children admitted to the Otolaryngology Department of the Medical University of Wroclaw | Przeglad Pediatryczny (2001) 31:3 (215-218). Date of Publication: 2001 | Reviewed in abstract only |
| 20873100 | Elzbieta Hassmann-Poznańska and Artur Goździewski and Małgorzata Piszcz and Bozena Skotnicka | [Long term sequelae of otitis media with effusion during childhood] | Otolaryngologia polska = The Polish otolaryngology | Reviewed in abstract only |
| 26860606 | Yakup Yegin and Mustafa Çelik and Burak Olgun and Hasan Emre Koçak and Fatma Tülin Kayhan | Is ventilation tube insertion necessary in children with otitis media with effusion? | Dec | Reviewed in abstract only |
| 26752135 | Kate J Fitzsimons and Lynn P Copley and Jan H {van der Meulen} and Channa Panagamuwa and Scott A Deacon | Grommet Surgery in Children With Orofacial Clefts in England | Jan | Reviewed in abstract only |

# Appendix C. Study Design

**Table C1. Key Question 1 design**

| Study | Study design | Funding source | Inclusion criteria | Tympanography | Hearing test | Age range (y) | Subgroups | Number of assessments/followup duration (weeks) |
|---|---|---|---|---|---|---|---|---|
| Bernard 1991 1861917 Canada | RCT | Government | middle ear effusion for greater than 3 months | yes | yes | 2.5-7 | Down's syndrome, Cleft palate, Speech/Language disorder, documented immune insufficiency | 5/78 |
| Casselbrant 2009 19819563 1997-2005 U.S. | RCT | Not reported | bilateral middle-ear effusion (MEE) for at least 3 months, unilateral for 6months or longer or unilateral for 3 months after extrusion of a tympanostomy tube | . | | 2-4 | Down's syndrome, Cleft palate, Other craniofacial anomalies | nd/78 |
| Chaudhuri 2006 23120310 India | RCT | Not reported | . | yes | yes | 0-12 | | 2/8 weeks |
| Gates 1987 3683478 4/1980-6/1984 U.S. | RCT | Government/Industry | Middle ear effusion without pain, redness, or bulging of the tympanic membrane | . | yes | 0-8 | | 18/104 |
| Mandel 1992 1565550 11/1981-06/1987 U.S. | RCT | Government/Academic/Hospital | middle ear effusion lasted at least 2 months; middle ear effusion persisting after at least one 14-day abx and pseudoephedrine hydrochloride-maleate syrup; middle ear effusion persisting after at least one 14-day abx and pseudoephedrine hydrochloride-maleate syrup | . | yes | 0.58-12 | excluded Down's syndrome, Other craniofacial anomalies, Pre-existing hearing loss, Speech/Language disorder, cystic fibrosis, DM, seizure, AOM, purulent rhinitis | 36/156 |
| Mandel 1989 2789777a 09/1979- | RCT | Government | documented MEE of at least 2 months' duration; no symptoms consisting of otalgia or vertigo; MEE | . | yes | 0.58-12 | excluded Down's syndrome, Other craniofacial anomalies, asthma, cystic fibrosis, diabetes mellitus, seizure | 36/156 |

| Study | Study design | Funding source | Inclusion criteria | Tympanography | Hearing test | Age range (y) | Subgroups | Number of assessments/followup duration (weeks) |
|---|---|---|---|---|---|---|---|---|
| 09/1984 U.S. | | | persisting after at least one 14-day course of an antimicrobial drug and pseudoephedrine hydrochloride-chlorpheniramine maleate syrup; no symptoms consisting of otalgia or vertigo; MEE persisting after at least one 14-day course of an antimicrobial drug and pseudoephedrine hydrochloride-chlorpheniramine maleate syrup | | | | | |
| Mandel 1989 2789777b 09/1979-09/1984 U.S. | RCT | Government | documented MEE of at least 2 months' duration; no symptoms consisting of otalgia or vertigo; MEE persisting after at least one 14-day course of an antimicrobial drug and pseudoephedrine hydrochloride-chlorpheniramine maleate syrup; no symptoms consisting of otalgia or vertigo; MEE persisting after at least one 14-day course of an antimicrobial drug and pseudoephedrine hydrochloride-chlorpheniramine maleate syrup | . | yes | 0.58-12 | excluded Down's syndrome, Other craniofacial anomalies, asthma, cystic fibrosis, diabetes mellitus, seizure | 36/156 |
| Maw 1999 10459904, Hall-2009-19260880, | RCT | Government | confirmation of bilateral OME by otoscopy; disruptions to speech, language, learning, or behaviour | yes | yes | DOB 4/1/1991-DOB 12/31/1 | | 2/78 |

| Study | Study design | Funding source | Inclusion criteria | Tympanography | Hearing test | Age range (y) | Subgroups | Number of assessments/followup duration (weeks) |
|---|---|---|---|---|---|---|---|---|
| Wilks-2000-10944051 4/1991-12/1992 UK | | | | | | 992 | | |
| MRC Multicentre Otitis Media Study Group 2012 (TARGET) 22443163 15373863 12680834 4/1994-10/1998 UK | RCT | Government | bilateral OME over 12-week watchful waiting period | yes | yes | 3.25-6.75 | excluded History of ear or adenoid surgery | 5/104 |
| Nguyen 2004 15126745 01/1998-01/2003 Canada | RCT | Not reported | OM with effusion persisting for more than 3 months or producing a conductive hearing loss (HL) greater than 30 dB with a type B tympanogram; or 3) both; more than three episodes during the preceding 6-month period or more than four during the preceding 12 month period; first surgical treatment of OM; first surgical treatment of OM | yes | yes | 1.5-18 | excluded Down's syndrome, Other craniofacial anomalies, Primary ciliary dyskinesia, immune deficiency | >=2/52 |
| Paradise 2001 11309632, 2005 16093466, | RCT | Government/Industry | middle ear effusion that appeared substantial in quantity and persisted despite treatment with anti-microbial drugs for 90 days in the case | yes | yes | 0.04-1.17 | | nr/104 |

| Study | Study design | Funding source | Inclusion criteria | Tympanography | Hearing test | Age range (y) | Subgroups | Number of assessments/followup duration (weeks) |
|---|---|---|---|---|---|---|---|---|
| 2003 12897272, 2007 17229952, Johnston2004 15231974 6/1991-12/1995 U.S. | | | of bilateral effusion or 135 days in the case of unilateral effusion.audiometric examinations; audiometric examinations | | | | | |
| Popova 2010 20399511 2007-2009 Bulgaria | RCT | No funding | OME is defined as asymptomatic middle ear effusion without signs of inflammation characteristic of the acute otitis media (AOM). | yes | yes | 3-7 | | 12/52 weeks |
| Rach 1991 2070526 Netherlands | RCT | Government | bilateral flat tympanograms (type B) at two consecutive screenings at any time during the follow-up period | yes | | 2-2 | excluded congenital ear disorders (sensonneural loss) or defects in their speech-producing apparatus (e.g. cleft palate), nehrological or serious visual disorders, emotional aberrations or mental defects | 1/26 |
| Rovers 2000 10969126, 2001 11124783, 2001 11409855, 2001 11470387, Ingels 2005 16429748, Hartman 2001 | RCT | Government | persistent (4–6 months) bilateral OME (confirmed by tympanometry and otoscopy) by the ENT surgeon during subsequent observations | yes | yes | 0-0.75 | excluded Down's syndrome, Cleft palate, schisis, asthma, cystic fibrosis, and sensorineural hearing loss | 3 successive tests; 3 monthly tympanometry and otoscopy measurements, audiometry every 6 months/52 weeks |

| Study | Study design | Funding source | Inclusion criteria | Tympanography | Hearing test | Age range (y) | Subgroups | Number of assessments/followup duration (weeks) |
|---|---|---|---|---|---|---|---|---|
| 11735817 01/1996-04/1997 Netherlands | | | | | | | | |
| Velepic 2011 21397957 2004-2009 Croatia | RCT | No funding | CSOM lasting at least 3 months | . | yes | 2-12 | | >=6/>=26 |
| Vlastos 2011 21205368 5/2007-5/2008 Greece | RCT | Not reported | The diagnosis of OME was based on otoscopy, tympanography and pure tone audiometry. Specifically, the presence of an opaque or thickened tympanic membrane, air–fluid level, or bubbles, or the inability to visualise the incudostapedial joint, were considered signs of OME, in children with a type B tympanogram (compliance <0.2 ml) and an audiogram with an air–bone gap of 20 dB or a hearing loss of 30 dB but no more than 55 dB in at least one frequency in both ears. Absence of the light reflex was not regarded as a specific sign of OME.; Absence of the light reflex was not regarded as a specific sign of OME; Absence of the light reflex was not regarded as a specific sign of OME | yes | yes | 3-7 | | 3/52 weeks |

| Study | Study design | Funding source | Inclusion criteria | Tympanography | Hearing test | Age range (y) | Subgroups | Number of assessments/followup duration (weeks) |
|---|---|---|---|---|---|---|---|---|
| De Beer 2004 15224825 1982-1983 Netherland | NRCS, prospective | Not reported | birth cohort of 1,439 subjects born in 1982 or 1983, chronic OME diagnosed as presence of ventilation tubes had been observed before the screening (0 to 24 months), during the screening at 2 to 4 years of age, in the period between both studies (4 to 8 years), and/or at the examination at 8 years, recurrent AOM diagnosed as parents had reported events of otalgia with fever and/or otorrhea during the screening at to 4 years of age, in the period between both studies (4 to 8 years), and/or at the examination at 8 years | | | | | nr/up to 18 years |
| Grievink 1993 8246466 (Nijmegen Otitis Media study) 9/1982-8/1983 Netherlands | NRCS, prospective | Not reported | . | yes | | | | nr/7 years |
| Hu-2015-26429601 2014 US | NRCS, retrospective | No funding | Conductive hearing loss caused by OME, preoperative audiometry performed no more than one month prior to the surgery, postoperative audiometry completed at two weeks and six to ten weeks following the procedure for | | yes | 1-18 | excluded trisomy 21, mixed hearing loss, congenital cholesteatoma | 3/10 |

| Study | Study design | Funding source | Inclusion criteria | Tympanography | Hearing test | Age range (y) | Subgroups | Number of assessments/followup duration (weeks) |
|---|---|---|---|---|---|---|---|---|
| | | | each patient | | | | | |
| Hubbard 1985 4039792 1/1979-1/1979 U.S. | NRCS, prospective | Not reported | cleft palate, previous myringotomy | . | | 5-11 | included cleft palate | . |
| Kuşcu 2015 26545930 2008-2013 Turkey | NRCS, retrospective | No funding | Patients operated in our university or in other centers and admitted to our university for further follow-up with a follow-up time of at least two years or more after palate reconstruction surgery were included in the study. OME diagnosis was confirmed with pneumatic otoscopy and tympanometry for the study. | yes | yes | | included cleft palate | nr/>=104 |
| Li 2015 26281253a 2002-2012 China | NRCS, retrospective | Government | Patients with adenoid hypertrophy and OME admitted to the hospital during the study period, chronic OME diagnosed based on the diagnostic criteria in the Chinese guideline (tympanography type B or C, difference in air and bone conduction by pure tone hearing test) | yes | yes | | included adenoid hypertrophy | nr/52 |
| Li 2015 26281253b 2002-2012 China | NRCS, retrospective | Government | Patients with cleft palate and OME admitted to the hospital during the study period, chronic OME diagnosed based on the diagnostic criteria in the Chinese guideline (tympanography type B or C, difference in air and bone conduction by pure | yes | yes | | included cleft palate | nr/52 |

| Study | Study design | Funding source | Inclusion criteria | Tympanography | Hearing test | Age range (y) | Subgroups | Number of assessments/followup duration (weeks) |
|---|---|---|---|---|---|---|---|---|
| | | | tone hearing test) | | | | | |
| Niclasen-2016-27063746 1990 Danmark | NRCS, retrospective | No funding | Aarhus Birth Cohort from 1990 and onwards, the primary exposure of the study was two items concerned with parent-reported episodes (4+) of OM and tympanostomy tubes insertion, respectively. | | | 9-11 | | |
| Peters 1994 8195687 8/1982-7/1983 Netherlands | NRCS, prospective | Not reported | . | yes | | | | 364-416 weeks |
| Stenstrom 2005 16330739 1985-1989 Canada | NRCS, prospective | Academic/ Hospital | long-standing middle ear effusion [>3 months | . | yes | 2.5-7 | | 1/56 |
| Yagi 1977 321716 Sudan | NRCS, prospective | Not reported | secretory otitis media; Clinical evidence of fluid in the middle ear in addition to the audiometric findings | . | yes | 3-12 | | nd/6 weeks |
| Yousaf 2012 23855103 6/2008-12/2011 Pakistan | NRCS, prospective | Not reported | X-Ray nasopharynx lateral view was taken to see if there were adenoids. | . | yes | 2-8 | | nd/144 |
| Coyte 2001 11309633 1992-1997 Canada | NRCS, retrospective | Not reported | . | | | 0-19 | | |

| Study | Study design | Funding source | Inclusion criteria | Tympanography | Hearing test | Age range (y) | Subgroups | Number of assessments/followup duration (weeks) |
|---|---|---|---|---|---|---|---|---|
| Forquer 1982 6184891 U.S. | NRCS, retrospective | Not reported | chronic serous otitis media | | | 0-9 | excluded cleft palate, Pre-existing hearing loss, history of mastoiditis or cholesteatoma | . |
| Kadhim 2007 17279052 1981-2004 Australia | NRCS, retrospective | Not reported | . | | | | | |
| Kobayashi 2012 22386274 1996-1999 Japan | NRCS, retrospective | Not reported | . | | | | included cleft palate | every 6 months from 0-6 years of age, annually after 7 years of age |
| Marshak 1980 6778336 Israel | NRCS, retrospective | Not reported | chronic secretory otitis media | | yes | 0-8 | | 4 to 8/104 weeks |
| Motta 2006 17465378 1/1/2001-12/31/2001 Italy | NRCS, retrospective | Not reported | AAP definition (2004): Tympanic mucosa congestion, possibly with exudate, without acute infection; Recurrent febrile episodes related to adenotonsillar inflammation (>=2 episodes in previous 12 months), with OME or AOM. Underwent adenoidectomy; Recurrent febrile episodes related to adenotonsillar inflammation (>=2 episodes in previous 12 months), with OME or AOM. Underwent adenoidectomy | . | | 2-11 | excluded other craniofacial anomalies, genetic syndromes | minimum 104 |
| Reiter 2009 | NRCS, retrosp | Not reported | OME lasting more than 3 months; atelectasis/tympanic | . | yes | 0-14 | included cleft palate | 12/312 |

| Study | Study design | Funding source | Inclusion criteria | Tympanography | Hearing test | Age range (y) | Subgroups | Number of assessments/followup duration (weeks) |
|---|---|---|---|---|---|---|---|---|
| 19929085 Germany | ective | | membrane retraction pockets | | | | | |
| Robson 1992 1431515 1976-1988 UK | NRCS, retrospective | Not reported | operated on by one plastic surgeon for cleft lip, cleft palate or a combination of cleft lip and palate | . | | | included cleft palate | |
| Schilder 1997 9372253 09/1982-08/1983 Netherlands | NRCS, retrospective | Government? | . | yes | | 2-4 | | nd/from 2-4 yo to 7-8 yo |
| Wolter 2012 22883987 1991-2009 Canada | NRCS, retrospective | Not reported | . | | yes | 0.7-17 | included primary ciliary dyskinesia | nr |
| Xu 2003 12930655 09/1997-05/2000 China | NRCS, retrospective | Government | . | yes | | 1.3-10 | included cleft palate | 2/nd |
| Youssef 2013 24265883 03/2007-01/2009 Egypt | NRCS, retrospective | Not reported | bilateral OM, eligible for surgical intervention, no previous myringotomy or TT | yes | | | | nd/52 |

**Table C2. Key Question 2 design**

| Author Year PMID Years of recruitment Country | Design | Number of participants | Age Range (y) | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|---|
| Casselbrant 1992 1565551 3/1981-1/1988 U.S. | RCT | 264 | 0.6, 2.9 | 3 or more episodes of AOM during the preceding 6 months or 4 or more episodes during the preceding 12 months, but free of middle ear effusion at the time of entry | Exclusion criteria: potentially complicating or confounding conditions, e.g. asthma, chronic sinusitis or previous tonsillectomy or adenoidectomy |
| El-Sayed 1996 noPMID Saudi Arabia | RCT | 68 | 0, 3 | >= 3 attacks of acute otitis media diagnosed, documented and treated by their referring physician in the 6 month period prior to referral | |
| Gonzalez 1986 3537596 1/1982-2/1983-12/1983-11/1985 U.S. | RCT | 63 | 0.5, 10 | >= 3 episodes of AOM during the past 6 months, or >=4 episodes in the past 18 months | Exclusion criteria: Down syndrome, cleft palate, previous tympanostomy tubes |
| Grindler 2014 24627408 1/2009-2/2012 U.S. | NRCS, prospective | 1208 | 0.5, 2 | | Exclusion criteria: caregivers unable to provide consent; caregivers unable to complete the survey forms in English |
| Hammarén-Malmi 2005 15995051 03/2001-12/2002 Finland | RCT | | 12 months; ; | . as judged by examination with a pneumatic otoscope; >=3 episodes of acute otitis media during the preceding 6 months or ?5 episodes of acute otitis media during the preceding | excluded cleft palate, asthma, diabetes |

| Author Year PMID Years of recruitment Country | Design | Number of participants | Age Range (y) | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|---|
| Kujala 2012 22466327, 24445832 3/2002-6/2004 Finland | RCT | 300 | 0, 2 | at least 3 AOM episodes during the past 6 months | Exclusion criteria: Cranial abnormalities, chronic otitis media with effusion, a prior adenoidectomy or tympanostomy tubes, documented immunological disorders or ongoing antimicrobial prophylaxis for a disease other than AOM |
| Mattila 2003 12578443 RCT 1996-1999 Finland | RCT | 137 | 0.83, 2 | >3-5 episodes within six months or 4-6 episodes during the last year; a visually abnormal membrane on a flat B-type tympanogram, signs of effusion in the middle ear cavity and symptoms that related to acute otitis | |
| Mattila 2003 12578443 NRCS 1996-1999 Finland | NRCS, prospective | 169 | 0.83, 2 | >3-5 episodes within six months or 4-6 episodes during the last year; a visually abnormal membrane on a flat B-type tympanogram, signs of effusion in the middle ear cavity and symptoms that related to acute otitis | |

**Table C3. Key Question 4 design**

| Author Year PMID Date Country | Study design | Age range (years) | Inclusion criteria | No. assessments/planned duration (weeks) |
|---|---|---|---|---|
| Becker 1987 3586818 4/1985-9/1985 U.S. | NRCS, prospective | | All patients undergoing tympanostomy and insertion of ventilation tubes. Most cases were chronic otitis media with effusion unresponsive to medical management for 3 or more months. Any occasional indication was recurrent acute otitis media. | 0 |
| Cohen 1994 8289048 1990-1992 | NRCS, prospective | 3, 12 | Underwent plastic ventillation tube insertion because of recurrent otitis media or serious otitis media complicated by impared hearing | 78-130 |

| Author Year PMID Date Country | Study design | Age range (years) | Inclusion criteria | No. assessments/planned duration (weeks) |
|---|---|---|---|---|
| Israel | | | | |
| el Silimy 1986 3780019 UK | NRCS, prospective | 4, 14 | Grommets inserted, after myringotomy and aspiration of the middle ear contents, in the anterosuperior quadrant of the tympanic membrane. none | 3/26 |
| Francois-1992-1485779.pdf | NRCS | | Patients getting tubes a minimum of 3 months prior to summer vacation. | nr/12-16 |
| Goldstein 2005 15689760 7/1996-6/1999 U.S. | RCT | 0.5, 6 | Children undergoing tube insertion at the Children's Hospital of Pittsburgh. bilateral myringotomy and tube insertion for recurrent AOM or chronic otitis media with effusion (OME). Exclusion: Children who were immunocompromised (immunodeficiency syndrome, AIDS or HIV-positive status, diabetes mellitus, undergoing chemotherapy, chronic steroid dependence), had a craniofacial syndrome or a history of a cleft palate, or had undergone prior ear surgery except for tympanostomy tube placement | 12/52 |
| Kaufmann 1999 10546304 1/1996-1/1997 Switzerland | NRCS, prospective | 0.23, 0.67 | Got tubes at the same clinic, but by different surgeons. | every 8-12 weeks until tubes extruded |
| Konradsson-1986-3784716.pdf | NRCS (odd-even day assignment) | < 15 | TT placed for chronic secretory otits media or recurrent acute otitis. | nr/24 |
| Parker 1993 8024107 12/1989-2/1991 U.S. | RCT | | Patients with tympanostomy tubes | 4/52 |
| Salata 1996 8607955 U.S. | NRCS, prospective | | Children who were undergoing myringotomy with placement of tympanostomy tubes | every 12 weeks until tubes extruded |
| Sharma 1986 3472335 | NRCS, prospective | 3, 11 | Children with grommets, seen on first followup at 6 weeks. | Until spontaneous |
| Smelt 1984 6538215 UK | NRCS, prospective | 2, 15 | The operations were done by the authors. A Shepard grommet was inserted into the antero-inferior quadrant of the drumhead if myringotomy liberated thick glue or copious thin fluid. This was done either as the only procedure or combined with tonsillectomy or adenotonsillectomy. | every 8 weeks until tubes extruded |

**Table 4. Key Question 5 design**

| Study | Study design | Age range (y) | Inclusion criteria | Exclusion criteria | Assessment times/follow up (weeks) |
|---|---|---|---|---|---|

| Study | Study design | Age range (y) | Inclusion criteria | Exclusion criteria | Assessment times/follow up (weeks) |
|---|---|---|---|---|---|
| Dohar 1999 10326811 | NRCS | 1,12 | Premenarchal if female; had patent TT with mucopurulent otorrhea of presumed bacterial origin for less than 3 weeks | Menarchal, otorrhea for 3 weeks or more | 4 visits over 2.9 weeks |
| Dohar 2006 16880248 5/2003-5/2004 U.S., Finland | RCT | 0.5, 12 | Definition of otorrhea: clinical diagnosis of uncomplicated AOM with otorrhea >3 weeks duration | otorrhea present for ?3 weeks and those with acute or malignant otitis externa. Additional enrollment exclusions included known or suspected fungal or mycobacterial ear infections, a history of or active viral infections of the tympanic membrane, mastoiditis, or infections requiring systemic antibiotic therapy. Patients were also excluded for otologic surgery (except that confined to the tympanic membrane) in the previous year or if they presented with or had a history of diabetes, immunosuppressive disorders, acute or chronic renal disease, active hepatitis, chronic nasal obstruction and/or persistent rhinorrhea, complicating structural abnormalities, known or suspected quinolone hypersensitivity, and, in girls, menarche | 4/3 |
| Goldblatt 1998 10190709 U.S. | RCT | 4+ | recurrent acute otitis media (AOM) | | 4/3 |
| Granath 2008 18565598 Sweden | RCT | < 3 years | TT associated otorrhea in children with rAOM | Craniomaxillar malformation, chromosomal aberration, known immunological deficiency or other severe underlying disease | 24 |
| Heslop 2010 20979100 5/2003-5/2007 Chile | RCT | 0, 10 | secretory otitis media (SOM) for more than 3 months or recurrent acute otitis media (AOM) | non-Caucasians, otorrhea due to other ear diseases other diseases or handicaps, or treatment with systemic or local antibiotics during the preceding 3 weeks, taking topical or systemic steroids or nonsteroidal anti-inflammatory drugs | 1 |
| Roland 2003 14660913 3/2000-2/2001 U.S. | RCT | 0.5, 12 | Definition of otorrhea: clinical diagnosis of acute otitis media with visible otorrhea of 3 weeks duration or less, patent tympanostomy tube | fungal or mycobacterial ear infections, active herpes simplex, vaccinia, varicella, or overt viral infections of the tympanic membrane, mastoiditis or other suppurative noninfectious ear infections, chronic nasal obstruction or persistent rhinorrhea, a prior or current history of immunosuppressive disorders or immunosuppressive therapy, acute renal disorders, active hepatitis, diabetes, or conditions that may predispose to neurosensory hearing loss | 4/3 |

| Study | Study design | Age range (y) | Inclusion criteria | Exclusion criteria | Assessment times/follow up (weeks) |
|---|---|---|---|---|---|
| Roland 2004 14702493 U.S. | RCT | 0.5, 12 | Definition of otorrhea: drainage visible to the parent or guardian of >3 weeks duration | otorrhea had been present for > ?3 weeks, acute or malignant otitis externa, known or suspected fungal or mycobacterial ear infections, a history of or active viral infection of the tympanic membrane, mastoiditis, or infections requiring systemic antibacterial therapy, requirement for otologic surgery (except that confined to the tympanic membrane) in the previous year or when they presented with or had a history of diabetes, immunosuppressive disorders, acute or chronic renal disease, active hepatitis, chronic nasal obstruction and/or persistent rhinorrhea, complicating structural abnormalities, known or suspected quinolone hypersensitivity, and, in girls, menarche. | 4/3 |
| Ruohola 1999 10190921 03/1996-05/1997 Denmark | RCT | 0.5, 12 | Definition of otorrhea: drainage started within 48 hours before examination at the study clinic | Down syndrome, Cleft palate, diabetes mellitus, known immunodeficiency, middle ear granulomatous tissue or polyp, TT or abx in preceding 2 weeks, otorrhea during preceding 4 weeks, steroids use, allergy to penicillin or amoxicillin | 1/2 |
| Ruohola 2003 12728089 09/1998-06/1999 Finland | RCT | 0.6, 6 | Definition of otorrhea: started within 48 hours before recruitment | Down syndrome, Cleft palate, granulation of polyp in the tympanic membrane, immunodeficiency, TT or antibiotics/steroid use in the preceding 2 weeks, TT in the preceding 4 weeks, allergy to penicillin, | 2/3 |
| Strachan 2000 10865480 UK | RCT | | Definition of otorrhea: a degree of discharge from the ear with ventilation tubes in-situ | | 2/3 |
| van Dongen 2014 24552319 25896832 6/2009-5/2012 Netherlands | RCT | 1, 10 | otorrhea that had lasted for up to 7 days | Down syndrome, Cleft palate, craniofacial anomalies, immunodeficiency, temperature >38.5 C, received antibiotics during the previous 2 weeks, TT placed within the previous 2 weeks, had an episode of etorrhea in the previous 4 weeks, >=3 episodes in the previous 6 months, or >=4 episodes in the previous year | 2/26 |

# Appendix D. Arm Details

**Table D1. Key Question 1 arm details**

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| Augustsson 2006 16214225 Sweden | Tympanostomy tubes | . | | | |
| Augustsson 2006 16214225 Sweden | Control (those who were referred to an ENT-department from screening or from other doctors because of ear disease, usually SOM, but never so longstanding that they qualified for treatment with tympanostomy tubes up to 14 years of age) | . | | | |
| Bernard 1991 1861917 Canada | Antibiotic prophylaxis | sulfisoxazole, 75 mg/kg bid, 6 mo. | otomicroscopic findings (redness of the TM, absence of landmarks), acute -onset ear pair w/w/o fever or otorrhea | an oral non-sulfa-based antibiotics (usually amoxicillin) | . |
| Bernard 1991 1861917 Canada | Myringotomy+TT | | discharge from the ear and presence of pathogens commonly associated with AOM | an oral non-sulfa-based antibiotics (usually amoxicillin) | Reuter bobbin VTs for the 1st 10 pts, then Richard "T" VTs |
| Casselbrant 2009 19819563 1997-2005 U.S. | Myringotomy+TT | amoxicillin, 40 mg/kg/day in two divided doses, 10 d. | . | fever, earache or recent onset of ear tugging; and irritability; Otoscopic criteria: erythema and/or white opacification (other than from scarring) of the tympanic membrane, fullness or bulging of the tympanic membrane, white fluid level, and otorrhea from a perforation | Teflon Armstrong-type tympanostomy tube |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| | | | | of a previously intact tympanic membrane. | |
| Casselbrant 2009 19819563 1997-2005 U.S. | TT AND myringotomy AND adenoidectomy | amoxicillin, 40 mg/kg/day in two divided doses, 10 d. | . | fever, earache or recent onset of ear tugging; and irritability; Otoscopic criteria: erythema and/or white opacification (other than from scarring) of the tympanic membrane, fullness or bulging of the tympanic membrane, white fluid level, and otorrhea from a perforation of a previously intact tympanic membrane. | Teflon Armstrong-type tympanostomy tube |
| Casselbrant 2009 19819563 1997-2005 U.S. | Myringotomy AND adenoidectomy | amoxicillin, 40 mg/kg/day in two divided doses, 10 d. | . | fever, earache or recent onset of ear tugging; and irritability; Otoscopic criteria: erythema and/or white opacification (other than from scarring) of the tympanic membrane, fullness or bulging of the tympanic membrane, white fluid level, and otorrhea from a perforation of a previously intact tympanic membrane. | . |
| Chaudhuri 2006 23120310 India | Antibiotic prophylaxis (Amoxicillin + carbocisteine) | Amoxicillin, 125 mg (infants), 250 mg (older children), 2 wks; carbocisteine, 5 | . | | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| | | mL, 2 wks | | | |
| Chaudhuri 2006 23120310 India | TT + myringotomy +/- adenoidectoy (radial myringotomy in antero inferior quadrant of tympanic membrane with insertion of grommet with or without adenoidectomy under general anesthesia) | . | | | grommet |
| Coyte 2001 11309633 1992-1997 Canada | TT (Tympanostomy tubes) | . | | | |
| Coyte 2001 11309633 1992-1997 Canada | TT AND adenoidectomy | . | | | |
| De Beer 2004 15224825 1982-1983 Netherland | TT (Tympanostomy tubes) | | parents had reported events of otalgia with fever and/or otorrhea during the screening at 2 to 4 years of age, in the period between both studies (4 to 8 years), and/or at the examination at 8 years | | |
| De Beer 2004 15224825 1982-1983 Netherland | Control (No Tympanostomy tubes) | | parents had reported events of otalgia with fever and/or otorrhea during the screening at 2 to 4 years of age, in the period between both studies (4 to 8 years), and/or at the examination at 8 years | | |
| | | | | | |
| | | | | | |
| Forquer 1982 6184891 U.S. | Treated medically, then surgically | | . | | collar-button or mesh-type tubes |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| Forquer 1982 6184891 U.S. | Initially treated surgically | | | | collar-button or mesh-type tubes |
| Gates 1985 4040338 (University of Texas Otitis Media Study Center) U.S. | TT (Tympanostomy tubes) | . | | | Shepherd type with an internal opening of 1.1 mm |
| Gates 1985 4040338 (University of Texas Otitis Media Study Center) U.S. | Myringotomy (Myringotomy only) | . | | | |
| Gates 1987 3683478 4/1980-6/1984 U.S. | TT (Tympanostomy tubes) | . | effusion + inflammation | | Shepard-type |
| Gates 1987 3683478 4/1980-6/1984 U.S. | TT AND adenoidectomy | . | effusion + inflammation | | Shepard-type |
| Gates 1987 3683478 4/1980-6/1984 U.S. | Myringotomy (Myringotomy only) | . | effusion + inflammation | | |
| Gates 1987 3683478 4/1980-6/1984 U.S. | Myringotomy AND adenoidectomy | . | effusion + inflammation | | |
| Gates 1988 3336263 | Myringotomy+TT (placement of TT after bilateral myringotomy) | . | | Shepard-type | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| U.S. | | | | | |
| Gates 1988 3336263 U.S. | TT AND myringotomy AND adenoidectomy | . | | Shepard-type | |
| Gates 1989 2492178 U.S. | Myringotomy (Myringotomy only) | erythromycin ethyl succinate. 50 mg/kg, 10 d.; sulfisoxazole, 150 mg/kg, 10 d. | . | | |
| Gates 1989 2492178 U.S. | Myringotomy+TT | erythromycin ethyl succinate. 50 mg/kg, 10 d.; sulfisoxazole, 150 mg/kg, 10 d. | . | | Shepard-type |
| Gates 1989 2492178 U.S. | Myringotomy AND adenoidectomy | erythromycin ethyl succinate. 50 mg/kg, 10 d.; sulfisoxazole, 150 mg/kg, 10 d. | . | | |
| Gates 1989 2492178 U.S. | TT AND myringotomy AND adenoidectomy | erythromycin ethyl succinate. 50 mg/kg, 10 d.; sulfisoxazole, 150 mg/kg, 10 d. | . | | Shepard-type |
| Hammarén-Malmi 2005 15995051 03/2001-12/2002 Finland | TT (Tympanostomy tubes) | . | | antibiotics | |
| Hammarén-Malmi 2005 15995051 03/2001- | TT AND adenoidectomy | . | | antibiotics | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| 12/2002 Finland | | | | | |
| Hu-2015-26429601 2014 US | TT (Tympanostomy tubes) | | | | collar button tube |
| Hu-2015-26429601 2014 US | TT and adenotonsillectomy | | | | collar button tube |
| Hubbard 1985 4039792 1/1979-1/1979 U.S. | Early TT (University center) | . | | | tympanostomy tube |
| Hubbard 1985 4039792 1/1979-1/1979 U.S. | Late TT (Hospital center) | . | | | tympanostomy tube |
| Kadhim 2007 17279052 1981-2004 Australia | TT (Tympanostomy tubes) | . | | | |
| Kadhim 2007 17279052 1981-2004 Australia | TT AND adenoidectomy | . | | | |
| Kobayashi 2012 22386274 1996-1999 Japan | Control (no TT) | . | | | |
| Kobayashi 2012 22386274 1996-1999 Japan | TT (Tympanostomy tubes) | . | | | the Grommet-type ventilation tube (Nagashima, inner diameter 1.0 mm) or the |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| | | | | | Bobbin-type ventilation tube (Koken B type, inner diameter, 1.6 mm) |
| | | | | | |
| | | | | | |
| Kuşcu 2015 26545930 2008-2013 Turkey | Early routine TT (Tympanostomy tubes) | | | | grommet |
| Kuşcu 2015 26545930 2008-2013 Turkey | TT during follow-up | | | | grommet |
| Kuşcu 2015 26545930 2008-2013 Turkey | No TT | | | | |
| Li 2015 26281253a 2002-2012 China | Myringotomy (Myringotomy only) | Cefathiamidine, 30 mg/kg, 5 days | | | |
| Li 2015 26281253a 2002-2012 China | Myringotomy+TT | Cefathiamidine, 30 mg/kg, 5 days | | | |
| Li 2015 26281253b 2002-2012 China | Myringotomy (Myringotomy only) | Cefathiamidine, 30 mg/kg, 5 days | | | |
| Li 2015 26281253b 2002-2012 China | Myringotomy+TT | Cefathiamidine, 30 mg/kg, 5 days | | | |
| Mandel 1989 | Control (unspecified intervantion) | usually amoxicillin, 14 | at least one symptom (fever, otalgia, irritability) | an antimicrobial drug, usually amoxicillin, and a | . |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| 2789777a 09/1979-09/1984 U.S. | | d. | and one sign (bulging or fullness of the tympanic membrane, white fluid level, acute perforation with otorrhea) of acute infection | decongestant-antihistamine combination for 14 days for recurrent OME | |
| Mandel 1989 2789777a 09/1979-09/1984 U.S. | Myringotomy (Myringotomy only) | usually amoxicillin, 14 d. | at least one symptom (fever, otalgia, irritability) and one sign (bulging or fullness of the tympanic membrane, white fluid level, acute perforation with otorrhea) of acute infection | an antimicrobial drug, usually amoxicillin, and a decongestant-antihistamine combination for 14 days for recurrent OME | . |
| Mandel 1989 2789777a 09/1979-09/1984 U.S. | Myringotomy+TT | usually amoxicillin, 14 d. | at least one symptom (fever, otalgia, irritability) and one sign (bulging or fullness of the tympanic membrane, white fluid level, acute perforation with otorrhea) of acute infection | an antimicrobial drug, usually amoxicillin, and a decongestant-antihistamine combination for 14 days for recurrent OME | Teflon Armstrong-type tympanostomy tube |
| Mandel 1989 2789777b 09/1979-09/1984 U.S. | Myringotomy (Myringotomy only) | usually amoxicillin, 14 d. | at least one symptom (fever, otalgia, irritability) and one sign (bulging or fullness of the tympanic membrane, white fluid level, acute perforation with otorrhea) of acute infection | an antimicrobial drug, usually amoxicillin, and a decongestant-antihistamine combination for 14 days for recurrent OME | . |
| Mandel 1989 2789777b 09/1979-09/1984 U.S. | Myringotomy+TT | usually amoxicillin, 14 d. | at least one symptom (fever, otalgia, irritability) and one sign (bulging or fullness of the tympanic membrane, white fluid level, acute perforation with otorrhea) of acute infection | an antimicrobial drug, usually amoxicillin, and a decongestant-antihistamine combination for 14 days for recurrent OME | Teflon Armstrong-type tympanostomy tube |
| Mandel 1992 1565550 11/1981-06/1987 | Watchful waiting (no surgery) | . | at least one symptom (fever, otalgia, irritability), and one sign (bulging or fullness of the tympanic membrane, white fluid | . | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| U.S. | | | level, acute perforation with otorrhea) of acute infection | | |
| Mandel 1992 1565550 11/1981-06/1987 U.S. | Myringotomy (Myringotomy only) | . | at least one symptom (fever, otalgia, irritability), and one sign (bulging or fullness of the tympanic membrane, white fluid level, acute perforation with otorrhea) of acute infection | . | |
| Mandel 1992 1565550 11/1981-06/1987 U.S. | Myringotomy+TT | . | at least one symptom (fever, otalgia, irritability), and one sign (bulging or fullness of the tympanic membrane, white fluid level, acute perforation with otorrhea) of acute infection | . | |
| Marshak 1980 6778336 Israel | TT (Tympanostomy tubes) | . | | | |
| Marshak 1980 6778336 Israel | Myringotomy AND adenoidectomy | . | | | |
| Maw 1999 10459904, Hall-2009-19260880, Wilks-2000-10944051 4/1991-12/1992 UK | TT (Tympanostomy tubes within 6 weeks) | . | confirmation of bilateral OME by otoscopy and tympanometry | . | |
| Maw 1999 10459904, Hall-2009-19260880, Wilks-2000-10944051 | Watchful waiting (for 9 months then tubes if needed) | . | confirmation of bilateral OME by otoscopy and tympanometry | . | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| 4/1991-12/1992 UK | | | | | |
| Motta 2006 17465378 1/1/2001-12/31/2001 Italy | TT AND adenoidectomy | . | | | |
| Motta 2006 17465378 1/1/2001-12/31/2001 Italy | Adenoidectomy (Adenoidectomy only) | . | | | |
| MRC Multicentre Otitis Media Study Group 2012 (TARGET) 22443163 15373863 12680834<br><br>4/1994-10/1998 UK | TT AND adenoidectomy | . | | | Shepard |
| MRC Multicentre Otitis Media Study Group 2012 (TARGET) 22443163, 2004 15373863 4/1994-1/1998 UK | TT (Tympanostomy tubes) | . | | | Shepard |
| MRC Multicentre Otitis Media | Medical Management | | | | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| Study Group 2012 (TARGET) 22443163, 2004 15373863 4/1994-1/1998 UK | | | | | |
| Niclasen-2016-27063746 1990 Danmark | No TT | | | | |
| Niclasen-2016-27063746 1990 Danmark | TT (Tympanostomy tubes) | | | | |
| Nguyen 2004 15126745 01/1998-01/2003 Canada | TT (Tympanostomy tubes) | 10 d. | | | pressure equalization tubes |
| Nguyen 2004 15126745 01/1998-01/2003 Canada | TT AND adenoidectomy | 10 d. | | | pressure equalization tubes |
| Paradise 2001 11309632, 2005 16093466, 2003 12897272, 2007 | Early TT | . | | Antimicrobial drugs were routinely prescribed for episodes of acute otitis media | Armstrong |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| 17229952, Johnston2004 15231974 6/1991-12/1995 U.S. | | | | | |
| Paradise 2001 11309632, 2005 16093466, 2003 12897272, 2007 17229952, Johnston2004 15231974 6/1991-12/1995 U.S. | Late TT (six months later if bilateral effusion persisted or nine months later if unilateral effusion persisted) | . | | Antimicrobial drugs were routinely prescribed for episodes of acute otitis media | Armstrong |
| Paradise 2001 11309632, 2005 16093466, 2003 12897272, 2007 17229952, Johnston2004 15231974 6/1991-12/1995 U.S. | Randomization withheld | . | | | Armstrong (optional tube insertion) |
| Paradise | Not eligible for randomization | . | | . | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| 2001 11309632, 2005 16093466, 2003 12897272, 2007 17229952, Johnston2004 15231974 6/1991-12/1995 U.S. | | | | | |
| Popova 2010 20399511 2007-2009 Bulgaria | TT AND myringotomy AND adenoidectomy | . | Diagnosis of AOM required the finding of middle ear effusion on otoscopy with at least one symptom, i.e., fever, earache or recent ear tugging, irritability and one sign of inflammation, i.e., erythema and/or white opacification of the tympanic membrane, otorrhea from a perforation of a previously intact tympanic membrane. For proper differentiation of otorrhea episodes from AOM episodes we defined otorrhea as mucous or mucopurulent discharge from the ear with no symptoms of acute inflammation. | . | fluoroplastic Donaldson grommets (Micromedics, Inc.) |
| Popova 2010 20399511 | Myringotomy AND adenoidectomy | . | Diagnosis of AOM required the finding of middle ear effusion on otoscopy with | . | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| 2007-2009 Bulgaria | | | at least one symptom, i.e., fever, earache or recent ear tugging, irritability and one sign of inflammation, i.e., erythema and/or white opacification of the tympanic membrane, otorrhea from a perforation of a previously intact tympanic membrane. For proper differentiation of otorrhea episodes from AOM episodes we defined otorrhea as mucous or mucopurulent discharge from the ear with no symptoms of acute inflammation. | | |
| Rach 1991 2070526 Netherlands | TT (Tympanostomy tubes) | . | | silicone ventilating tubes, Donaldson design | . |
| Rach 1991 2070526 Netherlands | Control (unspecified intervantion) | . | | | |
| Reiter 2009 19929085 Germany | palate cleft repair + TT (cleft palate or lip) | . | | | gold grommet |
| Reiter 2009 19929085 Germany | palate cleft repair (cleft palate or lip) | . | | | |
| Robson 1992 1431515 1976-1988 UK | TT (Tympanostomy tubes) | . | | | 10 (26.3%) had long term ventilation tubes ('Goode tubes') |
| Robson 1992 1431515 | Control (conservative treatment) | . | | | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| 1976-1988 UK | | | | | |
| Rovers 2000 10969126, 2001 11124783, 2001 11409855, 2001 11470387, Ingels 2005 16429748, Hartman 2001 11735817 01/1996-04/1997 Netherlands | TT (Tympanostomy tubes; some pts received andenoidectomy, equally distributed) | . | | | Bevel Bobbins, Entermed BV, The Netherlands; grommets |
| Rovers 2000 10969126, 2001 11124783, 2001 11409855, 2001 11470387, Ingels 2005 16429748, Hartman 2001 117358170 1/1996-04/1997 Netherlands | Watchful waiting (no surgery; some pts received andenoidectomy, equally distributed) | . | | | |
| Schilder 1997 | TT | . | | | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| 9372253<br>09/1982-08/1983<br>Netherlands | | | | | |
| Schilder 1997<br>9372253<br>09/1982-08/1983<br>Netherlands | control (no TT) | . | | | |
| Stenstrom 2005<br>16330739<br>1985-1989<br>Canada | TT (Tympanostomy tubes) | . | | | 50 (83%) of 60 patients received T-type VTs |
| Stenstrom 2005<br>16330739<br>1985-1989<br>Canada | Control (medical treatment (low-dose sulfisoxazole for 6 months) | . | | | |
| Velepic 2011<br>21397957<br>2004-2009<br>Croatia | TT AND adenoidectomy | . | | | |
| Velepic 2011<br>21397957<br>2004-2009<br>Croatia | Adenoidectomy (Adenoidectomy only) | . | | | |
| Vlastos 2011<br>21205368<br>5/2007-5/2008<br>Greece | TT AND adenoidectomy | . | | | Shepard type |
| Vlastos 2011 | Myringotomy AND adenoidectomy | . | | | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| 21205368 5/2007-5/2008 Greece | | | | | |
| Wolter 2012 22883987 1991-2009 Canada | TT (Tympanostomy tubes) | . | | | |
| Wolter 2012 22883987 1991-2009 Canada | Treated medically (periodic antibiotics or hearing aids) | . | | | |
| Xu 2003 12930655 09/1997-05/2000 China | palate cleft repair (cleft palate or lip) | . | | | |
| Xu 2003 12930655 09/1997-05/2000 China | palate cleft repair + TT (cleft palate or lip) | . | | | |
| Yagi 1977 321716 Sudan | Adenoidectomy (Adenoidectomy only) | . | | | |
| Yagi 1977 321716 Sudan | TT AND myringotomy AND adenoidectomy | . | | | |
| Yousaf 2012 23855103 6/2008-12/2011 Pakistan | TT (Tympanostomy tubes) | 10 d. | | | |
| Yousaf 2012 23855103 6/2008- | Myringotomy (Myringotomy only) | 10 d. | | | |

| Study | Arm (Description) | Antibiotic name, dose, duration | Diagnostic criteria for AOM | Management of acute infections | Tube type |
|---|---|---|---|---|---|
| 12/2011 Pakistan | | | | | |
| Youssef 2013 24265883 03/2007-01/2009 Egypt | TT + myringotomy +/- adenoidectoy | . | | | |
| Youssef 2013 24265883 03/2007-01/2009 Egypt | Laser myringotomy +/- adenoidectomy | . | | | |

**Table D2. Key Question 2 arm details**

| Study | Arm (description) | Tube type |
|---|---|---|
| Casselbrant 1992 1565551 3/1981-1/1988 U.S. | prophylaxis (Amoxicillin) | |
| Casselbrant 1992 1565551 3/1981-1/1988 U.S. | Tympanostomy tubes | Teflon Armstrong-type |
| El-Sayed 1996 Saudi Arabia | prophylaxis (sulfamethoxazole and trimethoprim) | . |
| El-Sayed 1996 Saudi Arabia | Tympanostomy tubes | |
| Gonzalez 1986 3537596 1/1982-2/1983-12/1983-11/1985 U.S. | prophylaxis (sulfisoxazole) | . |
| Gonzalez 1986 3537596 1/1982-2/1983-12/1983-11/1985 U.S. | Tympanostomy tubes | Paparella |
| Gonzalez 1986 3537596 1/1982-2/1983-12/1983-11/1985 U.S. | no treatment | |
| Grindler 2014 24627408 1/2009-2/2012 U.S. | Tympanostomy tubes | |
| Grindler 2014 24627408 1/2009-2/2012 U.S. | control | |
| Hammaren-Malmi 2005 15995051 | TT | Donaldson silicon |
| Hammaren-Malmi 2005 15995051 | TT & Adenoidectomy | Donaldson silicon |

| Study | Arm (description) | Tube type |
|---|---|---|
| Kujala 2012 22466327, 24445832 3/2002-6/2004 Finland | TT & adenoidectomy | |
| Kujala 2012 22466327, 24445832 3/2002-6/2004 Finland | No treatment | |
| Mattila 2003 12578443 RCT 1996-1999 Finland | TT AND adenoidectomy | |
| Mattila 2003 12578443 RCT 1996-1999 Finland | Tympanostomy tubes | |
| Mattila 2003 12578443 NRCS 1996-1999 Finland | TT AND adenoidectomy | |
| Mattila 2003 12578443 NRCS 1996-1999 Finland | Tympanostomy tubes | |

**Table D3. Key Question 4 arm details**

| Study | Arm | Comments/Notes about interventions |
|---|---|---|
| Becker 1987 3586818 4/1985-9/1985 U.S. | ear plugs | Silicon putty ear plugs: no restrictions on frequency, duration, location or type of swimming |
| Becker 1987 3586818 4/1985-9/1985 U.S. | no ear plugs | no restrictions on frequency, duration, location or type of swimming |
| Becker 1987 3586818 4/1985-9/1985 U.S. | nonswimming | custom-fitted molded ear plugs |
| Cohen 1994 8289048 1990-1992 Israel | swimming | participated in swimming 4-6 times a week; in chlorinated pool water or seawater without restrictions; swimming season lasted April through September; duration of swimming was 1/2-2 hours/day; mandatory use of neomycin-polymyxin-hydrocortizone eardrops at bedtime on the day that the child had been swimming. |
| Cohen 1994 8289048 1990-1992 Israel | nonswimming | |
| el Silimy 1986 3780019 UK | swimming | children swam with ears unprotected on average once every 2 weeks for an average of three-quarters of an hour. This swimming was in Council indoor heated swimming pools |
| el Silimy 1986 3780019 UK | nonswimming | |
| Francois 1992 1485779 France | nonswimming | |
| Francois 1992 1485779 France | swimming | Swam in pool, the Atlantic or Mediteranean |
| Goldstein 2005 15689760 7/1996-6/1999 U.S. | ear plugs | A soft, plastic, prefabricated ear plug (Doc's Proplugs, International Aquatic Trades, Inc., Santa Cruz, CA) or, if their ear canals were too small, with a moldable silicone ear plug (Insta-Putty, Insta-Mold Products, Inc., Oaks, PA). |
| Goldstein 2005 15689760 7/1996-6/1999 U.S. | no ear plugs | |
| Kaufmann 1999 10546304 1/1996-1/1997 Switzerland | ear plugs | ear plugs, bathing caps, and/or water-absorbent padding |

| Study | Arm | Comments/Notes about interventions |
|---|---|---|
| Kaufmann 1999 10546304 1/1996-1/1997 Switzerland | no precautions | |
| Konràdsson 1986 3784716 6/1983-11/1983 Sweden | no precautions | |
| Konràdsson 1986 3784716 6/1983-11/1983 Sweden | ear protection | War cotton wadding in ear(s) and bathing cap when bathing |
| Parker 1993 8024107 12/1989-2/1991 U.S. | swimming | patients were allowed to swim and bathe without precautions |
| Parker 1993 8024107 12/1989-2/1991 U.S. | nonswimming | patients were instructed not to swim or submerge their heads while bathing |
| Salata 1996 8607955 U.S. | no precautions | children who were allowed to swim without ear protection or postexposure medication |
| Salata 1996 8607955 U.S. | ear drops | children who were allowed to swim without any ear protection (on days when they were exposed to water, their parents were to instill three drops of a suspension that contained polymyxin B sulfate, neomycin sulfate, and hydrocortisone into each ear before bedtime) |
| Salata 1996 8607955 U.S. | ear plugs | children who were fitted with prefabricated ear molds and instructed to use the ear molds whenever they were swimming |
| Salata 1996 8607955 U.S. | nonswimming | children who were assigned to groups 1 through 3 but never actually went swimming during the study period |
| Sharma 1986 3472335 UK | swimmers | Swimming in chlorinated pools allowed (6 weeks after TT placed), avoid jumping from a high board and swimming with a cold |
| Sharma 1986 3472335 UK | nonswimmers | No swimming |
| Smelt 1984 6538215 UK | swimming | Surface swimming in a clean, chlorinated, outdoor swimming pool without earplugs or other ear protection. The patients spent about 1 hour swimming in the pool, and diving was prohibited during swimming |
| Smelt 1984 6538215 UK | swimming | Surface swimming in a clean, chlorinated, outdoor swimming pool without earplugs or other ear protection. The patients spent about 1 hour swimming in the pool, and diving was prohibited during swimming |
| Smelt 1984 6538215 UK | nonswimming | |

**Table D4. Key Question 5 arm details**

| Study | Arm | Antibiotic name, dose |
|---|---|---|
| Dohar 1999 10326811 U.S. | antibiotic drop | Ofloxacin, 0.25 ml twice daily, 10 days |
| Dohar 1999 10326811 U.S. | historic controls | at the discretion of the treating physician (not Ofloxacin), , |
| Dohar 1999 10326811 U.S. | current usual treatment | at the discretion of the treating physician (not Ofloxacin), , |
| Dohar 2006 16880248 5/2003-5/2004 U.S., Finland | antibiotic drop | Ciprodex Sterile Otic Suspension, 4 drops twice daily, 7 days |
| Dohar 2006 16880248 5/2003-5/2004 U.S., Finland | oral antibiotic | Augmentin ES-600, 90 mg/kg per day divided every 12 hours, 10 days |
| Goldblatt 1998 10190709 U.S. | antibiotic drop | ofloxacin, 40 mg/kg, 10 days |
| Goldblatt 1998 10190709 U.S. | oral antibiotic | amoxicillin/cavulanate, 0.25 ml, 10 days |
| Granath 2008 18565598 -2/1998-12/2002 Sweden | antibiotic drop | hydrocortisone + oxytetracycline + polymyxine B, NR, 5-7 days |
| Granath 2008 18565598 -2/1998-12/2002 Sweden | antibiotic drop + oral antibiotic | hydrocortisone + oxytetracycline + polymyxine B; amoxicillin, NR, 5-7 days |
| Heslop 2010 20979100 5/2003-5/2007 Chile | oral antibiotic | amoxicillin, 25 to 50 mg/kg/d divided into three daily doses, 1 week |
| Heslop 2010 20979100 5/2003-5/2007 Chile | Saline | |
| Roland 2003 14660913 3/2000-2/2001 U.S. | antibiotic-glucocorticoid drops | Ciprofloxacin, ciprofloxacin 0.3% plus dexamethasone 0.1% otic suspension, 7 days |
| Roland 2003 14660913 3/2000-2/2001 U.S. | antibiotic drop | Ciprofloxacin, ciprofloxacin 0.3% ophthalmic solution, 7 days |
| Roland 2004 14702493 U.S. | antibiotic-glucocorticoid drops | Ciprofloxacin/Dexamethasone, 4 drops twice daily, 7 days |
| Roland 2004 14702493 U.S. | antibiotic drop | Ofloxacin, 5 drops twice daily, 10 days |
| Strachan 2000 10865480 UK | antibiotic-glucocorticoid drops | Otosporin, 3 drops, three times a day, 7-14 days |
| van Dongen 2014 24552319 25896832 6/2009-5/2012 Netherlands | antibiotic-glucocorticoid drops | bacicoline-B, five drops, tid, 7 days |
| van Dongen 2014 24552319 25896832 6/2009-5/2012 Netherlands | oral antibiotic | amoxicillin– clavulanate suspension, 30 mg of amoxicillin and 7.5 mg of clavulanate per kilogram of body weight, 7 days |

# Appendix E. Baseline Characteristics

**Table E1. Key Question 1 baselines**

| Study | Arm | Age (y), mean (range) | Age of onset (y) | Average hearing level mean (SD) | No. of siblings mean (SD) | No. of OME episodes mean | Hearing loss mean | Male gender n/N (%) | Poverty/low SES n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Augustsson 2006 16214225 | TT | | | | | | | 61/61 (100) | | | |
| Augustsson 2006 16214225 | Control | | | | | | | 173/173 (100) | | | |
| Bernard 1991 1861918 | Myringotomy+ TT | 4.7 | | 30.7 | | 2.9 | | 34/60 (56.7) | | | |
| Bernard 1991 1861919 | Antibiotic prophylaxis | 5 | | 29.6 | | 3.0 | | 34/65 (52.3) | | | |
| Casselbrant 2009 19819564 | Myringotomy+ TT | [2, 3.9] | | | | | | 19/32 (59.4) | | | |
| Casselbrant 2009 19819565 | TT AND myringotomy AND adenoidectomy | [2, 3.9] | | | | | | 24/32 (75.0) | | | |
| Casselbrant 2009 19819566 | Myringotomy AND adenoidectomy | [2, 3.9] | | | | | | 22/34 (64.7) | | | |
| Chaudhuri 2006 23120310 | Total | [0, 12] | | | | | | | | | |
| Coyte 2001 11309633 | TT | Median: 2 [IQR 1, 5] | | | | | | 16296/26714 (61) | | | |
| Coyte 2001 11309634 | TT AND adenoidectomy | Median: 4 [IQR 3, 6] | | | | | | 2475/4125 (60) | | | |
| De Beer 2004 15224825 | TT | | | | | | | 24/51 (47) | | | |
| De Beer 2004 15224825 | Control | | | | | | | 63/132 (48) | | | |
| Gates 1989 2492179 | Myringotomy | | 2.3 | | 0.43 (with otitis media) | | | 65/107 (61) | 52/107 (49) | | |
| Gates 1989 2492180 | Myringotomy+ TT | | 2.2 | | 0.48 (with otitis media) | | | 75/129 (58) | 70/129 (54) | | |

| Study | Arm | Age (y), mean (range) | Age of onset (y) | Average hearing level mean (SD) | No. of siblings mean (SD) | No. of OME episodes mean | Hearing loss mean | Male gender n/N (%) | Poverty/low SES n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Gates 1989 2492181 | Myringotomy AND adenoidectomy | | 2.3 | | 0.46 (with otitis media) | | | 77/130 (59) | 73/130 (56) | | |
| Gates 1989 2492182 | TT AND myringotomy AND adenoidectomy | | 2.3 | | 0.49 (with otitis media) | | | 73/125 (58) | 63/125 (50) | | |
| Gates 1988 3336263 | Total | [4, 8] | | | | | | | | | |
| Gates 1988 3336267 | TT AND myringotomy AND adenoidectomy | | | | | | | | | | |
| Gates 1987 3683478 | Myringotomy | 69% 4.0-6.5 | 2.3 | | | | | 65/107 (61) | 52/107 (49) | | |
| Gates 1987 3683479 | TT | 69% 4.0-6.5 | 2.2 | | | | | 75/129 (58) | 70/129 (54) | | |
| Gates 1987 3683480 | Myringotomy AND adenoidectomy | 73% 4.0-6.5 | 2.3 | | | | | 77/130 (59) | 73/130 (56) | | |
| Gates 1987 3683481 | TT AND adenoidectomy | 74% 4.0-6.5 | 2.3 | | | | | 73/125 (58) | 63/125 (50) | | |
| Gates 1985 4040338 | TT | | | | | | | | | | |
| Gates 1985 4040339 | Myringotomy | | | | | | | | | | |
| Grievink 1993 8246466 | Control | 7.75 (2) | | | | | | 80/151 (53%) | | | |
| Grievink 1993 8246466 | TT | -1.9 | | | | | | 23/37 (62.2%) | | | |
| Hall 2009 19260880 | Total | 3 [1.25, 4.67] | | | | | | | | | |
| Hall 2009 19260881 | Early TT | | | | | | | 49/88 (56) | | | |
| Hall 2009 19260882 | Watchful waiting | | | | | | | 44/74 (59) | | | |
| Hammarén-Malmi 2006 | TT | [1, 4] | | | 1.0 (0.9) | | | 56/96 (58.3) | | 48/96 (50.0) | |
| Hammarén-Malmi 2007 | TT AND adenoidectomy | [1, 4] | | | 1.1 (1.0) | | | 51/102 (50.0) | | 56/102 (54.9) | |
| Hu-2015- | Total | [0.83, 10] | | | | | | 20/34 (59) | | | |

| Study | Arm | Age (y), mean (range) | Age of onset (y) | Average hearing level mean (SD) | No. of siblings mean (SD) | No. of OME episodes mean | Hearing loss mean | Male gender n/N (%) | Poverty/low SES n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 26429601 | | | | | | | | | | | |
| Hubbard 1985 4039792 | Early TT | | | | | | | | | | |
| Hubbard 1985 4039793 | Late TT | | | | | | | | | | |
| Kadhim 2007 17279052 | TT (Tympanostomy tubes) | | | | | | | | | | |
| Kadhim 2007 17279052 | TT AND adenoidectomy | | | | | | | | | | |
| Kobayashi 2012 22386275 | TT | | | | | | | | | | |
| Kobayashi 2012 22386276 | Control | | | | | | | | | | |
| Kremer 1979 456299 | Total | [0, >7] | | | | | | 152/243 (62.4) | | | |
| Kuşcu 2015 26545930 | Early routine TT | 6.9 (4.3) | | | | | | 29/67 (43.3) | | | |
| Kuşcu 2015 26545930 | TT at follow-up | 9.1 (3.7) | | | | | | 13/22 (59.1) | | | |
| Kuşcu 2015 26545930 | No TT | 15.8 (8.9) | | | | | | 37/65 (56.9) | | | |
| Li 2015 26281253a 2002-2012 China | Total | 5.9 [3, 14] | | | | | | 109/208 (52.4) | | | |
| Li 2015 26281253b 2002-2012 China | Total | 5.7 [3, 14] | | | | | | 215/319 (67.4) | | | |
| Mandel 1992 1565550 | Watchful waiting | [0.58, 12] | | | | | | 22/35 (62.9) | 16/33 (48.5) | | |
| Mandel 1992 1565550 | Myringotomy | [0.58, 12] | | | | | | 25/39 (64.1) | 22/36 (61.1) | | |
| Mandel 1992 1565550 | Myringotomy+ TT | [0.58, 12] | | | | | | 27/37 (73.0) | 14/35 (40.0) | | |
| Mandel 1989 2789777a | Control | [0.58, 12] | | | | | | 22/29 (75.9) | 11/29 (37.9) | | |
| Mandel 1989 2789777a | Myringotomy | [0.58, 12] | | | | | | 12/27 (44.4) | 6/27 (22.2) | | |
| Mandel 1989 2789777a | Myringotomy+ TT | [0.58, 12] | | | | | | 20/30 (66.7) | 11/30 (36.7) | | |

| Study | Arm | Age (y), mean (range) | Age of onset (y) | Average hearing level mean (SD) | No. of siblings mean (SD) | No. of OME episodes mean | Hearing loss mean | Male gender n/N (%) | Poverty/low SES n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mandel 1989 2789777b | Myringotomy | [0.58, 12] | | | | | | 10/12 (83.3) | 2/12 (16.7) | | |
| Mandel 1989 2789777b | Myringotomy+ TT | [0.58, 12] | | | | | | 9/11 (81.8) | 1/11 (9.1) | | |
| Marshak 1980 6778336 | Total | [0, 8] | | | | | | | | | |
| Maw 1999 10459904, Hall-2009-19260880, Wilks-2000-10944051 | TT | 2.96 (0.84) [1.17, 4.62] | | | 13% 1, 47% 2, 30% >=3 | | | | | 40/88 (47) | |
| Maw 1999 10459904, Hall-2009-19260880, Wilks-2000-10944051 | Watchful waiting | 2.93 (0.87) [1.31, 4.69] | | | 17% 1, 39% 2, 44% >=3 | | | | | 35/72 (49) | |
| Motta 2006 17465378 | Total | 66% <6 [2, 11] | | | | | | 114/193 (59) | | | |
| MRC Multicentre Otitis Media Study Group (TARGET) 22443163 12680834 15373863 | TT AND adenoidectomy | 5.4 (0.86) | | 31.7 (6.4) | | | Mean reported hearing difficulty – RHD (sd) 14.0 (4.2) | 61/128 (48) | 81/125 (65) | 46/115 (40) | 120/120 (100) |
| MRC Multicentre Otitis Media Study Group 22443163 12680834 15373863 | TT | 5.2 (0.85) | | 32.2 (6.0) | | | Mean reported hearing difficulty – RHD (sd) 14.4 (4.1) | 60/126 (48) | 84/126 (67) | 35/110 (32) | 121/123 (98) |
| MRC Multicentre Otitis Media Study Group (TARGET) 22443163 12680834 15373863 | Watchful waiting | 5.2 (0.87) | | 33.5 (6.4) | | | Mean reported hearing difficulty – RHD (sd) 13.6 (4.5) | 62/122 (51) | 82/122 (67) | 29/101 (29) | 110/110 (100) |
| Niclasen-2016-27063746 | No TT | | | | | >= 4 | | 288/569 (50.6) | | Maternal: 250/569 (44.0); paternal | 0-3 years 521/569 |

| Study | Arm | Age (y), mean (range) | Age of onset (y) | Average hearing level mean (SD) | No. of siblings mean (SD) | No. of OME episodes mean | Hearing loss mean | Male gender n/N (%) | Poverty/low SES n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 261/569 (45.8) | (91.5); <3-6 years 558/569 (98.1) |
| Niclasen-2016-27063746 | TT (Tympanostomy tubes) | | | | | >= 4 | | 577/999 (57.8) | | Maternal: 452/999 (45.2); paternal 508/999 (50.9) | 0-3 years 924/999 (92.5); 3-6 years 982/999 (98.3) |
| Nguyen 2004 15126745 | TT | 3.4 [1.5, 9.5] | | | | | | 24/40 (60) | | | |
| Nguyen 2004 15126745 | TT AND adenoidectomy | 4.5 [1.5, 9.5] | | | | | | 13/23 (57) | | | |
| Paradise 2001 11309632, 2005 16093466, 2003 12897272, 2007 17229952, Johnston2004 15231974 | Early TT | | 39.7 % 1, 46.1 % 2, 14.2 % 3 | | | | | 115/204 (56.4) | | | |
| Paradise 2001 11309632, 2005 16093466, 2003 12897272, 2007 17229952, Johnston2004 15231974 | Late TT | | 40.9 % 1, 47.7 % 2, 11.4 % 3 | | | | | 112/193 (58.0) | | | |
| Peters 1994 8195687 | Control | 7.75 (2) | | | | | | 80/151 (53) | | | |
| Peters 1994 8195687 | TT | 7.75 (1.9) | | | | | | 23/37 (62.2) | | | |
| Popova 2010 20399511 | TT AND myringotomy AND adenoidectomy | 5 (1) [3.5, 7.2] | | | | | | 22/42 (52.4) | | 19/42 (45) | 40/42 (95) |

| Study | Arm | Age (y), mean (range) | Age of onset (y) | Average hearing level mean (SD) | No. of siblings mean (SD) | No. of OME episodes mean | Hearing loss mean | Male gender n/N (%) | Poverty/low SES n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Popova 2010 20399511 | Myringotomy AND adenoidectomy | 5.1 (3.8, 6.3) | | | | | | 20/36 (55.6) | | 31/36 (86) | 36/36 (100) |
| Rach 1991 2070526 | TT | [2, 4] | | | | | | | | | |
| Rach 1991 2070526 | Control | [2, 4] | | | | | | | | | |
| Reiter 2009 19929085 | Total | 8.5 (2.2) [0, 14] | | | | | | 28/53 (52.8) | | | |
| Robson 1992 1431515 | TT | 6.3 [2, 13] | | | | | | 22/38 (57.9) | | | |
| Robson 1992 1431515 | Control | 5.2 [0.5, 12] | | | | | | 14/32 (43.8) | | | |
| Rovers 2000 10969126, 2001 11124783, 2001 11409855, 2001 11470387, Ingels 2005 16429748, Hartman 2001 11735817 | Total | 1.62 (1.3) | 0.75 | 44.9 (0.82) best ear | | | | 110/187 (58.8) | | | 49/187 (26.1) |
| Rovers 2000 10969126, 2001 11124783, 2001 11409855, 2001 11470387, Ingels 2005 16429748, Hartman 2001 11735817 | TT | 1.625 (1.7) | 0.75 | 46.4 (1.1) best ear [IQR 44.2, 48.6] | | | | 55/93 (59.1) | | | |
| Rovers 2000 10969126, 2001 11124783, 2001 11409855, 2001 11470387, Ingels 2005 16429748, Hartman 2001 11735817 | Watchful waiting | 1.62 (1.9) | 0.75 | 43.4 (1.2) best ear [IQR 41.0, 45.8] | | | | 55/94 (58.5) | | | |
| Stenstrom 2005 16330739 | Control | 12.3 (3.8) [8, 16] | | | | 3.1 (1.6) | Mean hearing loss at | 14/27 (52) | | 14/27 (52) | 15/27 (56) |

| Study | Arm | Age (y), mean (range) | Age of onset (y) | Average hearing level mean (SD) | No. of siblings mean (SD) | No. of OME episodes mean | Hearing loss mean | Male gender n/N (%) | Poverty/low SES n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | entry into RCT, PTA at 0.5, 1, 2, 4 kHz: mean: 33.4, sd: 11.9 | | | | |
| Stenstrom 2005 16330739 | TT | 11.6 (4.3) [8, 16] | | | | 1.9 (1.8) | Mean hearing loss at entry into RCT, PTA at 0.5, 1, 2, 4 kHz: mean: 28.7, sd: 13 | 23/38 (60) | | 16/38 (42) | 25/38 (66) |
| Velepic 2011 21397957 | TT AND adenoidectomy | 5.56 | | | | | | | | | |
| Velepic 2011 21397957 | Adenoidectomy | 5.44 | | | | | | | | | |
| Vlastos 2011 21205368 | TT AND adenoidectomy | 4.6 (1.1) [3, 7] | | 31.2 (3.9) [21, 39] | | | | 14/25 (56) | | | |
| Vlastos 2011 21205368 | Myringotomy AND adenoidectomy | 4.4 (1.1) [3, 7] | | 32.7 (0.72) [27, 37] | | | | 15/27 (56) | | | |
| Wolter 2012 22883987 | Total | Median: 6 [0.7, 17] | Median: 5.74 | | | | | | | | |
| Xu 2003 12930655 | palate cleft repair | | | 43.9 | | | | | | | |
| Xu 2003 12930655 | palate cleft repair + TT | 4.8 [0.5, 10] | | 35.9 | | | | | | | |
| Yagi 1977 321716 | Total | Median: 6 [3, 12] | | 100% >20dB | | | | | | | |
| Yousaf 2012 23855103 | Total | [2, 8] | | | | | | 38/62 (61.3) | | | |
| Youssef 2013 24265883 | Total | 7.4 (2.0) | | | | | | 44/86 (51.1) | | | |
| Youssef 2013 | TT + | 7.8 (1.5) | | | | | | | | | |

| Study | Arm | Age (y), mean (range) | Age of onset (y) | Average hearing level mean (SD) | No. of siblings mean (SD) | No. of OME episodes mean | Hearing loss mean | Male gender n/N (%) | Poverty/low SES n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 24265883 | myringotomy +/- adenoidectoy | | | | | | | | | | |
| Youssef 2013 24265883 | Laser myringotomy +/- adenoidectomy | 6.9 (2.3) | | | | | | | | | |
| Schilder 1997 9372253 | TT | [2,4 ] | | 14.0 (12.8) | | | | 7/13 (53.8) | | | |
| Schilder 1997 9372253 | control (no TT) | [2,4 ] | | 8.4 (7.7) | | | | 8/14 (57.1) | | | |

**Table E2. Key Question 2 baselines**

| Study | Arm | Age (y), mean (range) | No. of OME episodes, mean | Males n/N (%) | In daycare n/N (%) |
|---|---|---|---|---|---|
| Casselbrant 1992 1565551 | Antibiotic prophylaxis (amoxicilin) | 43.3% 0.58-1.25, 40.0% 1.33-2.08, 16.7% 2.17-3* | | | |
| Casselbrant 1992 1565551 | Placebo | 43.2% 0.58-1.25, 37.5% 1.33-2.08, 19.3% 2.17-3* | | | |
| Casselbrant 1992 1565551 | TT | 45.3% 0.58-1.25, 34.9% 1.33-2.08, 19.8% 2.17-3* | | | |
| El-Sayed 1996 | TT | 1.66 | | 17/31 (48.6) | |
| El-Sayed 1996 | Antibiotic prophylaxis (sulfamethoxazole and trimethoprim) | 1.64 | | | |
| Gonzalez 1986 3537596 | TT | 1.68 | | | |
| Gonzalez 1986 3537596 | Antibiotic prophylaxis (sulfisoxazole) | 1.55 | | | |
| Gonzalez 1986 3537596 | Placebo | 1.39 | | | |
| Grindler 2014 24627408 | Total | 1.23 (0.38) | | 652/1208 (54.0) | 603/1006 (61.2) |
| Hammarén-Malmi 2006 | TT | [1,4] | | 56/96 (58.3) | |
| Hammarén-Malmi 2006 | TT & Adenoidectomy | [1,4] | | 51/102 (50.0) | |
| Kujala 2012 22466327, 24445832 | TT | 1.34 (0.33) | 6.7 | 36/100 (36) | |

| Study | Arm | Age (y), mean (range) | No. of OME episodes, mean | Males n/N (%) | In daycare n/N (%) |
|---|---|---|---|---|---|
| Kujala 2012 22466327, 24445832 | TT & Adenoidectomy | 1.48 (0.36) | 6.3 | 41/100 (41) | |
| Kujala 2012 22466327, 24445832 | Control | 1.33 (0.32) | 6.4 | 48/100 (48) | |
| Mattila 2003 12578443 RCT | Total | 1.42 | 3.5 | 86/137 (62.8) | 35/137 (25.5) |
| Mattila 2003 12578443 RCT | TT + adenoidectomy | 1.39 | 3.5 | 47/74 (64) | 17/74 (22) |
| Mattila 2003 12578443 RCT | TT | 1.45 | 3.4 | 39/63 (62) | 18/63 (27) |
| Mattila 2003 12578443 NRCS | Total | 1.45 | 3.5 | 91/169 (53.8) | 43/169 (25.4) |
| Mattila 2003 12578443 NRCS | TT + adenoidectomy | 1.46 | 3.5 | 64/124 (52) | 31/124 (25) |
| Mattila 2003 12578443 NRCS | TT | 1.44 | 3.5 | 27/45 (60) | 12/45 (27) |

*age given only in % in certain ranges

**Table E3. Key Question 4 baselines**

| Study | Arm | Age (y), mean (range) | Males n/N (%) | Hx of adenoidectomy n/N (%) | Hx of tonsilectomy n/N (%) | Other |
|---|---|---|---|---|---|---|
| Becker 1987 3586818 | nonswimming | 4.9 (1, 14) | 24/30 | | | Sheehy Teflon collar button tubes |
| Becker 1987 3586819 | ear plugs | 6.3 (2, 14) | 17/23 (17) | | | Sheehy Teflon collar button tubes |
| Becker 1987 3586820 | no ear plugs | 5,9 (1.5, 13) | 10/32 (31) | | | Sheehy Teflon collar button tubes |
| Cohen 1994 8289048 | nonswimming | (3, 12) | 11/20 (55) | | | |
| Cohen 1994 8289049 | swimming | (3, 12) | 12/22 (54.5) | | | |
| el Silimy 1986 3780019 | nonswimming | 7 (4, 14) | 24/41 (58.5) | 18/41 (43.9) | 7/41 (17.1) | 16/41 (39%) bilateral grommets |
| el Silimy 1986 3780019 | swimming | 7 (4, 14) | 25/45 (55.6) | 20/45 (44.4) | 7/45 (15.6) | 18/45 (40%) bilateral grommets |
| Francois 1992 1485779. | non-swimming | 5.58 (overall) | | | | |
| Francois 1992 1485779. | swimming | | | | | |

| Study | Arm | Age (y), mean (range) | Males n/N (%) | Hx of adenoidectomy n/N (%) | Hx of tonsilectomy n/N (%) | Other |
|---|---|---|---|---|---|---|
| Goldstein 2005 15689760 | ear plugs | 79%<=3 (0.5, 6)* | 59/103 (57) | 24/103 (23) | | |
| Goldstein 2005 15689760 | no ear plugs | 81%<=3 (0.5, 6)* | 60/98 (61) | 24/98 (24) | | |
| Kaufmann 1999 10546304 | Total | | | 15/86 (18) | 17/86 (20) | |
| Kaufmann 1999 10546305 | no precautions | 5.3 (1.2, 15.6) | 30/47 (63) | | | |
| Kaufmann 1999 10546306 | ear plugs | 5.8 (1.3, 12.3) | 11/16 (67) | | | |
| Konradsson 1986 3784716 | nonswimming | (1, 15) | | nr | nr | |
| Konradsson 1986 3784716 | swimming | | | | | |
| Parker 1993 8024107 | nonswimming | 3.1 (0.58, 9) | | | | |
| Parker 1993 8024107 | swimming | 3.1 (0.25, 8) | | | | |
| Salata 1996 8607955 | Total | 2.67 (0.5, 12) | 238/399 (59.6) | 80/399 (20) | | |
| Salata 1996 8607956 | no precautions | | | | | |
| Salata 1996 8607957 | ear drops | | | | | |
| Salata 1996 8607958 | ear plugs | | | | | |
| Salata 1996 8607959 | nonswimming | | | | | |
| Sharma 1986 3472335 | non-swimmers | nr | nr | | | |
| Sharma 1986 3472335 | swimmers | nr | nr | | | |
| Smelt 1984 6538215 | Total | | | | | 39 had grommet resinsertions |
| Smelt 1984 6538215 | swimming | | | | | |

* age given only in % below/above 3 years

**Table E4. Key Question 5 baselines**

| Study | Arm | Age (y), mean (SD) [range] | No. of previous episodes of otorrhea, mean (range) | Males n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) | Bilateral otorrhea n/N (%) |
|---|---|---|---|---|---|---|---|

| Study | Arm | Age (y), mean (SD) [range] | No. of previous episodes of otorrhea, mean (range) | Males n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) | Bilateral otorrhea n/N (%) |
|---|---|---|---|---|---|---|---|
| Dohar 1999 10326811 | antibiotic drop | 3.6 (2.7) | | 143/89 (62) | | | |
| Dohar 1999 10326811 | historic controls | 3.6 (2.5) | | 309/175 (57) | | | |
| Dohar 1999 10326811 | current usual treatment | 3.7 (2.5) | | 68/45 (67) | | | |
| Dohar 2006 16880248 | antibiotic drop | 59% <2* | | 39/20 (51) | | | 39/5 (13) |
| Dohar 2006 16880248 | oral antibiotic | 56% <2* | | 41/22 (54) | | | 41/11 (27) |
| Goldblatt 1998 10190709 | antibiotic drop | 3.7 (2.46) | | | | | |
| Goldblatt 1998 10190709 | oral antibiotic | 3.5 (2.62, p=0.521) | | | | | |
| Heslop 2010 20979100 | antibiotic drop | 0.9 [0.6-9] (all) | | 40/68 (59) (all) | | | |
| Heslop 2010 20979100 | oral antibiotic | | | | | | |
| Heslop 2010 20979100 | saline rinse | | | | | | |
| Roland 2003 14660913 | antibiotic-glucocorticoid drops | 2.57 (2.54) [0, 12] | | 87/46 (52.9) | | | 87/22 (25.3) |
| Roland 2003 14660913 | antibiotic drop | 2.26 (2.21) [0, 11] | | 80/41 (51.3) | | | 80/14 (17.5) |
| Roland 2004 (14702493, 15195060, Waycaster 2004_no PMID) | antibiotic-glucocorticoid drops | 49.2%<2, 49.8% 2-11, 1.0% >11* | | 297/172 (57.9) | | | |
| Roland 2004 14702493 | antibiotic drop | 49.0%<2, 51.0% 2-11* | | 302/201 (66.6) | | | |
| Ruohola 1999 10190921 | oral antibiotics and glucosteroids | [1.0,10.0] | | 23/14 (61) | | | |
| Ruohola 1999 10190921 | oral antibiotics and palcebo | [1.0,5.8] | | 27/14 (52) | | | |

| Study | Arm | Age (y), mean (SD) [range] | No. of previous episodes of otorrhea, mean (range) | Males n/N (%) | Cigarette smoke exposure n/N (%) | Daycare n/N (%) | Bilateral otorrhea n/N (%) |
|---|---|---|---|---|---|---|---|
| Ruohola 2003 12728089 | oral antibiotic | 2.25 (1.08) | 3.5 (IQR 3, 4.25) | 34/24 (71) | 34/19 (56) | 34/22 (65) | |
| Ruohola 2003 12728089 | oral placebo | 1.75 (0.92) | 3 (IQR 2, 4) | 32/20 (63) | 32/16 (50) | 32/18 (56) | |
| Strachan 2000 10865480 | antibiotic-glucocorticoid drops | 7.3 [2,25] (all) | | | | | |
| Strachan 2000 10865480 | antibiotic-glucocorticoid spray | | | | | | |
| van Dongen 2014 24552319 (25896832) | antibiotic-glucocorticoid drops | 4.6 (2.1) | (0, 5) | 76/50 (66) | 76/13 (17) | 32/29 (91) | 76/14 (18) |
| van Dongen 2014 24552319 (25896832) | oral antibiotic | 4.4 (2.0) | (0, 5) | 77/40 (52) | 77/4 (5) | 33/27 (82) | 77/11 (14) |
| van Dongen 2014 24552319 (25896832) | watchful waiting | 4.4 (2.0) | (0, 3) | 77/43 (56) | 77/9 (12) | 31/25 (81) | 77/13 (17) |

* age given only in % below/above threshold.

# Appendix F. Risk of Bias

**Table F1. Risk of bias, RCTs**

| Study | Random sequence generation | Allocation concealment | Blinding of participants | Blinding of personnel/care providers | Blinding of outcome assessor | Incomplete outcome data | Selective Reporting | Intention-to-treat-analysis | Group similarity at baseline | Co-interventions |
|---|---|---|---|---|---|---|---|---|---|---|
| Bernard 1991 1861917 | Unclear | Unclear | High | High | Low | Low | Unclear | Low | Low | Unclear |
| Casselbrant 2009 19819563 | Unclear | Unclear | High | High | Unclear | High | Unclear | Low | Low | Unclear |
| D'Eredità 2006 16406076 | Unclear | Unclear | High | High | High | Low | High | Low | Unclear | Low |
| Gates 1987 3683478 | Low | Low | High | High | Low | Low | Low | Low | Low | Unclear |
| Mandel 1989 2789777 | Unclear | Unclear | High | High | Unclear | Low | Unclear | High | Low | Unclear |
| Mandel 1992 1565550 | Unclear | Unclear | High | High | High | Low | Unclear | Unclear | Low | Unclear |
| Maw 1999 10459904 | Unclear | Unclear | High | High | High | High | Low | Low | Low | Unclear |
| MRC Multicenter Otitis Media Study Group 2003 12680834 | High | High | High | High | Unclear | High | Unclear | High | Unclear | Unclear |
| MRC Multicentre Otitis Media Study Group 2012 22443163 | High | Unclear | High | High | High | Low | Unclear | Low | Low | Unclear |
| Nguyen 2004 15126745 | Unclear | Unclear | High | High | High | Low | Unclear | Low | Low | Unclear |
| Paradise 2001 11309632 | Low | Low | High | High | High | Low | Low | Low | Low | Unclear |
| Popova 2010 20399511 | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | High | Low | Low |
| Rach 1991 2070526 | High | Unclear | High | High | High | High | Unclear | High | Unclear | High |
| Rovers 2000 10969126 | Unclear | Unclear | High | High | Unclear | Low | Unclear | Low | Low | Low |
| Velepic 2011 21397957 | Unclear | Unclear | High | Unclear | Unclear | Low | Low | Low | Low | Low |
| Vlastos 2011 21205368 | Low | Unclear | High | High | Unclear | High | Low | Low | Low | Low |
| Casselbrant 1992 1565551 | Unclear | Unclear | High | High | High | High | Low | Low | Low | Low |
| El-Sayed 1996 | Unclear | Unclear | High | High | High | Low | Unclear | Low | Low | Low |
| Gonzalez 1986 3537596 | Low | Unclear | High | High | High | Low | Unclear | Low | Low | High |
| Hammaren-Malmi 2005 15995051 | Unclear | Unclear | High | High | Unclear | High | Low | Low | Low | Low |
| Hammarén-Malmi 2005 15995051 | Unclear | Unclear | High | High | Unclear | Low | Unclear | Low | Low | Unclear |
| Kujala 2012 22466327, 24445832 | Low | Low | High | High | High | Low | Low | Low | Low | Unclear |
| Mattila 2003 12578443 | Unclear | Low | High | High | High | Low | Unclear | Low | Low | High |
| Goldstein 2005 15689760 | Unclear | Unclear | High | Unclear | Low | Low | Low | Low | Low | Unclear |
| Parker 1993 8024107 | Low | Unclear | High | Unclear | Unclear | High | Unclear | High | Unclear | Unclear |
| Dohar 2006 16880248 | Low | Low | High | High | Low | Low | Low | Low | Low | Low |
| Goldblatt 1998 10190709 | Low | High | High | High | Low | Low | Low | Low | Low | Low |
| Granath 2008 18565598 | Low | High | High | High | High | Low | Low | Low | Low | Low |
| Heslop 2010 20979100 | Unclear | Low | Low | Low | Low | Unclear | Low | Low | Low | Low |

| Study | Random sequence generation | Allocation concealment | Blinding of participants | Blinding of personnel/care providers | Blinding of outcome assessor | Incomplete outcome data | Selective Reporting | Intention-to-treat-analysis | Group similarity at baseline | Co-interventions |
|---|---|---|---|---|---|---|---|---|---|---|
| Roland 2003 14660913 | Unclear | Unclear | Low | Unclear | Unclear | Low | Low | Low | Low | Low |
| Roland 2004 14702493 | Unclear | Unclear | High | High | Low | High | Low | High | Low | Low |
| Ruohola 1999 10190921 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low | Low |
| Ruohola 2003 12728089 | Low | Low | Low | Low | Low | Low | Unclear | Low | Low | Low |
| Strachan 2000, 10865480 | Low | Low | High | Low | Low | Low | Low | Low | Unclear | Low |
| van Dongen 2014 24552319 | Low | Low | High | High | Low | Low | Low | Low | Low | Unclear |

**Table F2. Risk of bias, NRCSs**

| Study | Is the case definition adequate? | Representativeness of the cases | Selection of Controls | Definition of Controls | Ascertainment of Exposure | Same method of ascertainment for cases and controls | Non-Response rate | Allocation concealment | Dropout rate <20 percent | Blinded patient | Blinded outcome assessment | ITT | Appt. statistical analysis | If multicenter, was this accounted for in analysis? | Were potential confounders properly accounted for? | Clear reporting with no discrepancies | Were eligibility criteria clear? | Was selection bias likely? | Were interventions adequately described? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Li 2015 26281253 | Yes | Potential for selection biases or not stated | Hospital controls | No TT, no accumulation of fluid or serous fluid in the middle ear | No description | Yes | Non respondents described | | No | No | No | NA | No | | No | No | Yes | No | Yes |
| Tian 2015 26103659 | Yes | Potential for selection biases or not stated | Hospital controls | no TT | Surgical records | Yes | Non respondents described | | Not reported | No | No | NA | No | | No | Yes | Yes | No | No |
| Coyte 2001 11309633 | Yes | Potential for selection biases or not stated | Hospital controls | TT only | Written self report or medical record only | Yes | Same rate for both groups | Na | Yes | No | No | No | Yes | No | Yes | Yes | Yes | No | Yes |
| De Beer 2004 15224825 | Yes | Birth cohort | OM score | OM+ highest tercile, not treated with TT | Prospective cohort | Yes | Low | | | | | | Yes | No | Yes | Yes | Yes | No | Yes |
| Forquer 1982 6184891 | Unsure | Potential for selection biases or not stated | Hospital controls | Medical treatment (underwent medical treatment but not surgery for VT insertion) | Written self report or medical record only | Yes | Same rate for both groups | Na | Yes | No | No | No | No | Na | No | No | Yes | Yes | No |
| Grievink 1993 8246466 | Yes | Consecutive or obviously representative series of cases* | Community controls* | OME but no TT | Written self report or medical record | Yes | Rate different and no designation | Na | No | No | No | No | Yes | Na | Yes | Yes | Yes | Yes | Yes |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | only | | | | | | | | | | | | | | |
| Hu 2015 26429601 | | Potential for selection biases or not stated | Hospital controls | TT only | Medical record review | Yes | | | | | | | Unlcear | | No | Yes | Yes | Yes | Yes |
| Hubbard 1985 4039792 | Unsure | Potential for selection biases or not stated | No description | No description of source | No description | Yes | Same rate for both groups* | Na | Yes | No | No | Yes | Yes | Yes | Yes | No | No | No | Yes |
| Kadhim 2007 17279052 | No | Potential for selection biases or not stated | Hospital controls | TT | Written self report or medical record only | Yes | Same rate for both groups | Na | No | No | No | No | Yes | Na | Yes | Yes | No | No | Yes |
| Kobayashi 2012 22386274 | Yes | Potential for selection biases or not stated | Hospital controls | no TT | No description | unclear | Non respondents described | Na | Yes | No | No | No | Yes | Na | No | Yes | No | Yes | No |
| Kuşcu-2015-26545930.pdf | Yes | Potential for selection biases or not stated | Hospital controls | Late TT, never TT insertion | Medical record review | Yes | Unclear | | | | | | No | | No | Yes | Yes | Unclear | Yes |
| Marshak 1980 6778336 | Yes | Potential for selection biases or not stated | No description | No description of source | No description | Yes | Same rate for both groups* | No | No | No | No | No | Yes | Na | Nd | No | No | No | No |
| Motta 2006 17465378 | Yes | Consecutive or obviously representative series of cases* | Community controls (Appropriate controls) | No TT, otherwise same surgery | Secure record (eg surgical records)* | Yes | | | | | | | No | No | No | Yes | Yes | No | No |
| Niclasen 2016 27063746 | No | Parent report. Unclear defiinition of OM | Self report | 4+ incidences of OM without TT | Parental report | Yes | Unclear | | | | | | | | Yes | Yes | No | Unclear | No |
| Peters 1994 8195687 | Yes | Consecutive or obviously representative series of cases* | Community controls* | OME but no TT | | unclear | | Na | No | No | Nd | No | No | Na | No | No | Yes | Yes | No |
| Reiter 2009 19929085 | Yes | Consecutive or obviously representative series of cases* | Hospital controls | no TT | Written self report or medical record only (Case notes) | Yes | Same rate for both groups* | Na | Yes | No | Nd | Na | No | Na | No | Yes | Yes | Yes | No |
| Robson 1992 1431515 | Yes | Potential for selection biases or not stated | Hospital controls | No tubes (Undergone surgery for cleft palate but did not have tubes inserted) | Written self report or medical record only (Case notes) | Yes | Same rate for both groups* | Na | Yes | No | No | Nd | No | Na | No | No | Yes | Yes | Yes |
| Schilder 1997 9372253 | Yes | Consecutive or obviously representative series of cases* | No description | no TT | | unclear | unknown relative non-response rate | Na | unclear | No | Nd | Yes | No | unclear | Yes | Yes | Yes | no | No |
| Stenstrom 2005 16330739 | Yes | Potential for selection biases or | Hospital controls | medical treatment (underwent | based off an RCT | Yes | Same rate for both groups* | Nd | No | Nd | Yes | No | Yes | Na | Yes | Yes | Yes | Yes | Yes |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | not stated | | medical treatment but not surgery for VT insertion) | | | | | | | | | | | | | | | |
| Wolter 2012 22883987 | No | Potential for selection biases or not stated | Hospital controls | no TT | | Yes | Same rate for both groups* | No | Yes | No | No | Nd | No | Na | No | No | No | Yes | No |
| Xu 2003 12930655 | No | Potential for selection biases or not stated | Hospital controls | no TT | | no description | Same rate for both groups* | Na | unclear | No | Nd | Yes | No | Na | No | Yes | No | Yes | No |
| Xu 2003 12930655 | No | Potential for selection biases or not stated | Hospital controls | no TT | No description | no description | Non respondents decribed | Not Applicable | No | No | Unclear | Yes | | | No | Yes | No | Yes | No |
| Yagi 1977 321716 | Yes | Potential for selection biases or not stated | Hospital controls | no TT (only adenoidectomy) | | unclear | Same rate for both groups* | Na | Yes | No | No | Yes | No | Na | No | Yes | Yes | Yes | Yes |
| Yousaf 2012 23855103 | Yes | Potential for selection biases or not stated | No description | No TT (medical management) | | unclear | Same rate for both groups* | Na | No | Nd | Nd | No | No | Na | No | Yes | Yes | No | No |
| Youssef 2013 24265883 | Yes | Potential for selection biases or not stated | Hospital controls | no TT | | unclear | Non respondents described | Na | Yes | No | Nd | Nd | No | Na | No | Yes | Yes | Yes | Yes |
| Grindler 2014 24627408 | No | Potential for selection biases or not stated | Hospital controls | no TT insertion | Secure record)* | Yes | unknown relative non-response rate | Not Applicable | Not Applicable | No | No | No | Yes | No | Yes | No | Yes | No | Yes |
| Becker 1987 3586818 | Yes | Potential for selection biases or not stated | parental choice | Parental choice | Written self report or medical record only | Yes | unknown relative non-response rate | Not Applicable | No | No | No | No analysis done. | Not Applicable | Not Applicable | Yes | Yes | Yes | Yes | No |
| Cohen 1994 8289048 | Yes | Potential for selection biases or not stated | same cohort of tubes | same cohort of tubes, but nonswimmers | Written self report or medical record only | Yes | Same rate for both groups* | Not Applicable | Yes | No | No | No analysis done. | Not Applicable | Not Applicable | Yes | Yes | No | Yes | No |
| el Silimy 1986 3780019 | Yes | Potential for selection biases or not stated | same surgical cohort | nonswimmers | Written self report or medical record only | Yes | Same rate for both groups* | Not Applicable | Yes | No | No | No analysis done. | Not Applicable | Not Applicable | Yes | Yes | No | Yes | Yes |
| Francois 1992 1485779 | | Potential for selection biases or not stated | Parental and patient choice - observational only | Children who did not swim | Parental retrospective report | Yes | Unknown relative non-response rate | | | | | | Yes | No | No | Yes | No | Yes | No |
| Kaufmann 1999 10546304 | Yes | Consecutive or obviously representative series of cases* | same cohort | no water protection | Written self report or medical record only | Yes | Same rate for both groups* | Yes | No | No | Yes | Yes | Not Applicable | Yes | Yes | Yes | No | Yes | Yes |
| Konradsson 1986 3784716 | Yes | Even-odd randomization | Same surgical cohort | Children not given intructions to avoid swimming | Unclear | Yes | 11% | No | Yes | No | No | Unclear | No | | No | No | Yes | Yes | No |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Salata 1996 8607955 | Yes | Consecutive or obviously representati ve series of cases* | parent selection | recieved differnt prophylaxis | Written self report or medical record only | Yes | unknown relative non-response rate | Not Appl ica ble | No | No | No | Yes | Yes | Yes | Yes | Yes | uncle ar - high dropo ut | Yes | Yes |
| Sharma 1986 3472335 | Yes | Parental choice | Parental choice | Chldren whose parents chose to let them swim | Unclear | Yes | Unclear | | | | | | No | | No | No | Yes | Yes | No |
| Smelt 1984 6538215 | Yes | unclear | same surgical cohort | nonswimmers | Written self report or medical record only | Yes | unclear | Not Appl ica ble | No | No | Unclear | Not App iica ble | No | No | No | No | No | No | No |
| Dohar 1999 10326811 | Yes | Consecutive or obviously representati ve series of cases* | Hospital controls | historical and concurrent with the same dx | Secure record (eg surgical records)* | Yes | Same rate for both groups* | Not Appl ica ble | No | No | No | No | No | No | No | Yes | Yes | Yes | No |

# Appendix G. Patient-Centered and Quality of Life Outcomes

**Table G1. Patient-centered and quality of life outcomes**

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| *Paradise, 2001, 2003, 2004, 2005, 2007* | 11309632, 16093466, 12897272, 17229952, 15231974, 12690269 | 3 years | early treatment | 206 | cognitive | McCarthy General Cognitive index | delayed | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | delayed | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 3 years | early treatment | 206 | verbal | McCarthy Verbal Subscale | delayed | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | delayed | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 3 years | early treatment | 206 | cognitive | McCarthy Perceptual Performance Subscale | delayed | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | delayed | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 3 years | early treatment | 206 | cognitive | McCarthy Quantitative Subscale | delayed | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | delayed | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 3 years | early treatment | 206 | verbal | Peabody Picture Vocabulary Test–Revised | neither | | NS |
| | | | delayed | 196 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | treatment | | | | | | |
| | | 4 years | early treatment | 202-204 | | | delayed | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 3 years | early treatment | 206 | verbal | Number of Different Words | delayed | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | delayed | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | early | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 3 years | early treatment | 206 | verbal | Mean Length of Utterance in Morphemes | delayed | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | neither | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | early | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | 3 years | early treatment | 206 | verbal | Percentage of Consonants Correct–Revised | delayed | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | delayed | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 4 years | early treatment | 202-204 | verbal | Nonword repetition test | delayed | -3.4 (-6.2, -0.7) | <0.05 |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | delayed | -2 (-4.1, 0.1) | <0.05 |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 3 years | early treatment | 206 | QOL | Parenting Stress Index - parental distress subscale | delayed | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | delayed | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | 3 years | early treatment | 206 | QOL | Parenting Stress Index - parent-child dysfunction subscale | neither | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 3 years | early treatment | 206 | QOL | Parenting Stress Index - difficult child subscale | delayed | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | delayed | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 3 years | early treatment | 206 | QOL | Parenting Stress Index - total stress | delayed | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | neither | | NS |
| | | | delayed treatment | 194 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 3 years | early treatment | 206 | Behavior | Child Behavior Checklist - anxious/depressed scale | neither | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 3 years | early treatment | 206 | Behavior | Child Behavior Checklist - withdrawn scale | early | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | early | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 3 years | early treatment | 206 | Behavior | Child Behavior Checklist - sleep problems scale | neither | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 3 years | early treatment | 206 | Behavior | Child Behavior Checklist - somatic problems scale | early | | NS |
| | | | delayed | 196 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | treatment | | | | | | |
| | | 4 years | early treatment | 202-204 | | | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 3 years | early treatment | 206 | Behavior | Child Behavior Checklist - aggression scale | early | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | early | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 3 years | early treatment | 206 | Behavior | Child Behavior Checklist - delinquent/destructive scale | early | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | early | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for | 233 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | randomization | | | | | | |
| | | 3 years | early treatment | 206 | Behavior | Child Behavior Checklist - total problems | early | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | 4 years | early treatment | 202-204 | | | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 9-11 years | early treatment | 194 | | | early | 2 (0.1, 4.8) | <0.05 |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 4 years | early treatment | 202-204 | Behavior | Child Behavior Checklist - social problems | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 4 years | early treatment | 202-204 | Behavior | Child Behavior Checklist - thought problems | early | | NS |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 4 years | early treatment | 202-204 | Behavior | Child Behavior Checklist - attention | early | | NS |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | problems | | | |
| | | | delayed treatment | 193 | | | | | |
| | | 6 years | early treatment | 201 | | | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 6 years | early treatment | 201 | verbal | Screening Test for Auditory Processing Disorders | delayed | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 6 years | early treatment | 201 | cognitive | Wechsler Intelligence Scale for Children - full scale IQ | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 9-11 years | early treatment | 195 | | | not eligible | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 6 years | early treatment | 201 | cognitive | Wechsler Intelligence Scale for Children - Verbal IQ | neither | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization | 101 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | consent withheld | | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 6 years | early treatment | 201 | cognitive | Wechsler Intelligence Scale for Children - Performance IQ | delayed | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 101 | | | | | |
| | | | not eligible for randomization | 233 | | | | | |
| | | 9-11 years | early treatment | 195 | cognitive | Woodcock Reading Mastery Tests, revised, normative updated version - word identification subtest | delayed/not eligible | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 195 | cognitive | Woodcock Reading Mastery Tests, revised, normative updated version - word attack subtest | delayed/not eligible | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 195 | cognitive | Woodcock Reading Mastery Tests, revised, normative updated version - passage comprehension subtest | delayed/not eligible | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | grade 3 (9) | early treatment | 37 | verbal | Oral Reading Fluency Test | delayed | | NS |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | delayed treatment | 37 | | | | | |
| | | | randomization consent withheld | 28 | | | | | |
| | | | not eligible for randomization | 2 | | | | | |
| | | grade 4 (9-10) | early treatment | 87 | verbal | Oral Reading Fluency Test | not eligible | 20 (compared to rct both arms the same); -17 (compared to randomization consent withheld) | <0.05 |
| | | | delayed treatment | 97 | | | | | |
| | | | randomization consent withheld | 63 | | | | | |
| | | | not eligible for randomization | 81 | | | | | |
| | | grade 5 (10-11) | early treatment | 54 | verbal | Oral Reading Fluency Test | delayed/not eligible | | NS |
| | | | delayed treatment | 51 | | | | | |
| | | | randomization consent withheld | 29 | | | | | |
| | | | not eligible for randomization | 115 | | | | | |
| | | grade 6 (11) | early treatment | 12 | verbal | Oral Reading Fluency Test | early/not eligible | | NS |
| | | | delayed treatment | 9 | | | | | |
| | | | randomization consent withheld | 5 | | | | | |
| | | | not eligible for randomization | 24 | | | | | |
| | | 9-11 years | early treatment | 194 | cognitive | Woodcock-Johnson III Tests of Achievement, Standard Battery -- spelling subtest | not eligible | 5 (compared to early/randomization withheld); -4 (compared to late) | <0.05 |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 192 | cognitive | Woodcock-Johnson III Tests of Achievement, Standard Battery -- writing samples subtest | delayed/not eligible | | NS |
| | | | delayed treatment | 195 | | | | | |
| | | | randomization consent withheld | 125 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 194 | cognitive | Woodcock-Johnson III Tests of Achievement, Standard Battery -- calculation subtest | not eligible | | NS |
| | | | delayed treatment | 195 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 195 | verbal | Comprehensive Test of Phonologial Processing - Elision subtest | delayed/not eligible | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 195 | verbal | Comprehensive Test of Phonologial Processing - Rapid Letter Naming subtest | delayed/not eligible | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 195 | verbal | Children's Version of the Hearing in Noise Test - competing noise from the front | early | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 195 | verbal | Children's Version of the Hearing in Noise Test - competing noise from the right | randomization consent witheld | 1.4 (compared to not eligible) | <0.05 |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 195 | verbal | Children's Version of the Hearing in Noise Test - competing noise from the left | early | 0.8 (compared to not eligible) | <0.05 |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 194 | Behavior | Disruptive Behavior Disorders Rating Scale - inattention factor | early | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 126 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 194 | Behavior | Disruptive Behavior Disorders Rating Scale - impulsitivity and | early | 0.20 (compared to not eligible) | <0.05 |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | overactivity factor | | | |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 126 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 194 | Behavior | Disruptive Behavior Disorders Rating Scale - oppositional defiant factor | early/randomization withheld | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 126 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 194 | cognitive | Impairment Rating Scales - Overall functioning | early | 0.18 (compared to not eligible) | <0.05 |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 194 | Behavior | Social Skills Rating System | delayed/not eligible | | NS |
| | | | delayed treatment | 194 | | | | | |
| | | | randomization consent withheld | 126 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 195 | cognitive | Visual Continuous Performance Test - Inattention | early/randomization withheld | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | 9-11 years | early treatment | 195 | cognitive | Visual Continuous Performance Test - Impulsivity | early/randomization withheld | | NS |
| | | | delayed treatment | 196 | | | | | |
| | | | randomization consent withheld | 127 | | | | | |
| | | | not eligible for randomization | 223 | | | | | |
| | | 9-11 years | early treatment | 155 | verbal | Auditory Continuous Performance Test - Inattention | delayed/randomization withheld | | NS |
| | | | delayed treatment | 153 | | | | | |
| | | | randomization consent withheld | 100 | | | | | |
| | | | not eligible for randomization | 128 | | | | | |
| | | 9-11 years | early treatment | 155 | verbal | Auditory Continuous Performance Test - Inattention | delayed | | NS |
| | | | delayed treatment | 153 | | | | | |
| | | | randomization consent withheld | 100 | | | | | |
| | | | not eligible for randomization | 128 | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |
| *Rach 1991* | 2070526 | ND | TT | 22 | verbal | verbal comprehension score | TT | | NS |
| | | | control | 21 | | | | | |
| | | | TT | 21 | verbal | verbal expression score | TT | | NS |
| | | | control | 20 | | | | | |
| *Schilder 1997* | 9372253 | 2-4 years | TT | 13 | verbal | language measures: word forms production | TT | 26.4 (SD 0.92) | P=0.03 |
| | | | control | 14 | | | | | |
| | | 2-4 years | TT | 13 | verbal | language measures: concealed meaning | TT | | NS |
| | | | control | 14 | | | | | |
| | | 2-4 years | TT | 13 | verbal | language measures: phonemic segmentation | TT | | NS |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | control | 14 | | | | | |
| | | 2-4 years | TT | 13 | verbal | language measures: sound blending | control | | NS |
| | | | control | 14 | | | | | |
| | | 2-4 years | TT | 13 | verbal | language measures: auditory discrimination | TT | 0.08 (SD 0.03) | P=0.03 |
| | | | control | 14 | | | | | |
| *Rovers 2000* | 10969126 | 0.5 years | TT | 93 | verbal | Reynell test (comprehensive language development) | watchful waiting | | NS |
| | | | watchful waiting | 94 | | | | | |
| | | 1 year | TT | 93 | verbal | Reynell test (comprehensive language development) | TT | | NS |
| | | | watchful waiting | 94 | | | | | |
| | | 0.5 years | TT | 93 | verbal | Schlichting test (expressive language development) | watchful waiting | | NS |
| | | | watchful waiting | 94 | | | | | |
| | | 1 year | TT | 93 | verbal | Schlichting test (expressive language development) | watchful waiting | | NS |
| | | | watchful waiting | 94 | | | | | |
| *Peters 1994* | 8195687 | 93 months | TT | 37 | verbal | Grapheme (%) | TT | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Spelling: Words (%) | TT | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Spelling: Pseudowords (%) | TT | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | One-Minute (# correct) | TT | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Sentence Verification: Correct sentences (msec) | TT | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Sentence Verification: Incorrect sentences (msec) | TT | | NS |
| | | | Control | 151 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | 93 months | TT | 37 | cognitive | Sentence Verification: Correct sentences (%) | TT | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Sentence Verification: Incorrect sentences (%) | TT | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Teachers' Ratings: Writing 1 | TT | | <0.001 |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Teachers' Ratings: Writing 2 | Control | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Teachers' Ratings: Reading 3 | TT | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Teachers' Ratings: Reading 4 | neither | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Teachers' Ratings: Reading 5 | Control | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Teachers' Ratings: Arithmetic 6 | Control | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Teachers' Ratings: Arithmetic 7 | Control | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | cognitive | Teachers' Ratings: Arithmetic 8 | neither | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | verbal | Word Recognition: Words (msec) | TT | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | verbal | Word Recognition: Pseudowords (msec) | TT | | NS |
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | verbal | Word Recognition: Words (%) | TT | | NS |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | Control | 151 | | | | | |
| | | 93 months | TT | 37 | verbal | Word Recognition: Pseudowords (%) | Control | | NS |
| | | | Control | 151 | | | | | |
| *Grievink 1993* | 8246466 | 93 months | TT | 132 | verbal | Word Forms Production | neither | | NS |
| | | | Control | 51 | | | | | |
| | | 93 months | TT | 132 | cognitive | Concealed Meaning | Control | | NS |
| | | | Control | 51 | | | | | |
| | | 93 months | TT | 132 | verbal | Phonemic Segmentation: Words | Control | | NS |
| | | | Control | 51 | | | | | |
| | | 93 months | TT | 132 | verbal | Phonemic Segmentation: Pseudo | Control | | NS |
| | | | Control | 51 | | | | | |
| | | 93 months | TT | 132 | verbal | Sound Blending: Words | TT | | NS |
| | | | Control | 51 | | | | | |
| | | 93 months | TT | 132 | verbal | Sound Blending: Pseudo | Control | | NS |
| | | | Control | 51 | | | | | |
| | | 93 months | TT | 132 | verbal | Auditory Discrimination of Unequal Pairs: Words | Control | | NS |
| | | | Control | 51 | | | | | |
| | | 93 months | TT | 132 | verbal | Auditory Discrimination of Unequal Pairs: Pseudo | Control | | NS |
| | | | Control | 51 | | | | | |
| | | 93 months | TT | 132 | verbal | Auditory Discrimination of Equal Pairs: Words | TT | | NS |
| | | | Control | 51 | | | | | |
| | | 93 months | TT | 132 | verbal | Auditory Discrimination of Equal Pairs: Pseudo | TT | | NS |
| | | | Control | 51 | | | | | |
| *Hall 2009* | 19260880 | 4.5 years | Early surgery | 76 | cognitive | School entry: Language | Early surgery | OR: 3.45 (1.42, 8.39) | 0.006 |
| | | | Watchful waiting | 60 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | 4.5 years | Early surgery | 76 | cognitive | School entry: Reading | Watchful waiting | | NS (0.510) |
| | | | Watchful waiting | 60 | | | | | |
| | | 4.5 years | Early surgery | 76 | cognitive | School entry: Writing | Early surgery | OR: 3.74 (1.51, 9.27) | 0.004 |
| | | | Watchful waiting | 60 | | | | | |
| | | 4.5 years | Early surgery | 76 | cognitive | School entry: Mathematics | Early surgery | | NS (0.197) |
| | | | Watchful waiting | 60 | | | | | |
| | | 7-8 years | Early surgery | 27 | Behavior | Behaviour - teacher report: Prosocial | Early surgery | | NS (0.877) |
| | | | Watchful waiting | 24 | | | | | |
| | | 7-8 years | Early surgery | 27 | Behavior | Behaviour - teacher report: Hyperactivity | Early surgery | | NS (0.363) |
| | | | Watchful waiting | 24 | | | | | |
| | | 7-8 years | Early surgery | 27 | Behavior | Behaviour - teacher report: Emotional problems | Early surgery | OR: 4.11 (1.15, 14.64) | 0.029 |
| | | | Watchful waiting | 24 | | | | | |
| | | 7-8 years | Early surgery | 27 | Behavior | Behaviour - teacher report: Conduct problems | Watchful waiting | | NS (0.803) |
| | | | Watchful waiting | 24 | | | | | |
| | | 7-8 years | Early surgery | 27 | Behavior | Behaviour - teacher report: Peer problems | Early surgery | | NS (0.816) |
| | | | Watchful waiting | 24 | | | | | |
| | | 7-8 years | Early surgery | 27 | Behavior | Behaviour - teacher report: Total score | Early surgery | | NS (0.237) |
| | | | Watchful waiting | 24 | | | | | |
| | | 7-8 years | Early surgery | 35 | verbal | Speech/language: Comprehension | Early surgery | | NS (0.366) |
| | | | Watchful waiting | 33 | | | | | |
| | | 7-8 years | Early surgery | 34 | verbal | Speech/language: Oral expression | Early surgery | | NS (0.143) |
| | | | Watchful waiting | 32 | | | | | |
| | | 7-8 years | Early surgery | 35 | verbal | Speech/language: Non-word: 3 syllable | Early surgery | | NS (0.773) |
| | | | Watchful waiting | 32 | | | | | |
| | | 7-8 years | Early surgery | 35 | verbal | Speech/language: Non-word: 4 syllable | Early surgery | | NS (0.656) |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | Watchful waiting | 32 | | | | | |
| | | 7-8 years | Early surgery | 35 | verbal | Speech/language: Non-word: 5 syllable | Early surgery | | NS (0.101) |
| | | | Watchful waiting | 32 | | | | | |
| | | 7-8 years | Early surgery | 35 | verbal | Speech/language: Non-word: total | Early surgery | | NS (0.288) |
| | | | Watchful waiting | 32 | | | | | |
| | | 7-8 years | Early surgery | 36 | cognitive | IQ: Verbal IQ | Early surgery | | NS (0.265) |
| | | | Watchful waiting | 30 | | | | | |
| | | 7-8 years | Early surgery | 32 | cognitive | IQ: Performance IQ | Early surgery | | NS (0.145) |
| | | | Watchful waiting | 30 | | | | | |
| | | 7-8 years | Early surgery | 29 | cognitive | IQ: Total IQ | Early surgery | | NS (0.100) |
| | | | Watchful waiting | 29 | | | | | |
| | | 7-8 years | Early surgery | 81 | cognitive | SATS KS1: Reading overall | Early surgery | | NS (0.258) |
| | | | Watchful waiting | 64 | | | | | |
| | | 7-8 years | Early surgery | 81 | cognitive | SATS KS1: Writing | Early surgery | | NS (0.192) |
| | | | Watchful waiting | 64 | | | | | |
| | | 7-8 years | Early surgery | 81 | cognitive | SATS KS1: Mathematics | Early surgery | | NS (0.079) |
| | | | Watchful waiting | 64 | | | | | |
| *Maw 1999* | 10459904 | 18 months | TT (Tympanostomy tubes within 6 weeks) | 75 | verbal | Verbal comprehension: standardized score | TT | | NS (0.14) |
| | | | Watchful waiting (for 9 months then tubes if needed) | 67 | | | | | |
| | | 18 months | TT (Tympanostomy tubes within 6 weeks) | 75 | verbal | Expressive language: standardized score | TT | | NS (0.059) |
| | | | Watchful waiting | 67 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | (for 9 months then tubes if needed) | | | | | | |
| | | 18 months | TT (Tympanostomy tubes within 6 weeks) | 75 | verbal | Verbal comprehension: chronological age/equivalent age | TT | | NS (0.36) |
| | | | Watchful waiting (for 9 months then tubes if needed) | 67 | | | | | |
| | | 18 months | TT (Tympanostomy tubes within 6 weeks) | 75 | verbal | Expressive language: chronological age/equivalent age | TT | | NS (0.36) |
| | | | Watchful waiting (for 9 months then tubes if needed) | 67 | | | | | |
| | | 18 months | TT (Tympanostomy tubes within 6 weeks) | 75 | Behavior | Richman score >= 10 | TT | | NS (0.66) |
| | | | Watchful waiting (for 9 months then tubes if needed) | 67 | | | | | |
| | | 18 months | TT (Tympanostomy tubes within 6 weeks) | 75 | Behavior | Richman score | TT | | NS (0.13) |
| | | | Watchful waiting (for 9 months then tubes if needed) | 67 | | | | | |
| *Vlastos 2011* | 21205368 | 1 year | TT AND adenoidectomy | 22 | QOL | OM-6 | Myringotomy AND adenoidectomy | | NS |
| | | | Myringotomy | 23 | | | | | |

| *Study author, years* | PMIDs | Age | Interventions | No. analyzed | Outcome type | Outcome | Favors | If significant, net difference or OR (95%CI) | P between groups NS = not significant at alpha = 0.05 |
|---|---|---|---|---|---|---|---|---|---|
| | | | AND adenoidectomy | | | | | | |

# Appendix H. Harms

**Table H1. Evidence map of studies reporting adverse events**

| Author PMID Country | Design (Recruitment period) | Tube Type [arm description] | Perioperative Complications | Otorrhea | Tube Blockage | Granulation Tissue | Premature Extrusion | TT Displacement | Persistent Perforation | Myringosclerosis | Atrophy\|Atelectasis\|Retraction | Cholesteotoma | Hearing Loss |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ah-Tye 11389239 US | prosp cohort (1992-1996) | Teflon, Armstrong-type tube | | X | | | | | | | | | |
| Ahmet 11271428 Turkey | prosp cohort (1988-1997) | Paparella type-1, type-2, Shepard Grommet or Modified T tympanostomy tubes | | | | | | | | X | | | |
| Allen 16156910 US | prosp cohort (9/2001-11/2001) | Sheehy (0.12 cm diameter) tube | | | X | | | | | | | | |
| Baarle 1169745 Netherlands | prosp cohort | Double-flanged, Silastic tubes (Richards) | | | | | X | | X | | | | |
| Barfoed 7190819 Denmark | prosp cohort (nr) | nr | | | | | | | X | X | X | X | |
| Bernard 1991 1861917 Canada | prosp rct (nr) | Reuter bobbin, Richart "T" | | X | | X | | | X | X | | | |
| Birck 1267356 US | prosp cohort (1972-1974) | nr | | | X | X | | X | X | X | | X | |
| Bonding 4215997 US | cohort (1967-1969) | nr | | | | | | | | | X | X | |
| Bonding 4702615 Denmark | cohort | grommets | | | | | | | | | X | | |
| Brodsky 10591365 US | prosp cohort (1998-1999) | nr | X | X | X | | | | | | | | |
| Brown 8231117 US | cohort | Goode T-tubes | | X | | | X | | X | | | | X |
| Cannon 11797262 US | nrcs | Ultracil tube | | X | | | | | | | | | |

| Author PMID Country | Design (Recruitment period) | Tube Type [arm description] | Perioperative Complications | Otorrhea | Tube Blockage | Granulation Tissue | Premature Extrusion | TT Displacement | Persistent Perforation | Myringosclerosis | Atrophy\|Atelectasis\|Retraction | Cholesteotoma | Hearing Loss |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cannon 11797262 US | nrcs | Silastic tubes | | X | | | | | | | | | |
| Carignan 17049144 Canada | prosp cohort (2003-2004) | Goode T-tubes | | | | | | | X | | | | |
| Casselbrant 1565551 US | prosp rct (1981-1988) | Teflon Armstrong-type TT | | | | | | | X | | | | |
| Costa 3472336 Brazil | prosp cohort | nr | | | | | | | X | | | | X |
| Daly 12759263 US | prosp cohort (1987-1990) | nr | | | | | X | | X | X | X | | X |
| Daly 9738746 US | cross-sectional (1979-1985) | [adolescents and young adults treated with TT] | | | | | | | | | X | | X |
| Daly 9738746 US | cross-sectional (1985-1990) | [children treated with TT] | | | | | | | | X | X | | X |
| De Beer 15224825 Netherlands | prosp cohort (1982-1983) | nr | | | | | | | X | X | | | |
| De Beer 16151352 Netherlands | prosp ncrs | [positive history of otitis media and ventilation tube insertion] | | | | | | | X | X | X | | |
| Debruyne 3177616 Belgium | prosp cohort | nr | | X | | | | | X | | | | |
| Debruyne 3799183 Belgium | cohort | nr | | X | | | | | X | | | | |
| Debruyne 8336923 Belgium | prosp cohort (nr) | Sheppard tube | | X | | | | | | | | | |
| Djurhuus 25724629 Denmark | retro cohort (1997-2011) | nr | | | | | | | | | | X | |
| Djurhuus 25724629 Denmark | retro cohort (1997-2011) | various [data from National Registers | | | | | | | | | | X | |
| Dohar 16880248 US | prosp rct (2003-2004) | [underwent tympanostomy] | | | X | | | | | | | | |
| Eliachar 6613541 Israel | prosp cohort (1975-1981) | Goode long-term T-shaped silicone design tubes | | | X | X | X | | X | | X | X | |
| Fiebach 3570884 | prosp cohort | nr | | | | | | X | X | X | | | |

| Author PMID Country | Design (Recruitment period) | Tube Type [arm description] | Perioperative Complications | Otorrhea | Tube Blockage | Granulation Tissue | Premature Extrusion | TT Displacement | Persistent Perforation | Myringosclerosis | Atrophy\|Atelectasis\|Retraction | Cholesteotoma | Hearing Loss |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Germany | (1979-1984) | | | | | | | | | | | | |
| Fior 6526581 Italy | prosp cohort (1968-1978) | Shepard type | | | | | | X | X | | X | | |
| Florentzson 22648089 Sweden | prosp cohort (1/1996-12/1996) | Tympovent 0.9 mm diameter straight fluoroplastic tube from Atos Medical | | | | | | | X | | | | |
| Friedman 11551611 US | prosp cohort | nr | | | | | | | | X | | | |
| Gates 2492178 US | prosp rct | Shepard-type | | X | | | | | | | | | |
| Gates 2492178 US | prosp rct | Shepard-type [adenoidectomy + TT] | | X | | | | | | | | | |
| Gates 3128752 US | prosp cohort (1980-1986) | Shepard-type tube (1.1 mm inner diameter)[TT & Adenoidectomy] | | X | | | | | | | | | |
| Gates 3128752 US | prosp cohort (1980-1986) | Shepard-type tube (1.1 mm inner diameter)[TT] | | X | | | | | | | | | |
| Gates 3683478 US | prosp rct (1980-1984) | Shepherd tubes [TT and TT+ adenoidectomy arms] | | X | | | | X | X | | | X | |
| Golz 10187945 US, Israel | retro cohort (1980-1994) | 93% standard polyethylene tubes, 7% Goode T tubes | | X | | | | | X | | | | |
| Golz 10406312 Israel | retro cohort (1978-1997) | "homemade" polyethylene tubes in 5143 ears, Goode T-tubes in 432 ears | | | | | | | | | | X | |
| Gourin 10208683 US | prosp cohort (1995-1997) | Silver oxide-impregnated Sheehy-type tympanostomy tubes | | X | | | | | | | | | |
| Gundersen 1267702 Norway | prosp cohort | polyethylene ventilating tube | | | | | | | | X | | X | X |
| Håkansson 25554572 Sweden | prosp cohort (1996-2006) | nr [TT] | | | | | | | | | | | |
| Hammaren-Malmi 17582514 Finland | prosp cohort (2001-2002) | nr | | | | | X | | | | | | |
| Hampton 9118580 Ireland | prosp cohort | Armstrong ventilation tubes | | | | | | | X | | | | |
| Heaton 8877228 UK | prosp cohort (1986-1988) | nr | | X | | | X | | | | | X | |
| Hoffman 12220208 US | prosp/retro cohort | nr | X | | | | | | | | | | |

| Author PMID Country | Design (Recruitment period) | Tube Type [arm description] | Perioperative Complications | Otorrhea | Tube Blockage | Granulation Tissue | Premature Extrusion | TT Displacement | Persistent Perforation | Myringosclerosis | Atrophy\|Atelectasis\|Retraction | Cholesteotoma | Hearing Loss |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hormann -Iowa-Kollectiv 1816937 Germany | prosp nrcs | [cleft palate - University of Hamburg] | | X | | | | | X | | X | X | |
| Hormann -Iowa-Kollectiv 1816937 Germany | prosp nrcs | [cleft palate - University of Hamburg] | | | | | | | X | | | X | |
| Ida 19324425 US | prosp cohort | pressure equalization tube | | X | | | X | | | | | | |
| Ingels 16429748 Netherlands | prosp rct (1996-1997) | Bevel Bobbins, Entermed BV, The Netherlands [TT] | | X | | | | | | | | | |
| Isaacson 18722211 US | prosp cohort (1997-2007) | Armstrong beveled grommet tube | X | | X | | | | | | | | X |
| Jamal 7543180 Saudi Arabia | prosp ncrs | [TT] | | | X | | | | | | | | |
| Jamal 7543180 Saudi Arabia | prosp ncrs | [TT + xylometazoline hydrochloride] | | | X | | | | | | | | |
| Jung 19715725 Korea | cohort (2004-2008) | nr | | X | | | | | | | | | |
| Khan 16773972 Pakistan | prosp cohort (2001-2003) | nr | | | | | X | | X | X | | | |
| Kinnari 20122337 Finland | prosp rct (2001-2002) | Xomed Soileau Tytan | | X | X | X | X | X | X | | | X | |
| Kokko 1267359 Finland | cohort (1965-1971) | nr | | | | | X | X | X | | | X | |
| Kujala 22466327 Finland | prosp rct (2002-2004) | Donaldson silicone tubes | X | | | | | | | | | | |
| Levine 8179266 US | prosp cohort | Donaldson, Shephard, Paparella or Reuter/bobbin | | | | | | | X | | | | |
| Levinson 6819525 US | prosp cohort | | | X | | X | | | | | | | |
| Li 10547462 US | prosp cohort (1987-1991) | Donaldson tubes, Reuter Bobbin tubes, Shepard tubes or other | | | | | | | | | X | | |
| Luo 25465449 China | prosp nrcs (2011-2012) | [tympanostomy tube insertion] | | X | X | X | | | | X | | X | |
| Mackenzie 6541254 UK | prosp cohort (1978-1980) | Pappas 1974, Shah 1971 (Exmoor 142, Shepard 137, Bobbin 132, Arrow 58, Shah 131, Armstrong 138, Colar Button 141, | | | X | | | X | X | X | | | X |

| Author PMID Country | Design (Recruitment period) | Tube Type [arm description] | Perioperative Complications | Otorrhea | Tube Blockage | Granulation Tissue | Premature Extrusion | TT Displacement | Persistent Perforation | Myringosclerosis | Atrophy\|Atelectasis\|Retraction | Cholesteotoma | Hearing Loss |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Paparella 60) | | | | | | | | | | | |
| MacKinnon 4105168 UK | prosp cohort (1965-1971) | nr | | | | | X | | X | | | X | |
| Mandel 2789777 US | prosp rct (1979-1984) | Teflon Armstrong-type TT | | | | | | | X | | | | |
| Mandel 8085732 US | prosp cohort (1979-1990) | Teflon Armstrong-type | | X | | | | | | | | | |
| Marzouk 22183900 US | prosp cohort (2009-2010) | nr | | X | | | | | | | | | |
| Maw 10459904 UK | prosp rct | [TT after 9 months of watchful waiting] | | | | | | | | | | | |
| Maw 10459904 UK | prosp rct | [TT within 6 weeks] | | | | | | | | | | | |
| Moore 2396808 Australia | cohort | collar-button or Shephard | | | | | | | | | | | |
| Muenker 6778334 Germany | prosp cohort (1966-1978) | nr | | | | X | | X | X | | | X | |
| O'Niel 26115935 US | prosp cohort (2009-nr) | various, including Sheehy, Armstrong, T tube, Activent | | | | | | | X | | X | X | |
| O'Reilly 18594333 US | prosp cohort | nr | | X | | | | | | | | | |
| Owen 8436453 US | prosp cohort | Armstrong bevelled tube | | X | | | | | | | | | X |
| Paradise 11309632 US | prosp rct (1991-1995) | Armstrong [TT late treatment; underwent TT insertion 6-9 months after initiaition of symptoms] | | | | X | | | X | X | X | | |
| Paradise 11309632 US | prosp rct (1991-1995) | Armstrong [TT early treatment; underwent TT insertion at initiaition of symptoms] | | | | X | | | X | X | X | | |
| Paradise 2181158 US | prosp rct/nrcs (1971-1985) | [TT] | | | | | | | | | | | |
| Paradise 2181158 US | prosp rct/nrcs (1971-1985) | [TT & Adenoidectomy] | | | | | X | | | | | X | |
| Pereira 16446953 Brazil | prosp cohort (2001-2002) | Short-term ventilation tubes, made of silicone, measuring 1.2 x 2.6 mm, type Donaldson | | X | | | | | X | X | X | X | |
| Plotkin 7195446 US | prosp cohort (1977-1979) | Castelli membrane, Donaldson design, silicone tube (Xomed XO-1201) | | X | | X | | | X | | | | |
| Poetker 17178938 US | prosp rct (2002- | Teflon-coated, fluoroplastic Armstrong beveled TT [receiving | | X | | | | | | | | | |

| Author PMID Country | Design (Recruitment period) | Tube Type [arm description] | Perioperative Complications | Otorrhea | Tube Blockage | Granulation Tissue | Premature Extrusion | TT Displacement | Persistent Perforation | Myringosclerosis | Atrophy\|Atelectasis\|Retraction | Cholesteotoma | Hearing Loss |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2003) | ofloxacin otic drops] | | | | | | | | | | | |
| Poetker 17178938 US | prosp rct (2002-2003) | Teflon-coated, fluoroplastic Armstrong beveled TT [no postoperative otic drop prophylaxis] | | X | | | | | | | | | |
| Poetker 17178938 US | prosp rct (2002-2003) | Teflon-coated, fluoroplastic Armstrong beveled TT [receiving neomycin sulfate-polymyxin B sufate-hydrocortisone otic drops] | | X | | | | | | | | | |
| Postma 9350484 US | prosp cohort (1988-1991) | Amstrong grommt or straight Armstrong | | | | | | | X | | | | |
| Powell 25598389 UK | prosp cohort (2004-2005) | nr | | X | X | | | | X | | X | X | |
| Praveen 15992470 UK | prosp cohort (1998-2003) | Shah ventilation tubes | | | | | X | | | | X | | |
| Rakover 9176804 Israel | nrcs | T tube, Paparella TT [TT: no ear drops] | | | | | | | | | | | X |
| Rakover 9176804 Israel | nrcs | T tube, Paparella TT [TT with ear drops (preventive dexamethasone, neomycin and polymxin B)] | | | | | | | | | | | X |
| Roland 14702493 US, Canada | prosp rct | nr | | | X | | | | | | | | |
| Roos 2128487 Sweden | prosp cohort | polyethylene | | X | | | | | | | | | |
| Rosenfeld 10807325 US | prosp cohort (1997-1998) | short-acting grommet-type tubes, designed to extrude spontaneously within 6-18 months | | X | | | | | | | | | |
| Rothera 4040147 UK | prosp cohort (1980-1982) | Xomed silicone Goode T-Tubes (1.1 mm. internal diameter, 12 mm. length) | | X | | | | | X | | | X | |
| Saki 24303379 Iran | prosp cohort (2009-2011) | nr | | X | X | X | X | X | X | X | X | | |
| Siddiqui 9225174 UK | prosp cohort (1987-1992) | Mangat tube (Xomed) | | X | | | | | X | | | | |
| Siegel 12161732 US | prosp nrcs (1998-2000) | Reuter bobbin tubes [underwent Laser Office Ventilation of Ears with Insertion of Tubes (LOVE IT)] | | X | | | | | | | | | |
| Siegel 12161732 US | prosp nrcs (1998-2000) | Reuter bobbin tubes [underwent standard cold surgical myringotomy and tube placement (M&T)] | | X | | | | | | | | | |
| Slack 6470572 UK | prosp cohort | Shepard grommet | | | | | | | | X | | | |
| Smillie 25171763 | nrcs (2002-2012) | [cleft lip palate; underwent VT insertion] | | X | X | X | | | X | X | X | X | |

| Author PMID Country | Design (Recruitment period) | Tube Type [arm description] | Perioperative Complications | Otorrhea | Tube Blockage | Granulation Tissue | Premature Extrusion | TT Displacement | Persistent Perforation | Myringosclerosis | Atrophy\|Atelectasis\|Retraction | Cholesteotoma | Hearing Loss |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Scotland | | | | | | | | | | | | | |
| Smillie 25171763 Scotland | nrcs (2002-2012) | [no cleft lip palate; underwent VT insertion] | | X | X | X | | | X | X | X | X | |
| Spielmann 18047760 UK | prosp cohort (2003-2004) | nr [second cohort] | | X | X | | X | | | | | | X |
| Spielmann 18047760 UK | prosp cohort (2000-2000) | nr [first cohort] | | | | | | | | | | | |
| Spilsbury 23737350 Austalia | retro cohort (1980-2009) | nr | | | | | | | | | | X | |
| Suetake 2239252 Japan | prosp cohort (1986-1987) | nr | | X | | | | | X | | | | |
| Tavin 3372141 US | prosp cohort (1982-1985) | various | | X | | X | | | | | | | |
| Tos 3814387 Denmark | prosp cohort (1970-1975) | nr | | | | | | | | X | X | X | |
| Tos 7192477 Denmark | cohort | Armstrong tube | | | | | | | | | | X | |
| Tos 985199 Denmark | prosp cohort | nr | | | | | | | X | X | X | X | |
| Tuli 23119801 India | cohort | nr | | X | | | X | | X | | | | X |
| Valtonen 10435125 Finland | prosp cohort (1983-1984) | Shah vent Teflon tube, inner diameter 1.1 mm | | X | | X | X | | X | | | | |
| Valtonen 12150521 Finland | prosp cohort (1983-1984) | Shah vent Teflon tube, inner diameter 1.1 mm | | | | | | | X | | X | | |
| Valtonen 16094135 Finland | prosp cohort (1983-1993) | Shah vent Teflon tube (Xomed) | | X | | | | | X | | X | | |
| Van Cauwenberge 576016 Belgium | prosp cohort | nr | | | | | | | X | | | | |
| van Dongen 23874870 Netherlands | retro cohort (2009-2011) | nr | | X | | | | | | | | | |
| van Heerbeek 16510637 Netherlands | prosp rct (2000-2002) | fluoroplastic, Bevel Bobbin-type TTs (TympVent) | | | | | | | | | | | |
| van Heerbeek 16510637 | prosp rct (2000- | fluoroplastic, Bevel Bobbin-type TTs (TympVent) [pneumococcal | | | | | | | | | | | |

| Author PMID Country | Design (Recruitment period) | Tube Type [arm description] | Perioperative Complications | Otorrhea | Tube Blockage | Granulation Tissue | Premature Extrusion | TT Displacement | Persistent Perforation | Myringosclerosis | Atrophy\|Atelectasis\|Retraction | Cholesteotoma | Hearing Loss |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Netherlands | 2002) | vaccination] | | | | | | | | | | | |
| Velepic 21397957 Croatia | prosp rct (2004-2009) | nr | | | | | | | X | X | X | | |
| Walker 9287928 Australia | prosp cohort | Shepard grommet, Shah vent tube, Sheehy collar button vent tube | | X | X | | | | X | | | | |
| Wallace 15533143 UK | prosp rct (2001-2002) | Shepard or T tube | | X | X | | X | | | | | | |
| Weigel 2645490 US | prosp cohort (1983-1984) | Goode T-tubes, Armstrong Teflon, Reuter-Bobbin Stainless Steel, Shepard Teflon | | X | X | | | | X | | | | |

**Table H2. Perioperative complications**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Perioperative Complications | Definition |
|---|---|---|---|---|---|---|---|---|---|
| Brodsky 10591365 US | prosp cohort (1998-1999) | nr | 3.95 (5.09) [0.50, 23.67] | 56.6 | [75.8] | 1 to 3 months | 54 [96] | [1.04%] | ear canal abrasion |
| Hoffman 12220208 US | prosp/retro cohort | nr | nr | nr | nr | nr | 3198 | 0.81% | intraoperative, including upper airway obstruction, agitation, prolonged recovery, emesis, laryngospasm, desaturation, bradycardia, dysrhythmia, stridor |
| Isaacson 18722211 US | prosp cohort (1997-2007) | Armstrong beveled grommet tube | [0.11, 21.00] | nr | nr | nr | [10000] | [0.01%] | tympanic membrane tear |
| Kujala 22466327 Finland | prosp rct (2002-2004) | Donaldson silicone tubes | 16.1(4.) | 58 | 100[0] | 1 year | 200 | 0.00% | Hemorrhage or anesthetic complications |

**Table H3. Otorrhea**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Otorrhea | Definition |
|---|---|---|---|---|---|---|---|---|---|
| Ah-Tye 11389239 US | prosp cohort (1992-1996) | Teflon, Armstrong-type tube | 1.37 [0.50, 3.00] | 59.5 | nr | 24 months | 173 | 58.61% | nr |
| Bernard 1991 1861917 Canada | prosp rct (nr) | Reuter bobbin, Richart "T" | 4.7 | 56.7 | nr | 18 months | 60 | 13.30% | nr |
| Brodsky 10591365 US | prosp cohort (1998-1999) | nr | 3.95 (5.09) [0.50, 23.67] | 56.6 | [75.8] | 1 to 3 months | 54 [96] | 11.11% | nr |
| Brown 8231117 US | cohort | Goode T-tubes | nr | nr | nr | 6 months | 168 [328] | 52.38% | infections |
| Debruyne 3177616 Belgium | prosp cohort | nr | 4.92 | nr | 45.2% [54.8] | until extrusion | 906 [1685] | 14.79% [10.45%] | nr |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Otorrhea | Definition |
|---|---|---|---|---|---|---|---|---|---|
| Debruyne 3799183 Belgium | cohort | nr | 2.70+ | 55.4 | nr | 0.5 to 6 years | 906 [1685] | 14.90% [10.45%] | nr |
| Debruyne 8336923 Belgium | prosp cohort (nr) | Sheppard tube | nr | 58 | 100% | 1 year | 126 | 10.00% | 3 or more episodes |
| Gates 2492178 US | prosp rct | Shepard-type | [4.00, 8.00] | 58 | nr | 2 years | 129 | 28.68% | purulent otorrhea >=1 episode |
| Gates 3128752 US | prosp cohort (1980-1986) | Shepard-type tube (1.1 mm inner diameter)[TT & Adenoidectomy] | [4.00, 8.00] | 60.3 | nr | nr | 155 | 32.26% | purulent liquid was unequivocably present in external auditory canal, regardless of whether a tube was present or not, not ocunting dried secretions or blood clots |
| Gates 3128752 US | prosp cohort (1980-1986) | Shepard-type tube (1.1 mm inner diameter)[TT] | [4.00, 8.00] | 60.3 | nr | nr | 227 | 22.47% | purulent liquid was unequivocably present in external auditory canal, regardless of whether a tube was present or not, not ocunting dried secretions or blood clots |
| Golz 10187945 US, Israel | retro cohort (1980-1994) | 93% standard polyethylene tubes, 7% Goode T tubes | 4.20 (1.40) [0.83, 10.00] | 55 | 91 [7.5] | at least 1 year after extrusion or removal | 1360 [2604] | 10.45% | 3 or more episodes |
| Heaton 8877228 UK | prosp cohort (1986-1988) | nr | 5.00 [1.00, 12.00] | 60.6 | 0 [100] | nr | 127 | 14.17% | discharge via one or both of their tubes |
| Hörmann 1816937 Germany | prosp nrcs | [cleft palate - University of Hamburg] | 7.43 [5.00, 10.00] | nr | nr | 8 years | 126 [252] | 10.32% | chronic recurring OME through tubes |
| Ida 19324425 US | prosp cohort | pressure equalization tube | [0.67, 4.00] | nr | 0 [100] | 16 months | 50 | 4.00% | nr |
| Ingels 16429748 Netherlands | prosp rct (1996-1997) | Bevel Bobbins, Entermed BV, The Netherlands [TT] | 0.14 (0.01) | 58.8 | 0 [100] | 1 year | 93 | 82.80% | nr |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Otorrhea | Definition |
|---|---|---|---|---|---|---|---|---|---|
| Jung 19715725 Korea | cohort (2004-2008) | nr | 4.50 (2.20) [2.00, 7.00] | 65.7 | 0 [100] | 6 to 24 months | 289 | 23.18% | active otorrhea from middle ear cavity through tympanostomy tube |
| Kinnari 20122337 Finland | prosp rct (2001-2002) | Xomed Soileau Tytan | 4.1[0.5, 15] | 61 | 36[64] | until extrusion or removal | 170[298] | [6.7%] | chronic otorrhea |
| Levinson 6819525 US | prosp cohort | | [1.00, 11.00+] | nr | nr | 5 months | 64 [124] | [1.61%] | acute otitis media |
| Luo 25465449 China | prosp nrcs (2011-2012) | [tympanostomy tube insertion] | 4.80 (1.00) [2.00, 8.00] | 50.9 | nr | 2 years | 55 | 32.73% | otorrhea |
| Mandel 8085732 US | prosp cohort (1979-1990) | Teflon Armstrong-type | 3.60 [0.50, 12.00] | nr | nr | nr | 246 | 50.00% | nr |
| Marzouk 22183900 US | prosp cohort (2009-2010) | nr | 3.60 (1.80) [0.90, 9.00] | 67.1 | 15.8 [51.3] | 1 year | 79 | 34.18% | nr |
| O'Reilly 18594333 US | prosp cohort | nr | 2.70 (2.40) [0.25, 17.00] | 55.2 | nr | 6 months | 509 | 70.33% | nr |
| Owen 8436453 US | prosp cohort | Armstrong bevelled tube | 2.08 [0.42, 4.00] | nr | nr | 6 months | 52 [98] | [28.21%] | nr |
| Pereira 16446953 Brazil | prosp cohort (2001-2002) | Short-term ventilation tubes, made of silicone, measuring 1.2 x 2.6 mm, type Donaldson | 2.89 (1.54) [0.92, 9.33] | 60 | 69.3 [30.7] | 38 months | 75 [150] | 61.64% | otorrhea at some time |
| Plotkin | prosp cohort | Castelli membrane, | 5.20 | 60.7 | 0 [100] | nr | 89 [162] | 12.36% | purulent otitis media |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Otorrhea | Definition |
|---|---|---|---|---|---|---|---|---|---|
| 7195446 US | (1977-1979) | Donaldson design, silicone tube (Xomed XO-1201) | [2.50, 11.00] | | | | | | and serous otitis media |
| Powell 25598389 UK | prosp cohort (2004-2005) | nr | 4.60 | nr | nr | 9 weeks to 10 years | 89 | 19.10% | otorrhea at 9 weeks |
| Rosenfeld 10807325 US | prosp cohort (1997-1998) | short-acting grommet-type tubes, designed to extrude spontaneously within 6-18 months | med 1.40 [0.50, 9.90] | 60 | 56 [42] | 2 to 4 months | 248 | 29.91% | at first postoperative office visit |
| Rothera 4040147 UK | prosp cohort (1980-1982) | Xomed silicone Goode T-Tubes (1.1 mm. internal diameter, 12 mm. length) | nr | nr | 0 [100] | 30 months | 73 [131] | 20.55% | nr |
| Saki 24303379 Iran | prosp cohort (2009-2011) | nr | [0.83, 6.00] | 55.8 | 0 [100] | 12 to 18 months | 208 | 17.79% | transient otorrhea; delayed otorrhea; chronic otorrhea non-responsive to medical treatment |
| Siddiqui 9225174 UK | prosp cohort (1987-1992) | Mangat tube (Xomed) | mode 5.00 [0.50, 14.00] | 61.8 | 0 [100] | 3 years | 191 [322] | 13.09% [11.18%] | had ear discharge on one or more occasions, requiring abx and eardrops |
| Smillie 25171763 Scotland | nrcs (2002-2012) | [no cleft lip palate; underwent VT insertion] | med 3.50 [0.60, 10.40] | 55 | nr | nr | 60 | 60.00% | nr |
| Spielmann 18047760 UK | prosp cohort (2003-2004) | nr [second cohort] | 5.30 [0.83, 9.00] | 61.4 | 18.8 [81.2] | 3 months | 84 [195] | 14.29% | nr |
| Suetake | prosp cohort | nr | 6.20 | 59.6 | 0 [100] | nr | 52 [90] | 47.27% | recurrence of SOM |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Otorrhea | Definition |
|---|---|---|---|---|---|---|---|---|---|
| 2239252 Japan | (1986-1987) | | (2.00) [3.00, 11.00] | | | | | | |
| Tavin 3372141 US | prosp cohort (1982-1985) | various | 4.80 (1.50) [0.33, 16.00] | 63.2 | nr | 365 to 728 days | 95 [187] | [9.09%] | excluding post operative otorrhea |
| Tuli 23119801 India | cohort | nr | nr | 66.7 | 0 [100] | nr | 100 | 12.00% | excessive bleeding |
| Valtonen 10435125 Finland | prosp cohort (1983-1984) | Shah vent Teflon tube, inner diameter 1.1 mm | 0.84 [0.42, 1.33] | 58.4 | 34.2 [65.8] | 5 years | 281 [281] | [66.55%] | post-tympanostomy otorrhea during primary ventilation tube |
| Valtonen 16094135 Finland | prosp cohort (1983-1993) | Shah vent Teflon tube (Xomed) | nr | 51.4 | 0 [100] | 5 to 7.2 years | 72 [124] | 6.94% | ongoing OME |
| van Dongen 23874870 Netherlands | retro cohort (2009-2011) | nr | 4.40 (2.30) | 58 | nr | nr | 1184 | 67.00% | one or more episodes in first year after TT placement |
| Weigel 2645490 US | prosp cohort (1983-1984) | Goode T-tubes, Armstrong Teflon, Reuter-Bobbin Stainless Steel, Shepard Teflon | 3.80 [0.60, 13.00] | 59 | 45 [41] | 21 months | 75 [150] | [35.33%] | nr |

**Table H4. Tube blockage**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Tube Blockage | Defintion |
|---|---|---|---|---|---|---|---|---|---|
| Allen 16156910 US | prosp cohort (9/2001-11/2001) | Sheehy (0.12 cm diameter) tube | 4 [0.75, 11.83] | 68.1 | 74 [19.5] | 2 weeks | 112 | 10.71% | nr |
| Birck 1267356 US | prosp cohort (1972-1974) | nr | nr | 59.2 | nr | 6+ months | 736 [2327] | [2.49%] | tubes occluded |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Tube Blockage | Defintion |
|---|---|---|---|---|---|---|---|---|---|
| Brodsky 10591365 US | prosp cohort (1998-1999) | nr | 3.95 (5.09) [0.50, 23.67] | 56.6 | [75.8] | 1 to 3 months | 54 [96] | [4.05%] | nr |
| Dohar 16880248 US | prosp rct (2003-2004) | [underwent tympanostomy] | [0.50, 11.00] | 52.5 | nr | 3 weeks | 39 | 2.56% | device blockage |
| Eliachar 6613541 Israel | prosp cohort (1975-1981) | Goode long-term T-shaped silicone design tubes | 8.33 [4.50, 16.00] | nr | nr | 8 to 72 months | 122 [203] | [2.96%] | blockage |
| Isaacson 18722211 US | prosp cohort (1997-2007) | Armstrong beveled grommet tube | [0.11, 21.00] | nr | nr | nr | [10000] | [0.03%] | permanent |
| Jamal 7543180 Saudi Arabia | prosp ncrs | [TT] | nr | 54.2 | 0 [100] | 3 months | 40 [76] | 17.50% | nr |
| Kinnari 20122337 Finland | prosp rct (2001-2002) | Xomed Soileau Tytan | 4.1[0.5, 15] | 61 | 36[64] | until extrusion or removal | 170[298] | [37%] | tubes blocked at 9 months |
| Luo 25465449 China | prosp nrcs (2011-2012) | [tympanostomy tube insertion] | 4.80 (1.00) [2.00, 8.00] | 50.9 | nr | 2 years | 55 | 9.09% | tube blockage |
| Mackenzie 6541254 UK | prosp cohort (1978-1980) | Pappas 1974, Shah 1971 (Exmoor 142, Shepard 137, Bobbin 132, Arrow 58, Shah 131, Armstrong 138, Colar Button 141, Paparella 60) | 10.80 [0.75, 77.00] | 58.3 | 0 [100] | 2.25 years | 588 [939] | [17.15%] | not patent at 3 month f/u |
| Powell 25598389 UK | prosp cohort (2004-2005) | nr | 4.60 | nr | nr | 9 weeks to 10 years | 89 | 8.99% | blocked tube at 9 weeks |
| Roland 14702493 US, Canada | prosp rct | nr | 2.45 [0.50, 12.00] | 62.3 | nr | 18 days | 599 | 0.17% | tube blocakge |
| Saki 24303379 Iran | prosp cohort (2009-2011) | nr | [0.83, 6.00] | 55.8 | 0 [100] | 12 to 18 months | 208 | 3.85% | obstruction of the VT on the tympanic membrane |
| Smillie 25171763 Scotland | nrcs (2002-2012) | [no cleft lip palate; underwent VT insertion] | med 3.50 [0.60, 10.40] | 55 | nr | nr | 60 | 1.67% | grommet occlusion-wax |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Tube Blockage | Defintion |
|---|---|---|---|---|---|---|---|---|---|
| Spielmann 18047760 UK | prosp cohort (2003-2004) | nr [second cohort] | 5.30 [0.83, 9.00] | 61.4 | 18.8 [81.2] | 3 months | 84 [195] | 10.71% | nr |
| Walker 9287928 Australia | prosp cohort | Shepard grommet, Shah vent tube, Sheehy collar button vent tube | 3.80 | nr | 12 [85] | until extrusion | 106 | [2.83%] | lumenal obstruction |
| Wallace 15533143 UK | prosp rct (2001-2002) | Shepard or T tube | 6.00 [1.00, 13.00] | 63.6 | 75.8 | 1 month | 26 | [6.52%] | 1 month follow up |
| Weigel 2645490 US | prosp cohort (1983-1984) | Goode T-tubes, Armstrong Teflon, Reuter-Bobbin Stainless Steel, Shepard Teflon | 3.80 [0.60, 13.00] | 59 | 45 [41] | 21 months | 75 [150] | [37.33%] | temporary or permanent |

**Table H5. Granulation tissue**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Granulation Tissue | Defintion Granulation Tissue |
|---|---|---|---|---|---|---|---|---|---|
| Bernard 1991 1861917 Canada | prosp rct (nr) | Reuter bobbin, Richart "T" | 4.7 | 56.7 | nr | 18 months | 60 | 3.3 | purulent discharge and granuloma formation |
| Birck 1267356 US | prosp cohort (1972-1974) | nr | nr | 59.2 | nr | 6+ months | 736 [2327] | [0.17%] | |
| Eliachar 6613541 Israel | prosp cohort (1975-1981) | Goode long-term T-shaped silicone design tubes | 8.33 [4.50, 16.00] | nr | nr | 8 to 72 months | 122 [203] | [5.91%] | local granuloma |
| Kinnari 20122337 Finland | prosp rct (2001-2002) | Xomed Soileau Tytan | 4.1[0.5, 15] | 61 | 36[64] | until extrusion or removal | 170[298] | [20.1%] | nr |
| Levinson 6819525 US | prosp cohort | | [1.00, 11.00+] | nr | nr | 5 months | 64 [124] | [5.65%] | granulations and discharge |
| Luo 25465449 China | prosp nrcs (2011-2012) | [tympanostomy tube insertion] | 4.80 (1.00) [2.00, 8.00] | 50.9 | nr | 2 years | 55 | 12.73% | granulation formation |
| Muenker 6778334 Germany | prosp cohort (1966-1978) | nr | nr | nr | nr | nr | 631 [1060] | [1.79%] | |
| Plotkin 7195446 US | prosp cohort (1977-1979) | Castelli membrane, Donaldson design, silicone tube (Xomed | 5.20 [2.50, 11.00] | 60.7 | 0 [100] | nr | 89 [162] | [1.85%] | polypoid granulations fromed around the tube |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Granulation Tissue | Defintion Granulation Tissue |
|---|---|---|---|---|---|---|---|---|---|
| | | XO-1201) | | | | | | | |
| Saki 24303379 Iran | prosp cohort (2009-2011) | nr | [0.83, 6.00] | 55.8 | 0 [100] | 12 to 18 months | 208 | 3.37% | nr |
| Smillie 25171763 Scotland | nrcs (2002-2012) | [no cleft lip palate; underwent VT insertion] | med 3.50 [0.60, 10.40] | 55 | nr | nr | 60 | 1.67% | |
| Tavin 3372141 US | prosp cohort (1982-1985) | various | 4.80 (1.50) [0.33, 16.00] | 63.2 | nr | 365 to 728 days | 95 [187] | [2.14%] | resulted in granuloma formation between 90 and 183 days |
| Valtonen 10435125 Finland | prosp cohort (1983-1984) | Shah vent Teflon tube, inner diameter 1.1 mm | 0.84 [0.42, 1.33] | 58.4 | 34.2 [65.8] | 5 years | 281 [281] | [5.69%] | |

**Table H6. Premature extrusion**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Premature Extrusion | Definition Premature Extrucsion |
|---|---|---|---|---|---|---|---|---|---|
| van Baarle 1169745 Netherlands | prosp cohort | Double-flanged, Silastic tubes (Richards) | nr | nr | nr | 12+ weeks | 60 | 13.33% | |
| Brown 8231117 US | cohort | Goode T-tubes | nr | nr | nr | 6 months | 168 [328] | 0.00% | premature extrusion |
| Daly 12759263 US | prosp cohort (1987-1990) | nr | [0.50, 8.00] | 61 | nr | 3 to 8 years | 138 [275] | [56.00%] | nr |
| Eliachar 6613541 Israel | prosp cohort (1975-1981) | Goode long-term T-shaped silicone design tubes | 8.33 [4.50, 16.00] | nr | nr | 8 to 72 months | 122 [203] | 81.82% | extruded spontaneously |
| Hammaren-Malmi 17582514 Finland | prosp cohort (2001-2002) | nr | 1.90 [1.00, 4.00] | 54 | nr | 12 months | 217 | 73.74% | tympanostomy tube lost or non-patent during follow-up (12 months) |
| Heaton 8877228 UK | prosp cohort (1986-1988) | nr | 5.00 [1.00, 12.00] | 60.6 | 0 [100] | nr | 127 | 34.65% | undergone insertion of a subsequent tube or tubes |
| Ida 19324425 US | prosp cohort | pressure equalization tube | [0.67, 4.00] | nr | 0 [100] | 16 months | 50 | 58.00% | nr |
| Khan 16773972 Pakistan | prosp cohort (2001-2003) | nr | [2.00, 40.00] | 66.6 | 0 [100] | 18 to 24 months | 57 [114] | [0.88%] | nr |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Premature Extrusion | Definition Premature Extrucsion |
|---|---|---|---|---|---|---|---|---|---|
| Kinnari 20122337 Finland | prosp rct (2001-2002) | Xomed Soileau Tytan | 4.1[0.5, 15] | 61 | 36[64] | until extrusion or removal | 170[298] | [3.9%] | within 3 months |
| Kokko 1267359 Finland | cohort (1965-1971) | nr | nr | nr | nr | 3.167 years (average) | [290] | [0.24%] | nr |
| MacKinnon 4105168 UK | prosp cohort (1965-1971) | nr | =<16.00 | nr | nr | nr | 95 [165] | 37.89% [39.39%] | requiring grommets on more than one occassion |
| Paradise 2181158 US | prosp rct/nrcs (1971-1985) | [TT & Adenoidectomy] | nr | 67 | nr | nr | 97 | [5.60%] | perforations remaining unhealed for periods of 10 months to 4.5 years |
| Praveen 15992470 UK | prosp cohort (1998-2003) | Shah ventilation tubes | 5.00 [1.60, 14.50] | 64 | nr | nr | 606 [1174] | 8.42% | early extrusions |
| Saki 24303379 Iran | prosp cohort (2009-2011) | nr | [0.83, 6.00] | 55.8 | 0 [100] | 12 to 18 months | 208 | 5.77% | early extrusion from the membrane |
| Spielmann 18047760 UK | prosp cohort (2003-2004) | nr [second cohort] | 5.30 [0.83, 9.00] | 61.4 | 18.8 [81.2] | 3 months | 84 [195] | 10.71% | nr |
| Tuli 23119801 India | cohort | nr | nr | 66.7 | 0 [100] | nr | 100 | 4.00% | early dislocation of grommet |
| Valtonen 10435125 Finland | prosp cohort (1983-1984) | Shah vent Teflon tube, inner diameter 1.1 mm | 0.84 [0.42, 1.33] | 58.4 | 34.2 [65.8] | 5 years | 281 [281] | [1.78%] | ventilation tube extruded early, within two weeks post-operatively |
| Wallace 15533143 UK | prosp rct (2001-2002) | Shepard or T tube | 6.00 [1.00, 13.00] | 63.6 | 75.8 | 1 month | 26 | [4.35%] | 1 month |

**Table H7. TT displacement**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % TT Displacement | Definition TT displacement |
|---|---|---|---|---|---|---|---|---|---|
| Birck 1267356 US | prosp cohort (1972-1974) | nr | nr | 59.2 | nr | 6+ months | 736 [2327] | [0.60%] | tubes in tympanum |
| Fiebach 3570884 Germany | prosp cohort (1979-1984) | nr | [1.00, 6.00] | 60.5 | nr | nr | 534 [1000] | 0.37% | nr |
| Fior 6526581 | prosp cohort (1968-1978) | Shepard type | 3.00 [0.33, | 60.6 | 100 [0] | 5 to 15 years | 61 [108] | [0.93%] | Migration of the tube into the |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % TT Displacement | Definition TT displacement |
|---|---|---|---|---|---|---|---|---|---|
| Italy | | | 6.00] | | | | | | tympanic cavity |
| Kinnari 20122337 Finland | prosp rct (2001-2002) | Xomed Soileau Tytan | 4.1[0.5, 15] | 61 | 36[64] | until extrusion or removal | 170[298] | 0.00% | nr |
| Kokko 1267359 Finland | cohort (1965-1971) | nr | nr | nr | nr | 3.167 years (average) | [290] | [0.69%] | slippage of TT into tympanum |
| Mackenzie 6541254 UK | prosp cohort (1978-1980) | Pappas 1974, Shah 1971 (Exmoor 142, Shepard 137, Bobbin 132, Arrow 58, Shah 131, Armstrong 138, Colar Button 141, Paparella 60) | 10.80 [0.75, 77.00] | 58.3 | 0 [100] | 2.25 years | 588 [939] | [2.34%] | nr |
| Muenker 6778334 Germany | prosp cohort (1966-1978) | nr | nr | nr | nr | nr | 631 [1060] | [0.75%] | extrusion into the tympanic cavity |
| Saki 24303379 Iran | prosp cohort (2009-2011) | nr | [0.83, 6.00] | 55.8 | 0 [100] | 12 to 18 months | 208 | 0.48% | displacement into the middle ear |

**Table H8. Persistent perforation**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Persistent Perforation | Definition Persistent Perforation |
|---|---|---|---|---|---|---|---|---|---|
| van Baarle 1169745 Netherlands | prosp cohort | Double-flanged, Silastic tubes (Richards) | nr | nr | nr | 12+ weeks | 60 | 1.67% | perforation remained 2 months later |
| Barfoed 7190819 Denmark | prosp cohort (nr) | nr | nr | 57 | 0[100] | 4.5 to 7.5 years | 90[173] | nr[5.00%] | central perforations without suppuration |
| Bernard 1991 1861917 Canada | prosp rct (nr) | Reuter bobbin, Richart "T" | 4.7 | 56.7 | nr | 18 months | 60 | 0.00% | nr |
| Birck 1267356 US | prosp cohort (1972-1974) | nr | nr | 59.2 | nr | 6+ months | 736 [2327] | 1.90% | nr |
| Brown 8231117 US | cohort | Goode T-tubes | nr | nr | nr | 6 months | 168 [328] | [2.44%] | perforations persisted in tympanic membranes after extraction |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Persistent Perforation | Definition Persistent Perforation |
|---|---|---|---|---|---|---|---|---|---|
| Carignan 17049144 Canada | prosp cohort (2003-2004) | Goode T-tubes | 5.70 | 62 | 71 [29] | 18 months | nr | 1.79% | perforations persisted > 6 months |
| Casselbrant 1565551 US | prosp rct (1981-1988) | Teflon Armstrong-type TT | nr | 58.1 | 100[0] | 2 years | 86 | 13% | perforation after spontaneous extrusion |
| Costa 3472336 Brazil | prosp cohort | nr | nr | nr | 0 [100] | nr | 79 | 2.53% | perforation of the eardrum |
| Daly 12759263 US | prosp cohort (1987-1990) | nr | [0.50, 8.00] | 61 | nr | 3 to 8 years | 138 [275] | [67.64%] | perforation |
| De Beer 15224825 Netherlands | prosp cohort (1982-1983) | nr | nr | 47 | nr | 18 years | 51 [101] | [5.94%] | |
| De Beer 16151352 Netherlands | prosp ncrs | [positive history of otitis media and ventilation tube insertion] | nr | nr | nr | 16 years | 51[102] | [6.78%] | at 18 years old |
| Debruyne 3177616 Belgium | prosp cohort | nr | 4.92 | nr | 45.2% [54.8] | until extrusion | 906 [1685] | 1.14% | perforations persisted > 6 months |
| Debruyne 3799183 Belgium | cohort | nr | 2.70+ | 55.4 | nr | 0.5 to 6 years | 906 [1685] | [1.27%] | perforations persisted > 6 months |
| Eliachar 6613541 Israel | prosp cohort (1975-1981) | Goode long-term T-shaped silicone design tubes | 8.33 [4.50, 16.00] | nr | nr | 8 to 72 months | 122 [203] | [3.94%] | permanent unhealed perforations |
| Fiebach 3570884 Germany | prosp cohort (1979-1984) | nr | [1.00, 6.00] | 60.5 | nr | nr | 534 [1000] | [0.94%] | lasting perforation of the tympanic membrane |
| Fior 6526581 Italy | prosp cohort (1968-1978) | Shepard type | 3.00 [0.33, 6.00] | 60.6 | 100 [0] | 5 to 15 years | 61 [108] | [5.56%] | Persistent perforation of the tympanic membrane following extrusion of the tube |
| Florentzson 22648089 Sweden | prosp cohort (1/1996-12/1996) | Tympovent 0.9 mm diameter straight fluoroplastic tube from Atos Medical | 3.90 | 61 | nr | 10 years | 155 [280] | [2.1%] | permanent perforations |
| Golz 10187945 US, Israel | retro cohort (1980-1994) | 93% standard polyethylene tubes, 7% Goode T tubes | 4.20 (1.40) [0.83, | 55 | 91 [7.5] | at least 1 year after extrusion or | 1360 [2604] | [3.06%] | |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Persistent Perforation | Definition Persistent Perforation |
|---|---|---|---|---|---|---|---|---|---|
| | | | 10.00] | | | removal | | | |
| Hampton 9118580 Ireland | prosp cohort | Armstrong ventilation tubes | [0.75, 10.25] | 58.7 | nr | 17 months (mean) | 109 [218] | [2.75%] | tympanic membrane perforations |
| Hörmann 1816937 Germany | prosp nrcs | [cleft palate - University of Hamburg] | 7.43 [5.00, 10.00] | nr | nr | 8 years | 126 [252] | 8.73% | |
| Khan 16773972 Pakistan | prosp cohort (2001-2003) | nr | [2.00, 40.00] | 66.6 | 0 [100] | 18 to 24 months | 57 [114] | 2.63% | nr |
| Kinnari 20122337 Finland | prosp rct (2001-2002) | Xomed Soileau Tytan | 4.1[0.5, 15] | 61 | 36[64] | until extrusion or removal | 170[298] | [0.7%] | nr |
| Kokko 1267359 Finland | cohort (1965-1971) | nr | nr | nr | nr | 3.167 years (average) | [290] | [1.72%] | dry perforation (central 2-3 mm pars tensa defect); perforation with discharge |
| Levine 8179266 US | prosp cohort | Donaldson, Shephard, Paparella or Reuter/bobbin | [0.50, 8.00] | nr | 0 [100] | 4 years (mean) | 149 | 14.09% | tympanic membrane perforations |
| Mackenzie 6541254 UK | prosp cohort (1978-1980) | Pappas 1974, Shah 1971 (Exmoor 142, Shepard 137, Bobbin 132, Arrow 58, Shah 131, Armstrong 138, Colar Button 141, Paparella 60) | 10.80 [0.75, 77.00] | 58.3 | 0 [100] | 2.25 years | 588 [939] | 0.34% | perforation at long term f/u |
| MacKinnon 4105168 UK | prosp cohort (1965-1971) | nr | =<16.00 | nr | nr | nr | 95 [165] | [3.03%] | perforation after removal of grommets |
| Mandel 2789777 US | prosp rct (1979-1984) | Teflon Armstrong-type TT | nr | nr | 0[100] | until extrusion | 63[102] | [11.7%] | perforation after spontaneous extrusion |
| Muenker 6778334 Germany | prosp cohort (1966-1978) | nr | nr | nr | nr | nr | 631 [1060] | [2.45%] | |
| O'Niel 26115935 US | prosp cohort (2009-nr) | various, including Sheehy, Armstrong, T tube, Activent | 3 (2.8) [0.08 - 17' | 42.4 | 60[38] | 1 year post TT extrusion | 634[544] | 1.10% | post-extrusion performation |
| Paradise 11309632 US | prosp rct (1991-1995) | Armstrong [TT early treatment; underwent TT insertion at initiaition of | 5.00 | 52.6 | 0 [100] | ~2 years | 121 [242] | 4.96% [2.48%] | perforation with or without other abnormality |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Persistent Perforation | Definition Persistent Perforation |
|---|---|---|---|---|---|---|---|---|---|
| | | symptoms] | | | | | | | |
| Pereira 16446953 Brazil | prosp cohort (2001-2002) | Short-term ventilation tubes, made of silicone, measuring 1.2 x 2.6 mm, type Donaldson | 2.89 (1.54) [0.92, 9.33] | 60 | 69.3 [30.7] | 38 months | 75 [150] | [2.05%] | |
| Plotkin 7195446 US | prosp cohort (1977-1979) | Castelli membrane, Donaldson design, silicone tube (Xomed XO-1201) | 5.20 [2.50, 11.00] | 60.7 | 0 [100] | nr | 89 [162] | [2%] | perforation for ≥ 6 months |
| Postma 9350484 US | prosp cohort (1988-1991) | Amstrong grommt or straight Armstrong | nr | nr | nr | until extruded | 346 | 5.20% | nr |
| Powell 25598389 UK | prosp cohort (2004-2005) | nr | 4.60 | nr | nr | 9 weeks to 10 years | 89 | 6.67% | |
| Rothera 4040147 UK | prosp cohort (1980-1982) | Xomed silicone Goode T-Tubes (1.1 mm. internal diameter, 12 mm. length) | nr | nr | 0 [100] | 30 months | 73 [131] | [3.82%] | central perforations |
| Saki 24303379 Iran | prosp cohort (2009-2011) | nr | [0.83, 6.00] | 55.8 | 0 [100] | 12 to 18 months | 208 | 2.40% | |
| Siddiqui 9225174 UK | prosp cohort (1987-1992) | Mangat tube (Xomed) | mode 5.00 [0.50, 14.00] | 61.8 | 0 [100] | 3 years | 191 [322] | [5.28%] | perforation at a year follow-up |
| Smillie 25171763 Scotland | nrcs (2002-2012) | [no cleft lip palate; underwent VT insertion] | med 3.50 [0.60, 10.40] | 55 | nr | nr | 60 | 5.00% | tympanic membrane perforation |
| Suetake 2239252 Japan | prosp cohort (1986-1987) | nr | 6.20 (2.00) [3.00, 11.00] | 59.6 | 0 [100] | nr | 52 [90] | [14.55%] | nr |
| Tos 985199 Denmark | prosp cohort | nr | nr | 14 | nr | 1 to 8 years | 109 | 2.75% | |
| Tuli 23119801 India | cohort | nr | nr | 66.7 | 0 [100] | nr | 100 | 8.00% | permanent perforation |
| Valtonen 10435125 Finland | prosp cohort (1983-1984) | Shah vent Teflon tube, inner diameter 1.1 mm | 0.84 [0.42, 1.33] | 58.4 | 34.2 [65.8] | 5 years | 281 [281] | [2.49%] | |
| Valtonen 12150521 Finland | prosp cohort (1983-1984) | Shah vent Teflon tube, inner diameter 1.1 mm | 0.84 [0.42, 1.33] | 58.4 | 34.2 [65.8] | 5 years | 281 [281] | [4.63%] | |
| Valtonen | prosp cohort | Shah vent Teflon tube | nr | 51.4 | 0 [100] | 5 to 7.2 | 72 [124] | 6.94% | nr |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Persistent Perforation | Definition Persistent Perforation |
|---|---|---|---|---|---|---|---|---|---|
| 16094135 Finland | (1983-1993) | (Xomed) | | | | years | | | |
| Van Cauwenberge 576016 Belgium | prosp cohort | nr | [2.00, 14.00] | 49.3 | 0 [100] | 5 to 120 months | 148 | 2.70% | |
| Velepic 21397957 Croatia | prosp rct (2004-2009) | nr | 5.44 [2.00, 12.00] | nr | 0 [100] | nr | [161] | [0.00%] | eardrum peforation |
| Walker 9287928 Australia | prosp cohort | Shepard grommet, Shah vent tube, Sheehy collar button vent tube | 3.80 | nr | 12 [85] | until extrusion | 106 | [0.47%] | |
| Weigel 2645490 US | prosp cohort (1983-1984) | Goode T-tubes, Armstrong Teflon, Reuter-Bobbin Stainless Steel, Shepard Teflon | 3.80 [0.60, 13.00] | 59 | 45 [41] | 21 months | 75 [150] | [6.00%] | |

**Table H9. Myringosclerosis**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Myringosclerosis | def_myringosclerosis |
|---|---|---|---|---|---|---|---|---|---|
| Koc 11271428 Turkey | prosp cohort (1988-1997) | Paparella type-1, type-2, Shepard Grommet or Modified T tympanostomy tubes | nr | 58 | nr | nr | 251 [431] | [49.88%] | nr |
| Barfoed 7190819 Denmark | prosp cohort (nr) | nr | nr | 57 | 0[100] | 4.5 to 7.5 years | 90[173] | nr[23%] | tympanosclerosis along the whole anulus |
| Bernard 1991 1861917 Canada | prosp rct (nr) | Reuter bobbin, Richart "T" | 4.7 | 56.7 | nr | 18 months | 60 | 28.3 | localized without involvement of middle ear structures |
| Birck 1267356 US | prosp cohort (1972-1974) | nr | nr | 59.2 | nr | 6+ months | 736 [2327] | 0.95% | tympanosclerosis (43 tube insertions) |
| Daly 12759263 US | prosp cohort (1987-1990) | nr | [0.50, 8.00] | 61 | nr | 3 to 8 years | 138 [275] | [49.82%] | myringosclerosis |
| Daly 9738746 US | cross-sectional (1985-1990) | [children treated with TT] | 17.70 (3.50) [13.00, | 61 | 0 [100] | nr | 108 | 61.00% | 8- to 12-year-olds |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Myringosclerosis | def_myringosclerosis |
|---|---|---|---|---|---|---|---|---|---|
| | | | 28.00] | | | | | | |
| De Beer 15224825 Netherlands | prosp cohort (1982-1983) | nr | nr | 47 | nr | 18 years | 51 [101] | [64.36%] | |
| De Beer 16151352 Netherlands | prosp ncrs | [positive history of otitis media and ventilation tube insertion] | nr | nr | nr | 16 years | 51[102] | 55.93% | at 18 years |
| Fiebach 3570884 Germany | prosp cohort (1979-1984) | nr | [1.00, 6.00] | 60.5 | nr | nr | 534 [1000] | [11.29%] | scarring or calcification |
| Friedman 11551611 US | prosp cohort | nr | [0.08, 30.00] | 60.1 | nr | nr | 81 | 34.57% | tympanosclerosis in at least one ear |
| Gundersen 1267702 Norway | prosp cohort | polyethylene ventilating tube | 7.50 [1.00, 14.00] | nr | 0 [100] | 2 to 11 years | 100 [196] | [11.22%] | |
| Khan 16773972 Pakistan | prosp cohort (2001-2003) | nr | [2.00, 40.00] | 66.6 | 0 [100] | 18 to 24 months | 57 [114] | [5.26%] | nr |
| Luo 25465449 China | prosp nrcs (2011-2012) | [tympanostomy tube insertion] | 4.80 (1.00) [2.00, 8.00] | 50.9 | nr | 2 years | 55 | 34.55% | myringosclerosis |
| Mackenzie 6541254 UK | prosp cohort (1978-1980) | Pappas 1974, Shah 1971 (Exmoor 142, Shepard 137, Bobbin 132, Arrow 58, Shah 131, Armstrong 138, Colar Button 141, Paparella 60) | 10.80 [0.75, 77.00] | 58.3 | 0 [100] | 2.25 years | 588 [939] | 0.68% | tympanosclerosis at long term f/u |
| Paradise 11309632 US | prosp rct (1991-1995) | Armstrong [TT early treatment; underwent TT insertion at initiaition of symptoms] | 5.00 | 52.6 | 0 [100] | ~2 years | 121 [242] | 3.31% [4.13%] | tympanosclerosis |
| Pereira 16446953 Brazil | prosp cohort (2001-2002) | Short-term ventilation tubes, made of silicone, measuring 1.2 x 2.6 mm, type Donaldson | 2.89 (1.54) [0.92, 9.33] | 60 | 69.3 [30.7] | 38 months | 75 [150] | [2.74%] | nr |
| Saki | prosp cohort | nr | [0.83, | 55.8 | 0 [100] | 12 to 18 | 208 | 37.98% | nr |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Myringosclerosis | def_myringosclerosis |
|---|---|---|---|---|---|---|---|---|---|
| 24303379 Iran | (2009-2011) | | 6.00] | | | months | | | |
| Slack 6470572 UK | prosp cohort | Shepard grommet | [4.00, 10.00] | nr | nr | 21 months | 124 | 56.45% | nr |
| Smillie 25171763 Scotland | nrcs (2002-2012) | [no cleft lip palate; underwent VT insertion] | med 3.50 [0.60, 10.40] | 55 | nr | nr | 60 | 5.00% | nr |
| Tos 3814387 Denmark | prosp cohort (1970-1975) | nr | nr | nr | nr | nr | 278 [527] | 33.45% | nr |
| Tos 985199 Denmark | prosp cohort | nr | nr | 14 | nr | 1 to 8 years | 109 | 22.94% | diffuse tympanosclerosis |
| Velepic 21397957 Croatia | prosp rct (2004-2009) | nr | 5.44 [2.00, 12.00] | nr | 0 [100] | nr | [161] | [26.09%] | nr |

**Table H10. Atrophy or atelectasis or retraction**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Atrophy Atelectasis Retraction | Definition |
|---|---|---|---|---|---|---|---|---|---|
| Barfoed 7190819 Denmark | prosp cohort (nr) | nr | nr | 57 | 0[100] | 4.5 to 7.5 years | 90[173] | [25.00%] | atrophy at the former grommet site, anteriorly |
| Bonding 4215997 US | cohort (1967-1969) | nr | [=<3.00, 4.00] | 66.7 | 0 [100] | 16 to 48 months | 108 [175] | 13.89% | diffuse atrophy of the tympanic membrane |
| Bonding 4702615 Denmark | cohort | nr | nr | 66.7 | 0 [100] | nr | 117 [188] | 8.55% | atrophic drum |
| Daly 12759263 US | prosp cohort (1987-1990) | nr | [0.50, 8.00] | 61 | nr | 3 to 8 years | 138 [275] | [66.18%] | atrophy |
| Daly 9738746 US | cross-sectional (1985-1990) | [children treated with TT] | 17.70 (3.50) [13.00, 28.00] | 61 | 0 [100] | nr | 108 | 4.00% | severe TM retraction |
| De Beer 16151352 Netherlands | prosp ncrs | [positive history of otitis media and ventilation tube insertion] | nr | nr | nr | 16 years | 51[102] | 20.34% | atrophy at 18 years |
| Eliachar 6613541 | prosp cohort (1975-1981) | Goode long-term T-shaped silicone | 8.33 [4.50, | nr | nr | 8 to 72 months | 122 [203] | 100.00% | retraction pockets (75 in the attic, 82 - both in the |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Atrophy Atelectasis Retraction | Definition |
|---|---|---|---|---|---|---|---|---|---|
| Israel | | design tubes | 16.00] | | | | | | attic and posterior superior quandrant and 38 had other variations) |
| Fior 6526581 Italy | prosp cohort (1968-1978) | Shepard type | 3.00 [0.33, 6.00] | 60.6 | 100 [0] | 5 to 15 years | 61 [108] | [5.56%] | tympanic atrophy |
| Hörmann 1816937 Germany | prosp nrcs | [cleft palate - University of Hamburg] | 7.43 [5.00, 10.00] | nr | nr | 8 years | 126 [252] | 6.35% | retraction and atrophy |
| Li 10547462 US | prosp cohort (1987-1991) | Donaldson tubes, Reuter Bobbin tubes, Shepard tubes or other | nr | 57 | 0 [100] | 4 to 6 years | 109 [214] | 42.86% | severe pars tensa retraction |
| O'Niel 26115935 US | prosp cohort (2009-nr) | various, including Sheehy, Armstrong, T tube, Activent | 3 (2.8) [0.08 - 17' | 42.4 | 60[38] | 1 year post TT extrusion | 634[544] | 24.00% | nr |
| Paradise 11309632 US | prosp rct (1991-1995) | Armstrong [TT early treatment; underwent TT insertion at initiaition of symptoms] | 5.00 | 52.6 | 0 [100] | ~2 years | 121 [242] | [40.08%] | segmental atrophy |
| Pereira 16446953 Brazil | prosp cohort (2001-2002) | Short-term ventilation tubes, made of silicone, measuring 1.2 x 2.6 mm, type Donaldson | 2.89 (1.54) [0.92, 9.33] | 60 | 69.3 [30.7] | 38 months | 75 [150] | 39.73% | nr |
| Powell 25598389 UK | prosp cohort (2004-2005) | nr | 4.60 | nr | nr | 9 weeks to 10 years | 89 | 12.00% | tympanic membrane retraction pocket |
| Praveen 15992470 UK | prosp cohort (1998-2003) | Shah ventilation tubes | 5.00 [1.60, 14.50] | 64 | nr | nr | 606 [1174] | [4.43%] | attic reaction postoperatively |
| Saki 24303379 Iran | prosp cohort (2009-2011) | nr | [0.83, 6.00] | 55.8 | 0 [100] | 12 to 18 months | 208 | 27.88% | tympanic membrane atrophy |
| Smillie 25171763 Scotland | nrcs (2002-2012) | [no cleft lip palate; underwent VT insertion] | med 3.50 [0.60, 10.40] | 55 | nr | nr | 60 | 2.33% | retracted tympanic membrane; attic retraction |
| Tos 3814387 | prosp cohort | nr | nr | nr | nr | nr | 278 | [14.36%] | atrophy |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Atrophy Atelectasis Retraction | Definition |
|---|---|---|---|---|---|---|---|---|---|
| Denmark | (1970-1975) | | | | | | [527] | | |
| Tos 985199 Denmark | prosp cohort | nr | nr | 14 | nr | 1 to 8 years | 109 | 5.50% | Adhesive otitis with retracted, immobile drum, an entirely or partially atelectatic middle ear, and poor tubal function |
| Valtonen 12150521 Finland | prosp cohort (1983-1984) | Shah vent Teflon tube, inner diameter 1.1 mm | 0.84 [0.42, 1.33] | 58.4 | 34.2 [65.8] | 5 years | 281 [281] | 16.73% | retraction of pars flaccida (20); retraction of pars tensa (27) |
| Valtonen 16094135 Finland | prosp cohort (1983-1993) | Shah vent Teflon tube (Xomed) | nr | 51.4 | 0 [100] | 5 to 7.2 years | 72 [124] | 12.50% | pars tensa retraction of tympanic membrane |
| Velepic 21397957 Croatia | prosp rct (2004-2009) | nr | 5.44 [2.00, 12.00] | nr | 0 [100] | nr | [161] | [3.11%] | Severe Attic retractions |

**Table H11. Cholesteotoma**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Cholesteotoma | def_cholesteotoma |
|---|---|---|---|---|---|---|---|---|---|
| Barfoed 7190819 Denmark | prosp cohort (nr) | nr | nr | 57 | 0[100] | 4.5 to 7.5 years | 90[173] | 0% | nr |
| Birck 1267356 US | prosp cohort (1972-1974) | nr | nr | 59.2 | nr | 6+ months | 736 [2327] | [0.00%] | nr |
| Bonding 4215997 US | cohort (1967-1969) | nr | [=<3.00, 4.00] | 66.7 | 0 [100] | 16 to 48 months | 108 [175] | 1.85% | suppurative otitis media with cholesteatoma |
| Djurhuus 25724629 Denmark | retro cohort (1997-2011) | various [data from National Registers | nr | nr | nr | nr | 217206 | 0.17% | surgically treated |
| Eliachar 6613541 Israel | prosp cohort (1975-1981) | Goode long-term T-shaped silicone design tubes | 8.33 [4.50, 16.00] | nr | nr | 8 to 72 months | 122 [203] | [1.48%] | developed cholesteatoma in their pre-existing retractions pockets |
| Golz | retro cohort | "homemade" | 4.80 | 54.4 | 11.4 | 1 to 20 | 2829 | 2.19% | nr |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Cholesteotoma | def_cholesteotoma |
|---|---|---|---|---|---|---|---|---|---|
| 10406312 Israel | (1978-1997) | polyethylene tubes in 5143 ears, Goode T-tubes in 432 ears | (2.60) [1.20, 14.00] | | (ears) [88.6 (ears)] | years | [5575] | | |
| Gundersen 1267702 Norway | prosp cohort | polyethylene ventilating tube | 7.50 [1.00, 14.00] | nr | 0 [100] | 2 to 11 years | 100 [196] | [5.61%] | cholesteatoma |
| Heaton 8877228 UK | prosp cohort (1986-1988) | nr | 5.00 [1.00, 12.00] | 60.6 | 0 [100] | nr | 127 | 0.79% | nr |
| Hörmann 1816937 Germany | prosp nrcs | [cleft palate - University of Hamburg] | 7.43 [5.00, 10.00] | nr | nr | 8 years | 126 [252] | 0.00% | nr |
| Kinnari 20122337 Finland | prosp rct (2001-2002) | Xomed Soileau Tytan | 4.1[0.5, 15] | 61 | 36[64] | until extrusion or removal | 170[298] | 0.00% | |
| Kokko 1267359 Finland | cohort (1965-1971) | nr | nr | nr | nr | 3.167 years (average) | [290] | [0.69%] | attic cholesteatoma |
| Luo 25465449 China | prosp nrcs (2011-2012) | [tympanostomy tube insertion] | 4.80 (1.00) [2.00, 8.00] | 50.9 | nr | 2 years | 55 | 10.91% | cholesteatoma in the attic |
| MacKinnon 4105168 UK | prosp cohort (1965-1971) | nr | =<16.00 | nr | nr | nr | 95 [165] | 6.32% [4.85%] | cholesteatoma after previous exudative otitis media |
| Muenker 6778334 Germany | prosp cohort (1966-1978) | nr | nr | nr | nr | nr | 631 [1060] | 1.58% | preexisting cholesteatoma was revealed behind an intact tympanic membrane on 3 occasions |
| O'Niel 26115935 US | prosp cohort (2009-nr) | various, including Sheehy, Armstrong, T tube, Activent | 3 (2.8) [0.08 - 17' | 42.4 | 60[38] | 1 year post TT extrusion | 634[544] | 0.56% | nr |
| Paradise 2181158 US | prosp rct/nrcs (1971-1985) | [TT & Adenoidectomy] | nr | 67 | nr | nr | 97 | 0.80% | nr |
| Pereira 16446953 Brazil | prosp cohort (2001-2002) | Short-term ventilation tubes, made of silicone, measuring 1.2 x 2.6 mm, type Donaldson | 2.89 (1.54) [0.92, 9.33] | 60 | 69.3 [30.7] | 38 months | 75 [150] | [0.00%] | nr |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Cholesteotoma | def_cholesteotoma |
|---|---|---|---|---|---|---|---|---|---|
| Powell 25598389 UK | prosp cohort (2004-2005) | nr | 4.60 | nr | nr | 9 weeks to 10 years | 89 | 1.33% | otolaryngology-clinic-diagnosed cholesteatoma |
| Rothera 4040147 UK | prosp cohort (1980-1982) | Xomed silicone Goode T-Tubes (1.1 mm. internal diameter, 12 mm. length) | nr | nr | 0 [100] | 30 months | 73 [131] | 0.00% | nr |
| Smillie 25171763 Scotland | nrcs (2002-2012) | [no cleft lip palate; underwent VT insertion] | med 3.50 [0.60, 10.40] | 55 | nr | nr | 60 | 3.33% | posterior pars tensa cholesteatoma |
| Spilsbury 23737350 Austalia | retro cohort (1980-2009) | nr | nr | 59.7 | nr | 11.9 years | 56949 | 1.04% | nr |
| Tos 3814387 Denmark | prosp cohort (1970-1975) | nr | nr | nr | nr | nr | 278 [527] | [0.28%] | attic cholesteatoma |
| Tos 7192477 Denmark | cohort | Armstrong tube | nr | nr | 0 [100] | 6 months | [527] | 0.20% | deep retraction pocket, the bottom of which could not be seen |
| Tos 985199 Denmark | prosp cohort | nr | nr | 14 | nr | 1 to 8 years | 109 | 1.83% | cholesteatoma in the attic |

**Table H12. Hearing loss**

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Hearing Loss | Definition |
|---|---|---|---|---|---|---|---|---|---|
| Brown 8231117 US | cohort | Goode T-tubes | nr | nr | nr | 6 months | 168 [328] | 1.19% | conductive hearing loss |
| Costa 3472336 Brazil | prosp cohort | nr | nr | nr | 0 [100] | nr | 79 | 1.27% | unilateral sensorineural hearing loss |
| Daly 12759263 US | prosp cohort (1987-1990) | nr | [0.50, 8.00] | 61 | nr | 3 to 8 years | 138 [275] | [91.27%] | hearing loss |
| Daly 9738746 US | cross-sectional | [children treated with TT] | 17.70 (3.50) | 61 | 0 [100] | nr | 108 | 10.00% | nr |

| Author PMID Country | Design (recruitment period) | Tube Type [arm desc.] | Age (SD) [min, max] | % male | %rAOM [%COME] | Followup | N [ears] | % Hearing Loss | Definition |
|---|---|---|---|---|---|---|---|---|---|
| | (1985-1990) | | [13.00, 28.00] | | | | | | |
| Gundersen 1267702 Norway | prosp cohort | polyethylene ventilating tube | 7.50 [1.00, 14.00] | nr | 0 [100] | 2 to 11 years | 100 [196] | [20.92%] | hearing was not normal, varying from a pure-tone average (PTA) of 25 to 60 dB hearing level (PTA was measured as the mean hearing loss for the frequencies 500, 1,000 and 2,000 hertz.) |
| Isaacson 18722211 US | prosp cohort (1997-2007) | Armstrong beveled grommet tube | [0.11, 21.00] | nr | nr | nr | [10000] | 0.02% | profound hearing loss, both were found to have Mondini malformations by CT |
| Mackenzie 6541254 UK | prosp cohort (1978-1980) | Pappas 1974, Shah 1971 (Exmoor 142, Shepard 137, Bobbin 132, Arrow 58, Shah 131, Armstrong 138, Colar Button 141, Paparella 60) | 10.80 [0.75, 77.00] | 58.3 | 0 [100] | 2.25 years | 588 [939] | 28.38% | by audiometric assessment at 3 month |
| Owen 8436453 US | prosp cohort | Armstrong bevelled tube | 2.08 [0.42, 4.00] | nr | nr | 6 months | 52 [98] | [7.94%] | moderate hearing loss (27.5-50 dB) |
| Spielmann 18047760 UK | prosp cohort (2003-2004) | nr [second cohort] | 5.30 [0.83, 9.00] | 61.4 | 18.8 [81.2] | 3 months | 84 [195] | 35.62% | a mean hearing threshold greater than 20 dB |
| Tuli 23119801 India | cohort | nr | nr | 66.7 | 0 [100] | nr | 100 | 8.00% | worsening of hearing |

# Appendix I. Network Meta-Analysis Model, Inconsistency Analysis Results, and Illustrative Trace and Posterior Density Plots

The meta-analysis models used in this report are described here in a technical manner. We describe the network meta-analysis model, noting that the simple meta-analysis model is a special case of the network model, setting the number of treatments (nodes) to 2.

## Network Meta-Analysis Model

The network meta-analysis model is a hierarchical model that has an observational and a structural part (model).

## Observational Model

$y_{kj} \sim N(\mu_{kj}, \sigma_{kj}^2)$, and

$\mu_{kj} = \mu_k + \mathbf{X}\mathbf{T}_k$,

with $k = 1, \ldots, K$ indexing the $K$ studies, and $j = 1, 2, \ldots$ indexing treatment arms. $y_{kj}$ is the mean of the modeled continuous outcome in arm $j$ of study $k$. $\mathbf{X}$ is a design matrix corresponding arms to treatment effects. $\mathbf{T}_k = (T_{k1}, \ldots, T_{k,N-1})'$ is a column vector of study-specific treatment effects for the $N-1$ treatments versus a reference treatment , which is chosen arbitrarily. $\mu_k$ is the mean in study $k$ for the reference treatment.

## Structural Model

Between studies, the study-specific treatment effects are modeled with a multivariate normal distribution

$\mathbf{T}_k \sim N(\mathbf{T}, \Omega)$,

where $\Omega$ is a compound symmetry matrix of dimension $N-1$, with all diagonal elements equal to $\tau^2$ and all off diagonal elements equal to $\tau^2/2$, and $\mathbf{T} = (T_1, \ldots, T_{N-1})'$ is a column vector of $N-1$ between-study effect means.

## Hyperparameters

We used normal hyperpriors for means and a uniform prior for standard deviations. Specifically, $\mathbf{T} \sim N(\mathbf{0}, c\mathbf{I})$ and

$\tau \sim U(0, m)$

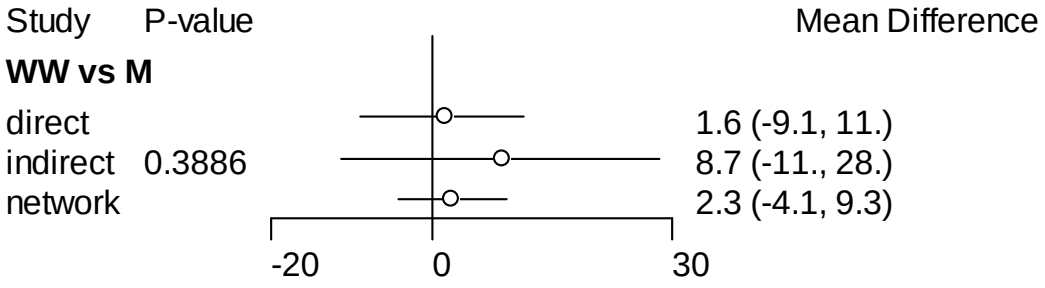
where $\mathbf{0}$ is a column vector of zeros, $\mathbf{I}$ a conformal identity matrix and $c$ and $m$ scaling factors that are set to 15 and 5 times the range of observed effects, respectively.

To check for inconsistency we conducted split node analyses. We replaced each treatment effect $T_j, j > 0$ that compares the $j$-th treatment with the baseline one $(j = 0)$, with a direct effect, and an indirect effect, separating the contributions of head-to-head evidence and indirect evidence and examined whether the difference between them was beyond 0.

## Inconsistency Analysis Results

An ensemble of relevant node-splitting models were generated. Results of direct vs. indirect vs. entire network are plotted below along with inconsistency Bayesian P values for each split comparison.

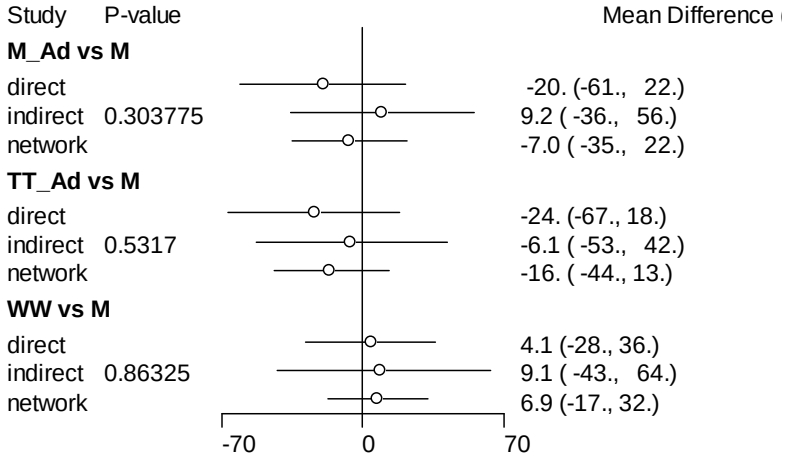
**Appendix Figure I1. Inconsistency analysis results for KQ1 – early hearing levels**



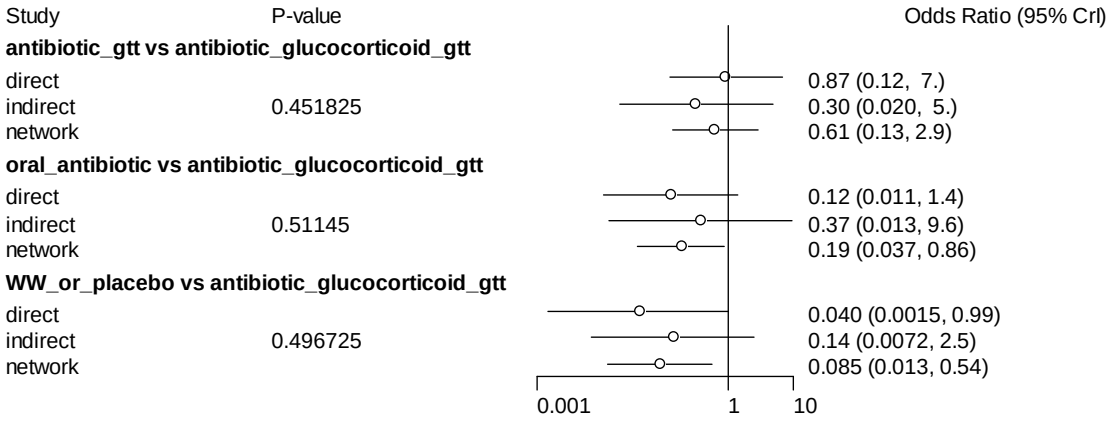

## KQ 1: Late Hearing Levels

There cannot be inconsistency in this network, given that estimates arise from a single trial with three arms.

**Appendix Figure I2. Inconsistency analysis results for KQ1 – duration of middle ear effusion**



**Appendix Figure I3. Inconsistency analysis results for KQ5**




**Appendix Figure I4. Illustrative trace and posterior density plot for KQ5 network meta-analysis**