

# **Tympanostomy Tubes in Children With Otitis Media**



# *Comparative Effectiveness Review*

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**Number 185**

## **Tympanostomy Tubes in Children With Otitis Media**

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**Prepared by:**

Brown Evidence-based Practice Center  
Providence, RI

**Investigators:**

Dale Steele, M.D., M.S.  
Gaelen P. Adam, M.L.I.S.  
Mengyang Di, M.D., Ph.D.  
Christopher Halladay, B.A., Sc.M.  
Ian Pan, M.A.  
Nathan Coppersmith, B.A.  
Ethan M. Balk, M.D., M.P.H.  
Thomas A. Trikalinos, M.D., Ph.D.

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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](http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm).

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Sharon B. Arnold, Ph.D.  
Acting Director  
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.  
Director  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.  
Director  
Evidence-based Practice Center Program  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Lionel L. Bañez, M.D.  
Task Order Officer  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

## Key Informants

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.

The list of Key Informants who provided input to this report follows:

Margaretha Casselbrandt, M.D., Ph.D.\*  
Department of Pediatric Otolaryngology  
Children's Hospital of Pittsburgh  
Pittsburgh, PA

Alison Grimes, Au.D.\*  
Audiology Department  
UCLA Medical Center  
Los Angeles, CA

David Hoelting, M.D.  
Pender Medical Clinic  
Pender Community Hospital  
Pender, NE

Alison Kelly, B.S.N., R.N., C.P.E.N.  
Hasbro Children's Hospital  
Providence, RI

Josiah Morse, M.P.H.  
Washington State Health Technology  
Assessment Program  
Olympia, WA

Richard Rosenfeld, M.D., M.P.H., FAAP\*  
Department of Otolaryngology  
SUNY Downstate Medical Center  
Brooklyn, NY

David E. Tunkel, M.D.\*  
Director of Pediatric Otolaryngology  
Johns Hopkins University School of Medicine  
Baltimore, MD

\*Provided input on draft report.

## Technical Expert Panel

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.

Technical Experts 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 conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:

Alison Grimes, Au.D.\*  
Audiology Department  
UCLA Medical Center  
Los Angeles, CA

David Hoelting, M.D.  
Pender Medical Clinic  
Pender Community Hospital  
Pender, NE

Howard J. Hoffman, B.S., M.A.\*  
Epidemiology and Statistics Program  
Division of Scientific Programs  
National Institute on Deafness and Other  
Communication Disorders  
National Institutes of Health  
U.S. Department of Health and Human Services  
Bethesda, MD

Richard Rosenfeld, M.D., M.P.H., FAAP\*  
Department of Otolaryngology  
SUNY Downstate Medical Center  
Brooklyn, NY

Lorry Rubin, MD\*  
Hofstra North Shore-LIJ School of Medicine  
Hempstead, NY

David E. Tunkel, M.D.\*  
Director of Pediatric Otolaryngology  
Johns Hopkins University School of Medicine  
Baltimore, MD

Roderick Venekamp, M.D., M.Sc., Ph.D.\*  
University Medical Center Utrecht  
Julius Center for Health Sciences and Primary  
Care &  
Department of Otorhinolaryngology  
The Netherlands

\*Provided input on draft report.

## Peer Reviewers

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.

The list of Peer Reviewers follows:

Christine Dollaghan, Ph.D.  
School of Behavioral and Brain Sciences  
University of Texas at Dallas  
Richardson, TX

Sharon Meropol, M.D., Ph.D.  
Case Western Reserve University School of Medicine  
Rainbow Babies and Children's Hospital  
Cleveland, OH

# 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<sup>®</sup>, the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, Embase<sup>®</sup>, and CINAHL<sup>®</sup>. 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.<sup>1,2</sup> OME is defined as chronic OME, if effusion persists for 3 months or longer.<sup>1</sup> 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.<sup>3</sup> 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.<sup>4</sup>

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.<sup>1,5</sup>

Myringotomy with TT placement is the most common ambulatory surgery performed on children in the United States<sup>6</sup>, with 667,000 TT placed in children under the age of 15 in 2006.<sup>7</sup> 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.<sup>8</sup>

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.<sup>9</sup>

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.<sup>1</sup>

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.<sup>10</sup> 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.<sup>11</sup>

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?

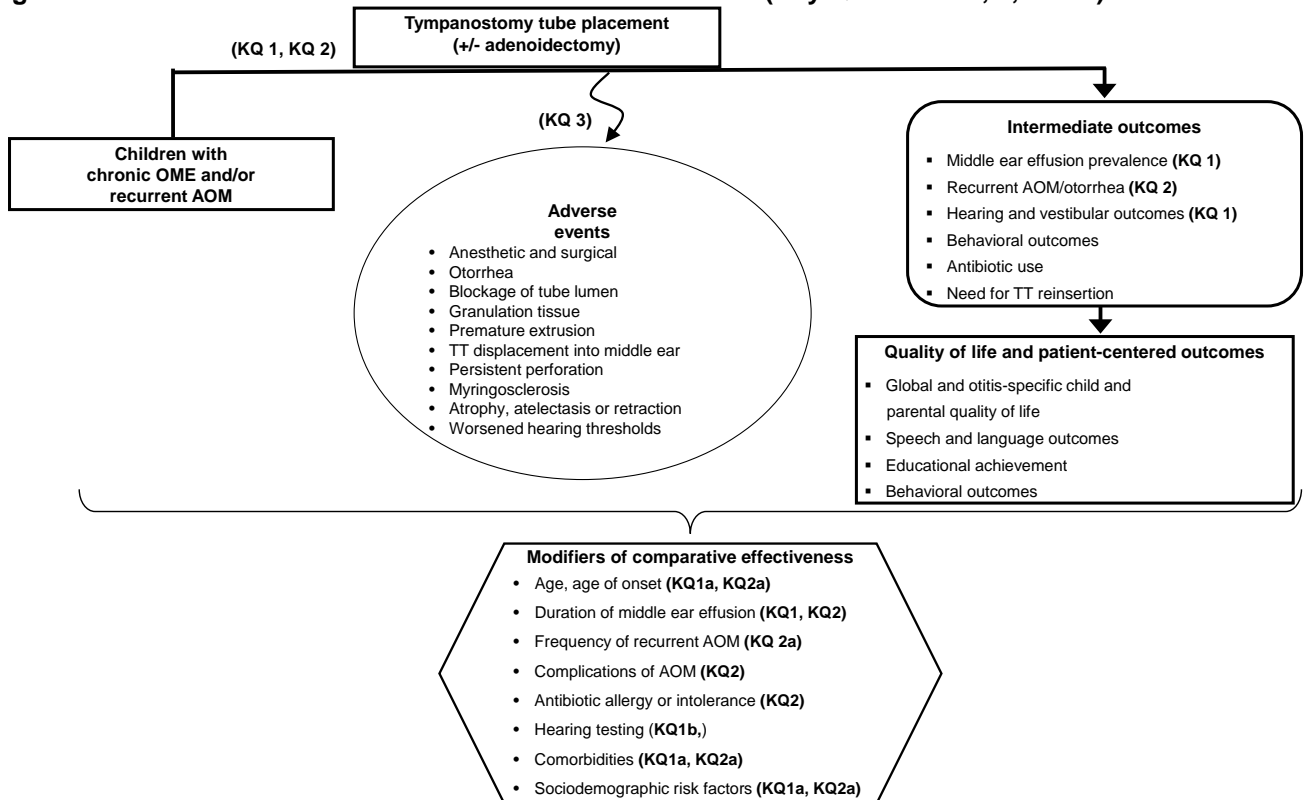
**Key Question 4:** Do water precautions reduce the incidence of TT otorrhea or affect quality of life?

**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

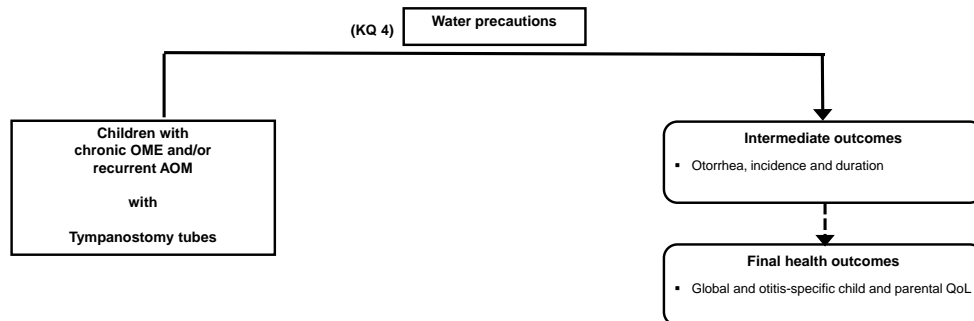
The analytic frameworks in Figures A through C describe the specific linkages associating the populations of interest, exposures, modifying factors, and outcomes of interest in the assessment of studies that examine the association between TT placement, intermediate and final health outcomes, and harms (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)**



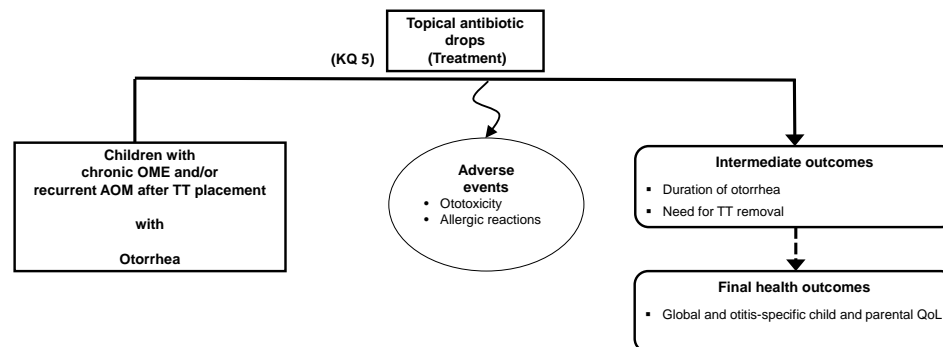
OME=otitis media with effusion; AOM=acute otitis media; TT=tympanostomy tubes; KQ=Key Question

**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.<sup>12</sup> 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,<sup>1</sup> 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.<sup>1</sup> 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 [NRCSSs]) 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<sup>®</sup>, the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, Embase<sup>®</sup>, and CINAHL<sup>®</sup> 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.<sup>13</sup> For observational studies, we used relevant questions from the Newcastle Ottawa Scale.<sup>14</sup>

## **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.<sup>15</sup>

## **Assessing Applicability**

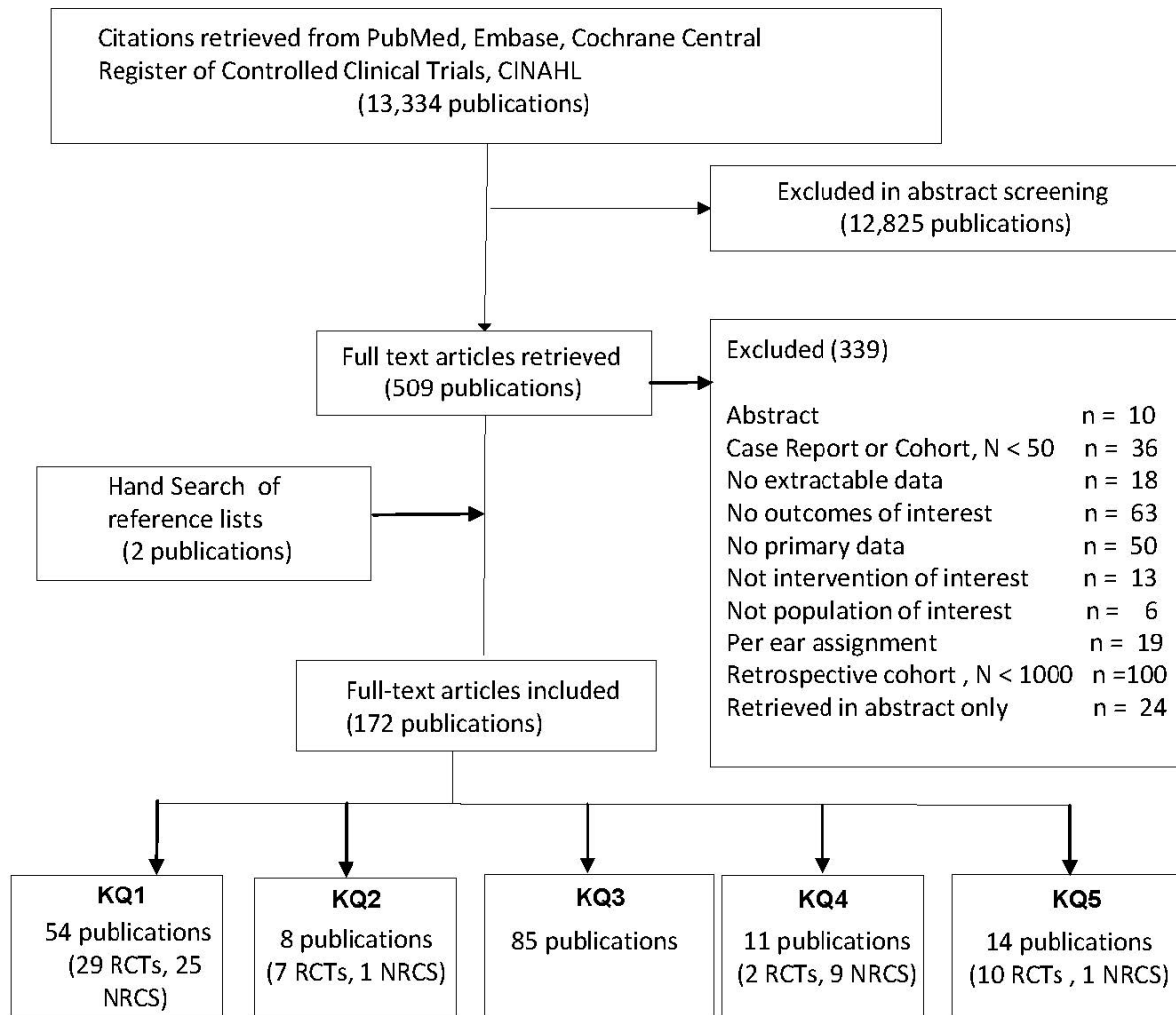
We assessed the direct applicability within and across studies with reference to children with specific comorbidities (Down syndrome, cleft palate, etc.), and whether interventions and comparators are used in current practice.

## **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

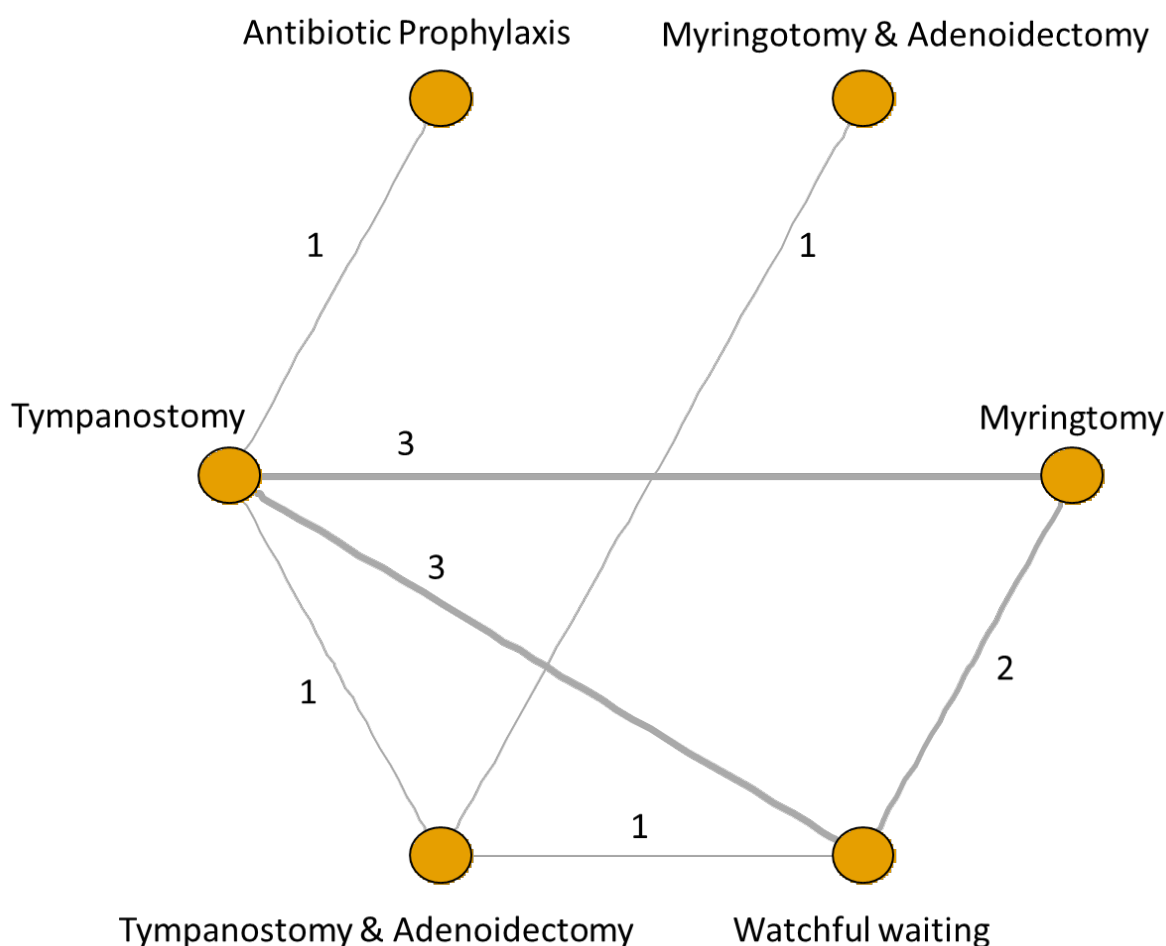
We identified 54 publications. Of these, there were 29 papers reporting results of 16 RCTs. There were 24 publications reporting 24 NRCSs that assessed the effectiveness of TT in pediatric patients with chronic middle ear effusion. These studies evaluated multiple interventions (TT, TT with adenoidectomy, myringotomy with adenoidectomy, myringotomy 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 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**



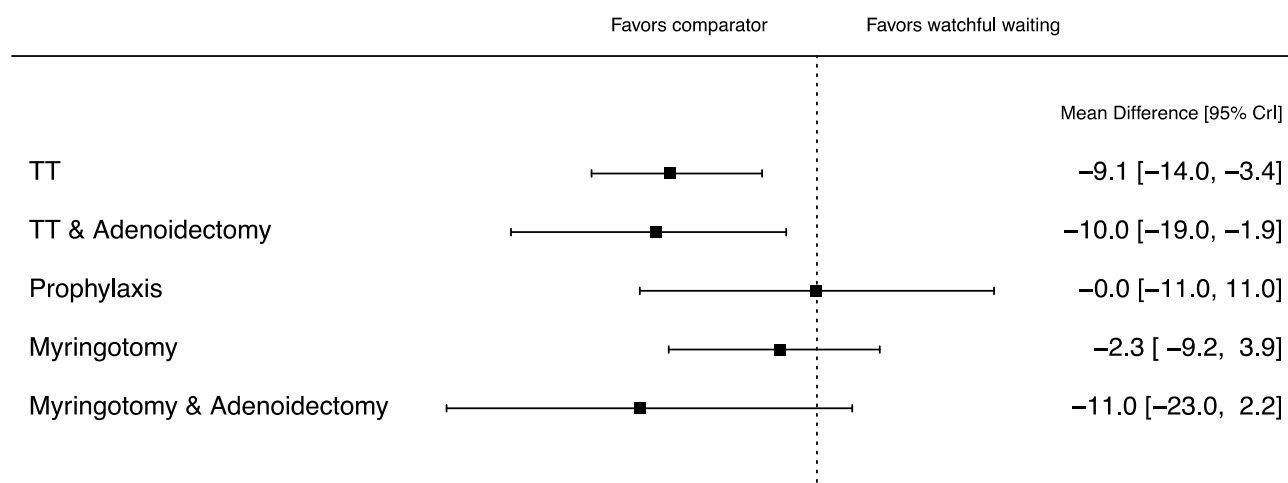
The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

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**

**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.

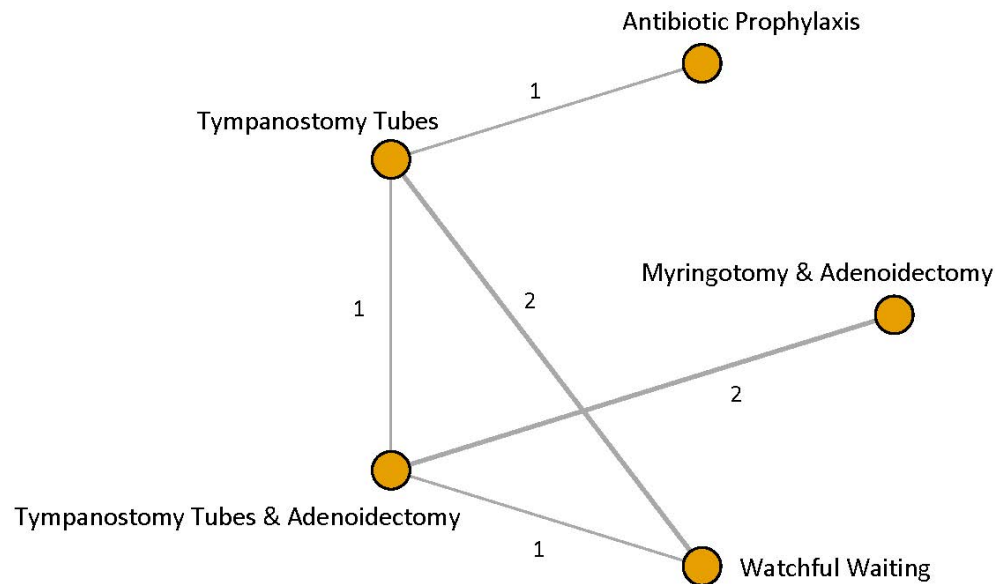
**Table A. Probabilities (percent) that an intervention is among the three most effective with respect to early hearing thresholds**

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**

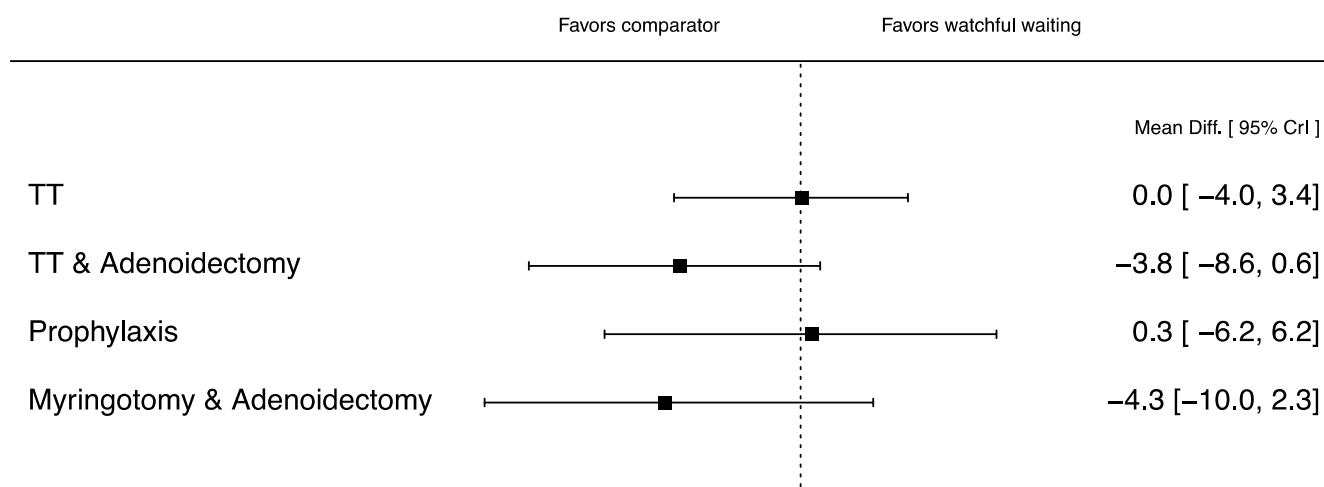


The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

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**

**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 in 169 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<sup>th</sup> and 75<sup>th</sup> 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 NRCs, 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 Enrollment dates Country (Design)	Followup time	Intervention	Population	n/N (%)	Odds ratio (95% CI)
Goldstein 2005 15689760 7/1996-6/1999 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 12/1989-2/1991 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]

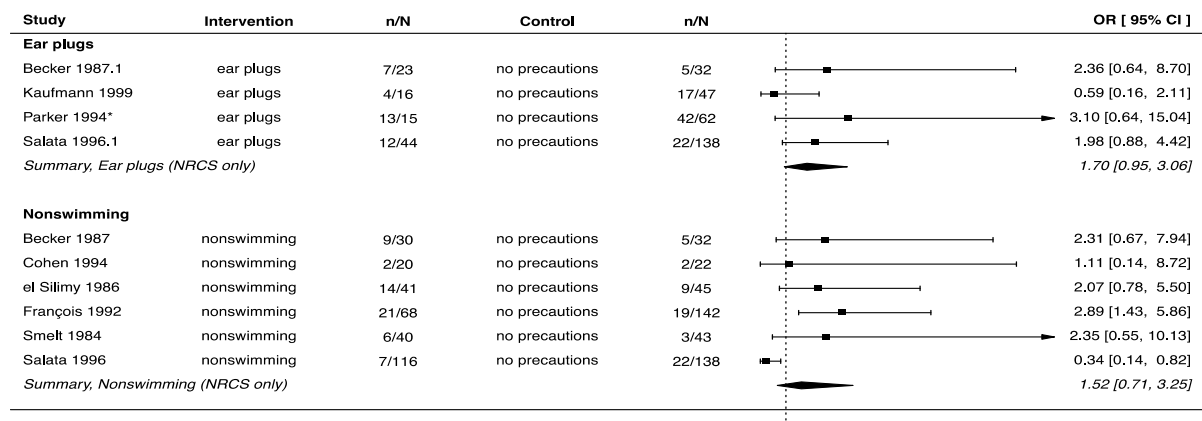
†Randomized to the nonswimming group, but self-selected to swim using ear precautions (e.g., ear plugs, wax, cotton with petroleum jelly) – considered an NRCS in the meta-analysis.

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))

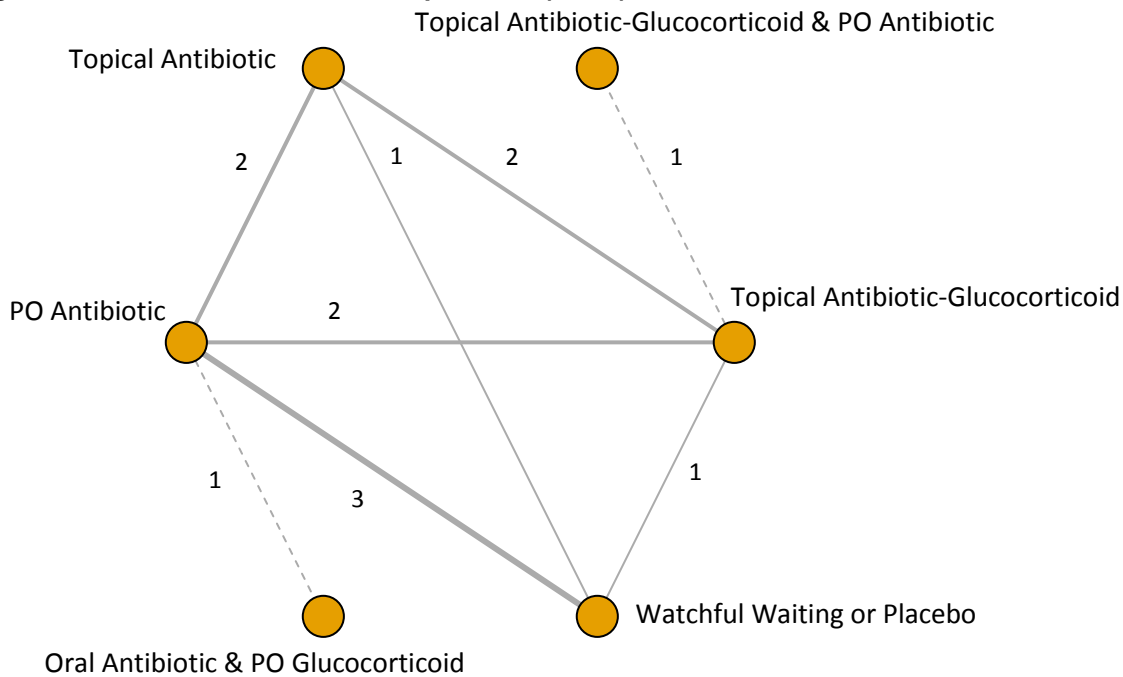
Overall, aside from the small reduction in mean number of episodes of otorrhea found in the Goldstein RCT, the available evidence does not support the conclusion that either ear plugs or avoidance of swimming reduces the risk of otorrhea related to swimming.

## 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).

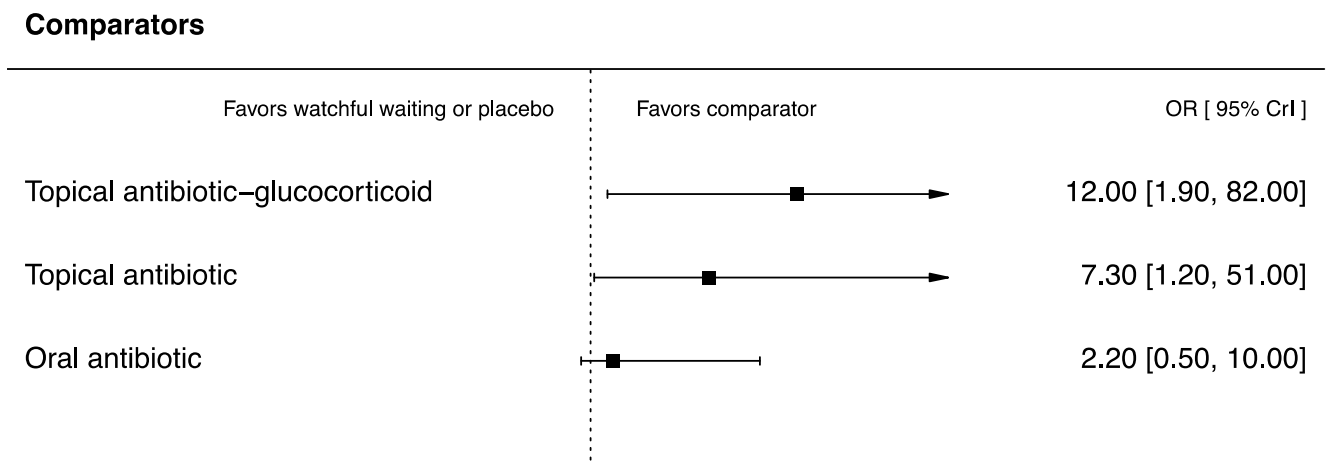
After excluding 4 studies, 7 studies were included in the network meta-analysis. We chose the time designated by each study as the test of cure (range 7 to 20 days after initiation of treatment). As shown in Table E, treatment strategies that include topical antibiotic drops predominate over both oral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

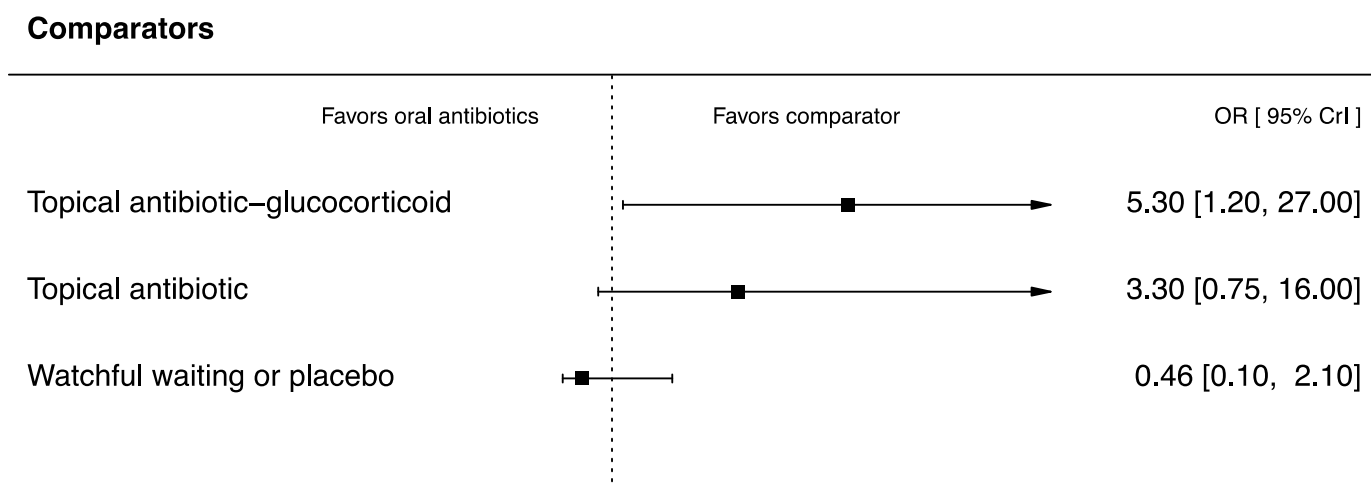
**Figure K. Relative effectiveness of interventions compared to watchful waiting or placebo therapy**



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% CrI 12% - 26%; NNT (Number Needed to Treat) = 6). No significant benefit of adenoidectomy was found in children less than 4 years old.<sup>3</sup>

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.<sup>16</sup>

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.<sup>17</sup> 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.<sup>18</sup> A second RCT, with high risk of bias, found a statistically nonsignificant difference in the odds ratio in nonswimmers versus swimmers.<sup>19</sup> 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)]<sup>a</sup> 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)]<sup>b</sup> 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)].<sup>c</sup> The odds ratio for topical antibiotic drops was 3.3 (95% CrI: 0.74 – 16)[NNT 5 (assuming a baseline rate of 0.69)]<sup>d</sup>, 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.

<sup>a</sup> 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)

<sup>b</sup> 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)

<sup>c</sup> 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)

<sup>d</sup> 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
<b>Key Question 1- effectiveness of TT in children with chronic otitis media with effusion</b>		
Treatment with TT results in short term improvements in <b>hearing thresholds</b> , compared to <b>Watchful waiting</b>	Moderate	Network metaanalysis -9.1 (CrI: -14.5, -3.2) dB at 1 to 3 months
Improvements in <b>hearing thresholds</b> are not sustained at 12 to 24 months.	Moderate	Network meta-analysis 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 -3.8 (CrI: -8.5, 0.62) at 12-24 months (92% probability one of 3 most effective interventions)
Periods of watchful waiting <b>do not</b> result in consistently <b>worse cognitive, language, behavioral or quality of life</b> outcomes in children without comorbidities.	Low	Limited number of studies (8), each using different outcome definitions No quantitative synthesis done
<b>Key Question 2 - Comparative effectiveness of TT in recurrent acute otitis media</b>		
Treatment with TT does not improve <b>quality of life</b>	Low	Limited number of RCTs (1) No quantitative synthesis done
<b>Key Question 4 – Effectiveness of ear plugs or avoidance of swimming</b>		
Ear plugs or avoidance of swimming <b>does not</b> reduce the risk of otorrhea after swimming	Low	Limited number of studies (2 RCTs) Meta-analysis of 7 NRCSs
<b>Key Question 5 – Effectiveness of topical antibiotic drops vs. systemic antibiotics or watchful waiting</b>		
Topical antibiotic-glucocorticoid drops are superior to oral antibiotics in achieving <b>clinical cure</b>	Moderate	Network meta-analysis OR: 5.3 (CrI: 1.2, 27.0)
Topical antibiotic drops are superior to oral antibiotics in achieving <b>clinical cure</b>	Low	Network meta-analysis OR: 3.3 (CrI: 0.75, 16.0) (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 OR: 12.0 (CrI: 1.9, 82) [antibiotic-glucocorticoid] 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.<sup>20</sup>

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

## 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.

## References

1. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: Tympanostomy tubes in children. *Otolaryngol Head Neck Surg*. 2013 Jul;149(1 Suppl):S1-35. doi: 10.1177/0194599813487302. PMID: 23818543.
2. Schilder AG, Chonmaitree T, Cripps AW, et al. Otitis media. *Nat Rev Dis Primers*. 2016;2:16063. doi: 10.1038/nrdp.2016.63. PMID: 27604644.
3. Boonacker CW, Rovers MM, Browning GG, et al. Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. *Health Technol Assess*. 2014 Jan;18(5):1-118. doi: 10.3310/hta18050. PMID: 24438691.
4. Grindler DJ, Blank SJ, Schulz KA, et al. Impact of Otitis Media Severity on Children's Quality of Life. *Otolaryngol Head Neck Surg*. 2014 Mar 13;151(2):333-40. doi: 10.1177/0194599814525576. PMID: 24627408.
5. Rosenfeld RM, Jang DW, Tarashansky K. Tympanostomy tube outcomes in children at-risk and not at-risk for developmental delays. *Int J Pediatr Otorhinolaryngol*. 2011 Feb;75(2):190-5. doi: 10.1016/j.ijporl.2010.10.032. PMID: 21106257.
6. Rettig E, Tunkel DE. Contemporary concepts in management of acute otitis media in children. *Otolaryngol Clin North Am*. 2014 Oct;47(5):651-72. doi: 10.1016/j.otc.2014.06.006. PMID: 25213276.
7. Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. *Natl Health Stat Report*. 2009 Jan 28(11):1-25. PMID: 19294964.
8. Proceedings from the National Summit on Overuse. 2012. The Joint Commission. [https://www.jointcommission.org/assets/1/6/National\\_Summit\\_Overuse.pdf](https://www.jointcommission.org/assets/1/6/National_Summit_Overuse.pdf). Accessed December 21, 2016.
9. Hoffman HJ, Daly KA, Bainbridge KE, et al. Panel 1: Epidemiology, natural history, and risk factors. *Otolaryngol Head Neck Surg*. 2013 Apr;148(4 Suppl):E1-E25. doi: 10.1177/0194599812460984. PMID: 23536527.
10. Casselbrant ML, Kaleida PH, Rockette HE, et al. In reference to What is the role of tympanostomy tubes in the treatment of recurrent acute otitis media? *Laryngoscope*. 2013 Dec;123(12):E127. doi: 10.1002/lary.24142. PMID: 24105683.
11. van Dongen TM, Schilder AG, Venekamp RP, et al. Cost-effectiveness of treatment of acute otorrhea in children with tympanostomy tubes. *Pediatrics*. 2015 May;135(5):e1182-9. doi: 10.1542/peds.2014-3141. PMID: 25896832.
12. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012.
13. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi: 10.1136/bmj.d5928. PMID: 22008217.
14. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.
15. Berkman ND, Lohr KN, Ansari M, et al. AHRQ Methods for Effective Health Care: Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
16. Rovers MM, Black N, Browning GG, et al. Grommets in otitis media with effusion: an individual patient data meta-analysis. *Arch Dis Child*. 2005 May;90(5):480-5. doi: 10.1136/adc.2004.059444. PMID: 15851429.
17. Gonzalez C, Arnold JE, Woody EA, et al. Prevention of recurrent acute otitis media: chemoprophylaxis versus tympanostomy tubes. *Laryngoscope*. 1986 Dec;96(12):1330-4. PMID: 3537596.

18. Goldstein NA, Mandel EM, Kurs-Lasky M, et al. Water precautions and tympanostomy tubes: a randomized, controlled trial. *Laryngoscope*. 2005 Feb;115(2):324-30. doi: 10.1097/01.mlg.0000154742.33067.fb. PMID: 15689760.
19. Parker GS, Tami TA, Maddox MR, et al. The effect of water exposure after tympanostomy tube insertion. *Am J Otolaryngol*. 1994 May-Jun;15(3):193-6. PMID: 8024107.
20. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. *Otolaryngol Head Neck Surg*. 2001 Apr;124(4):374-80. PMID: 11283489.
21. Idicula WK, Juncisek JA, Cass ND, et al. Identification of biofilms in post-tympanostomy tube otorrhea. *Laryngoscope*. 2016 Aug;126(8):1946-51. doi: 10.1002/lary.25826. PMID: 27426942.

# 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.<sup>1,2</sup> OME is defined as chronic OME, if effusion persists for 3 months or longer.<sup>1</sup> 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.<sup>3</sup>

Myringotomy with TT placement is the most common ambulatory surgery performed on children in the United States<sup>4</sup>, with 667,000 TT placed in children under the age of 15 in 2006.<sup>5</sup> 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.<sup>6</sup>

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.<sup>7</sup>

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.<sup>8</sup> 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.<sup>9</sup> 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.<sup>10</sup>

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.<sup>11</sup> 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.<sup>12</sup> 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.<sup>1</sup> 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.<sup>13</sup>

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.<sup>14</sup> 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.<sup>1</sup> The American Academy of Pediatrics CPG discourages routine use of prophylactic antibiotics to prevent recurrent AOM.<sup>15</sup> 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.<sup>16</sup> They discuss systematic reviews published in 1999 and 2002 and a randomized controlled trial published in 2005 and conclude that water precautions should not be routinely advised.

Acute otorrhea is common after TT placement.<sup>17</sup> 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.<sup>18</sup> 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.<sup>19</sup> 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 *Staphylococcus aureus* (MRSA), and *Pseudomonas* associated with biofilms.<sup>20</sup>

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?

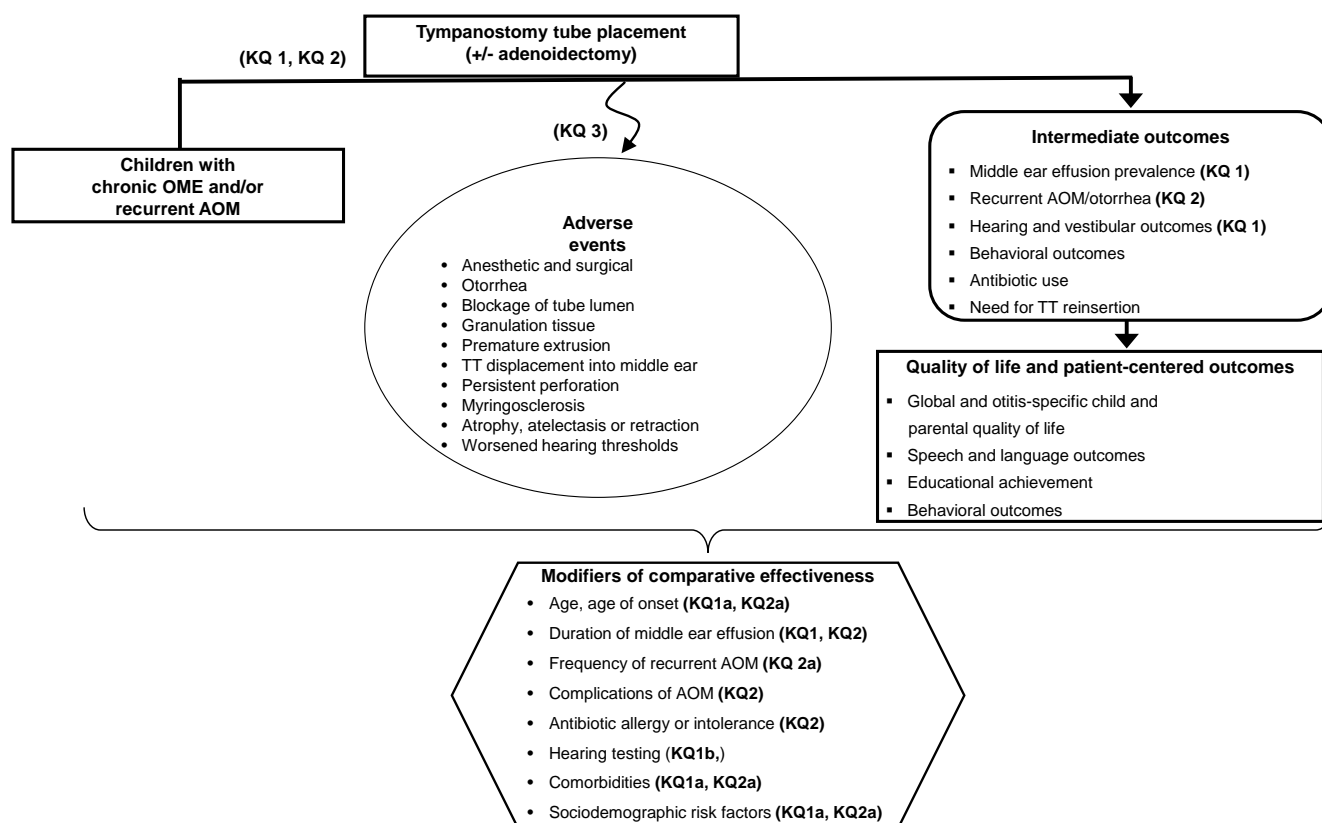
**Key Question 4:** Do water precautions reduce the incidence of TT otorrhea or affect quality of life?

**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**

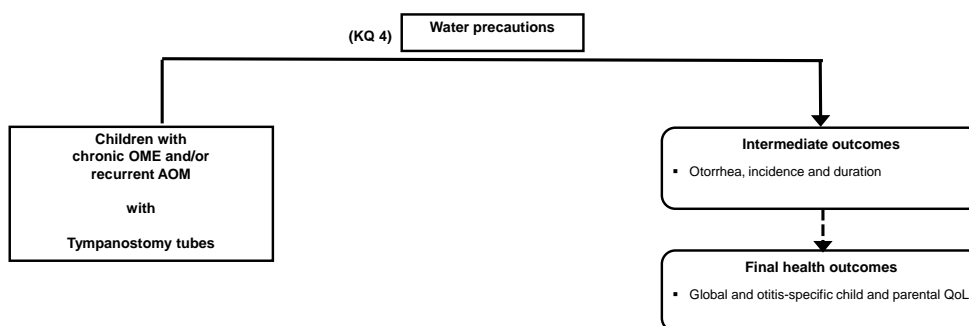
The analytic frameworks in Figures 1 through 3 describe the specific linkages associating the populations of interest, exposures, modifying factors, and outcomes of interest the assessment of studies that examine the association between TT placement and intermediate and final health outcomes and harms (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)**



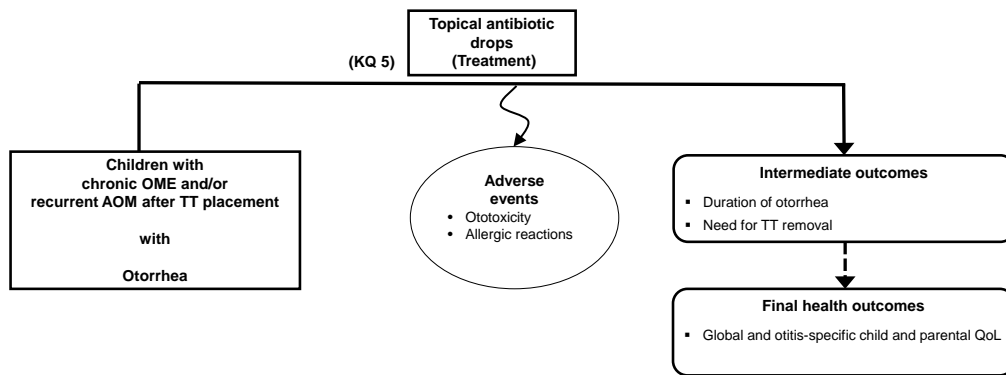
OME=otitis media with effusion; AOM=acute otitis media; TT=tympanostomy tubes; KQ=Key Question

**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=typanostomy 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.<sup>21</sup> 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).<sup>22</sup> 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,<sup>1</sup> 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.<sup>23</sup> 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 (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 NRCs with 50 or more patients) and population based retrospective single-group studies (registry studies) with  $\geq 1000$  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/](http://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,<sup>24</sup> 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.<sup>25</sup> 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,<sup>26</sup> and estimated them by maximizing the restricted likelihood in a generalized linear mixed model, using the R<sup>27</sup> package *metafor*.<sup>28</sup>

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.<sup>29, 30</sup> 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,<sup>31</sup> 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.<sup>32</sup> 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.<sup>33, 34</sup> 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.<sup>35</sup> 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.

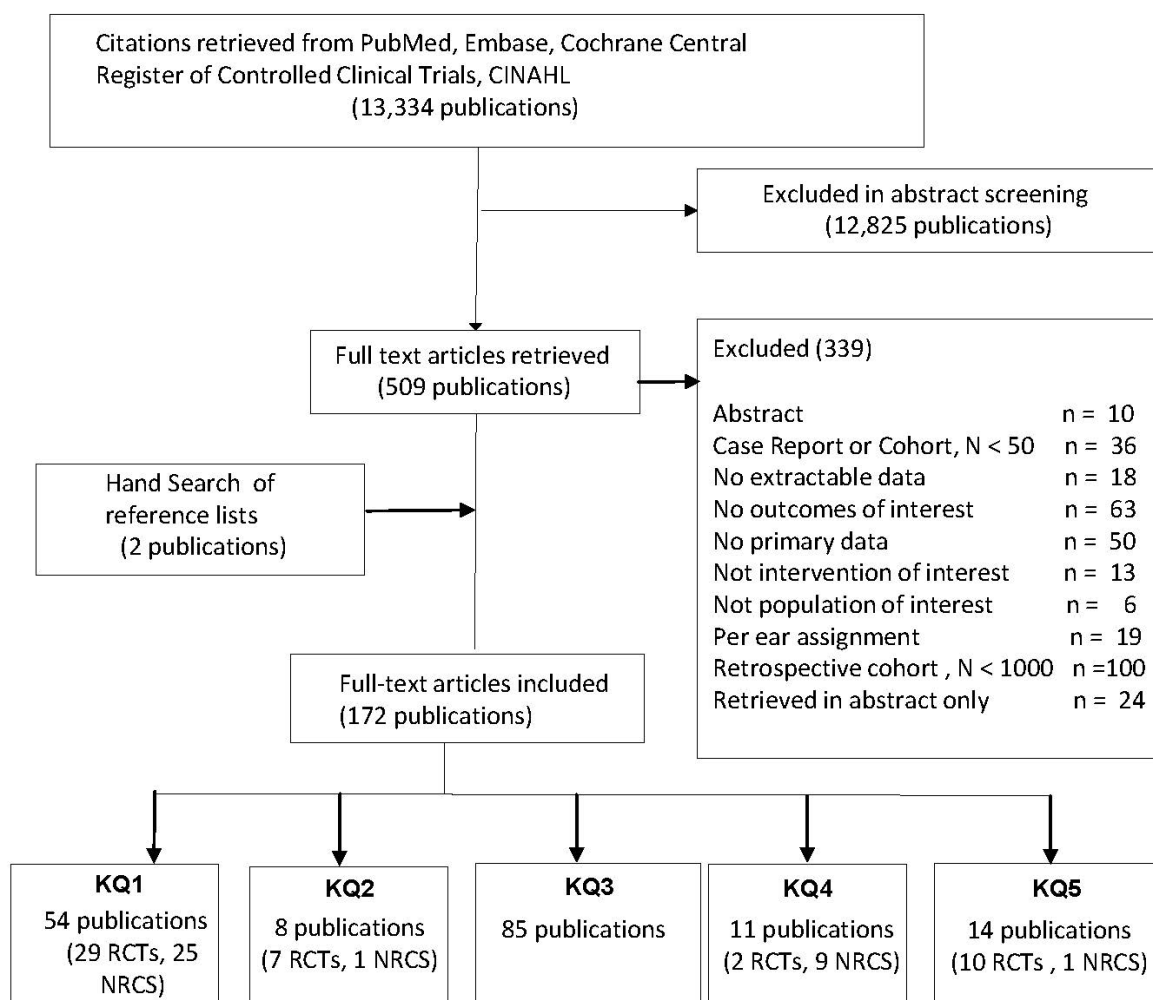
## Results

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 ( $\geq 1000$  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?

- 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?
- Does obtaining a hearing test help identify which children are more likely to benefit from the intervention?

## Eligible Studies

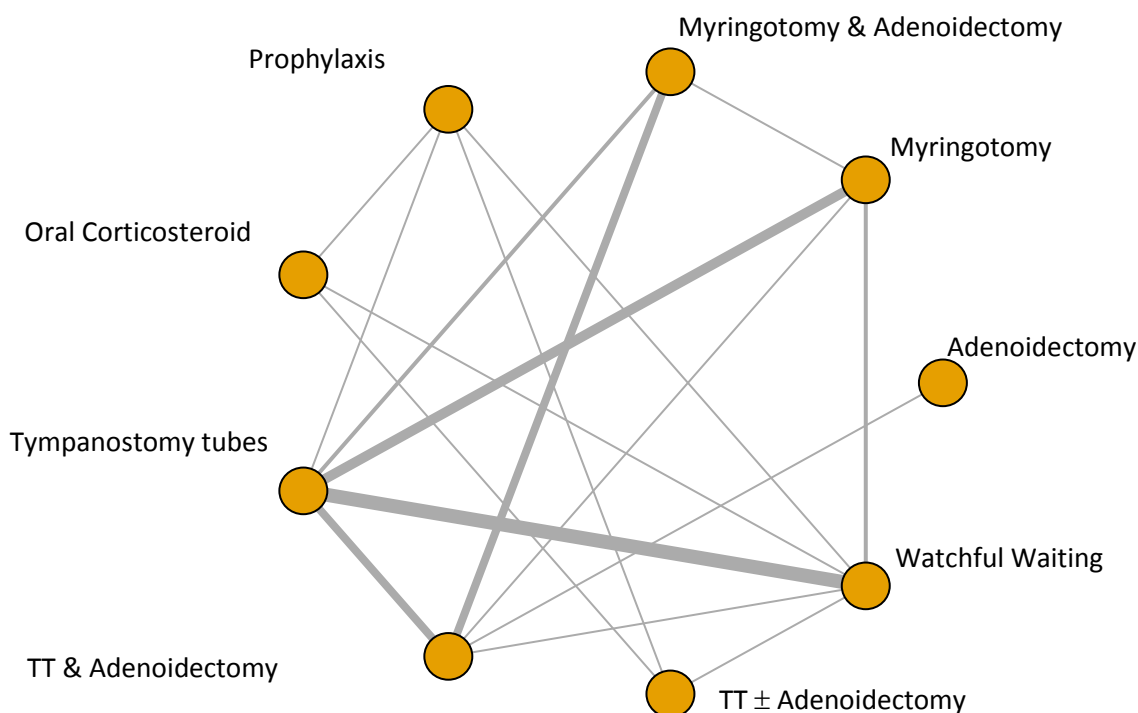
We identified 54 publications. Of these, there were 29 papers reporting 16 RCTs.<sup>4, 36-63</sup> There were 24 publications reporting 24 NRCSs that assessed the effectiveness of TT in children with chronic middle ear effusion.<sup>64-87</sup>

## 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.<sup>36, 49</sup> 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, myringotomy 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 <sup>36</sup>	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. <sup>37</sup>	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 <sup>38</sup>	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. <sup>88</sup>	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. <sup>44</sup>	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. <sup>44</sup>	MEE >= 2 mo	7 mo to 12	09/1979- 09/1984	TT (11) vs. Myringotomy (12)		
Mandel 1992 1565550 U.S. <sup>45</sup>	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 <sup>40, 46, 63</sup>	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 <sup>4, 47, 48</sup>	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 (0,3,6,9,12,15,18,21,2 4)	
Nguyen 2004 15126745 Canada <sup>49</sup>	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. <sup>43, 50-52, 54</sup>	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 <sup>55</sup>	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 <sup>56</sup>	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 <sup>41, 42, 57-60</sup>	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 <sup>61</sup>	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 <sup>62</sup>	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<sup>46</sup> and Gates 1987,<sup>88</sup> 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.<sup>4, 52, 62, 88</sup> 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.<sup>56</sup> 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.<sup>4</sup> 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 NRCSSs,<sup>64-87</sup> 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 further 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 (NRCSSs)**

Study, Year, PMID, Country	Enrollment period	Comparators (N)	Special populations	Covariate adjusted	Outcome(s)
Coyte 2001 11309633 Canada <sup>72</sup>	1992-1997	TT (10602) & adenoidectomy vs. TT (26714)		Yes	Rate of rehospitalization; reinsertion of TT
De Beer 2004 15224825 Netherlands <sup>74</sup>	2001	TT (51) vs. OME without TT (132) vs. control (174)		Yes	Hearing levels at 18 years
Forquer 1982 6184891 U.S. <sup>67</sup>	NR	TT (177) vs. medical treatment & delayed TT (170) vs. medical treatment (153)		No	Hearing level; Middle ear effusion
Grievink 1993 8246466 Netherlands <sup>70</sup>	9/1990-2/1991	TT (37) vs. OME (151) vs. control (82)		Yes	Language ability
Hu 2015 26429601 U.S. <sup>85</sup>	2014	TT (12) vs. TT & adenoidectomy or adenotonsillectomy (8)		No	Hearing level
Hubbard 1985 4039792 U.S. <sup>66</sup>	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 <sup>76</sup>		adenoidectomy (7534)			
Kobayashi 2012 22386274 Japan <sup>79</sup>	1996-1999	Early TT (82) vs. late TT (bilateral: 6 mo, unilateral: 3 mo) (100)	Cleft palate	No	Language development
Kuşcu 2015 26545930 Turkey <sup>86</sup>	2008-2013	early TT (67) vs. late TT (22) vs. no TT (65)	Cleft palate	No	Hearing level, otoscopic findings
Li 2015 26281253 China <sup>84</sup>	2002 - 2012	TT (248) vs. Myringotomy (276)	Cleft palate	No	Cure, Recurrence
Li 2015 26281253 China <sup>84</sup>	2003 - 2012	TT (78) vs. Myringotomy (168)	Adenoidal hypertrophy	No	Cure, Recurrence
Marshak 1980 6778336 Israel <sup>68</sup>	NR	TT (29) vs. myringotomy & adenoidectomy (29)		No	Middle ear effusion
Motta 2006 17465378 Italy <sup>77</sup>	1/1/2001- 12/31/2001	TT & adenoidectomy (34) vs. adenoidectomy (40)		No	Middle ear effusion
Niclasen 2016 27063746 Denmark <sup>87</sup>	2001-2002	4+ episodes of OM (569) vs. 4+ episodes of OM& TT (999)		Yes	Behavioral and Learning Difficulties
Peters 1994 8195687 Netherlands <sup>69</sup>	9/1990- 2/1991	.		Yes	Educational attainment, Reading & Spelling
Reiter 2009 19929085 Germany <sup>78</sup>	NR	TT & palate cleft repair (50) vs. palate cleft repair (66)	Cleft palate	No	Hearing level
Robson 1992 1431515 UK <sup>65</sup>	1976-1988	TT (38) vs. control (32)	Cleft palate	No	Hearing level; Middle ear effusion
Schilder 1997 9372253 UK <sup>71</sup>	1990	TT (56) vs. control (102)		Yes	Hearing levels; Language & Educational achievement
Stenstrom 2005 16330739 Canada <sup>75</sup>	1985-1989	TT (38) vs. sulfisoxazole (27)		No	Long term hearing thresholds
Tian 2015 26103659 China <sup>83</sup>	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 <sup>80</sup>	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 <sup>73</sup>	9/1997- 5/2000	TT & palate cleft repair (31) vs. palate cleft repair (31)	Cleft palate	No	Hearing level
Yagi 1977 321716 Sudan <sup>64</sup>	NR	TT & myringotomy & adenoidectomy (100) vs. adenoidectomy (100)		No	Middle ear effusion
Yousaf 2012 23855103 Pakistan <sup>81</sup>	6/2008- 12/2011	TT (44) vs. myringotomy (26)		No	Middle ear effusion
Youssef 2013 24265883 Egypt <sup>82</sup>	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.<sup>72</sup>

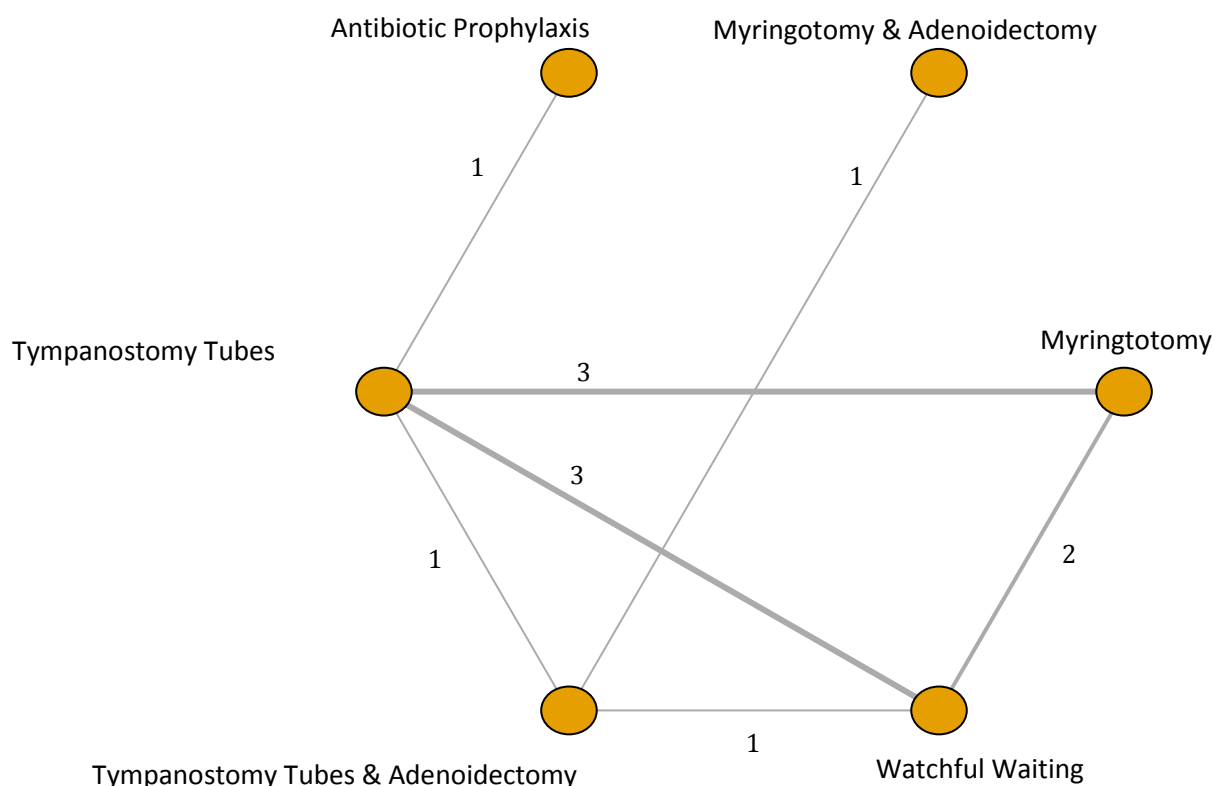
Schilder 1997 compared hearing levels and mean duration of otitis media with effusion (OME) at seven to eight years between children treated with TT at two to four years of age, with a (retrospectively) matched group of children who were not treated surgically. Pure tone average hearing levels measured 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 ≤ 0.08).<sup>71</sup>

## 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, 1000, 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”).<sup>4, 36, 44, 45, 55</sup> Five RCTs reported hearing thresholds at 12 to 24 months (classified as “late”).<sup>4, 36, 55, 58, 62</sup> 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.<sup>44</sup> Patients with no significant hearing loss (≤ 20 dB bilaterally or ≤ 40 dB unilaterally) were randomized to watchful waiting, myringotomy, 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)**

<b>TT</b>	-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)	<b>TT + Adenoidectomy</b>	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)	<b>Myringotomy</b>	-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)	<b>Myringotomy + Adenoidectomy</b>	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)	<b>Antibiotic prophylaxis</b>	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)	<b>Watchful waiting</b>

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**

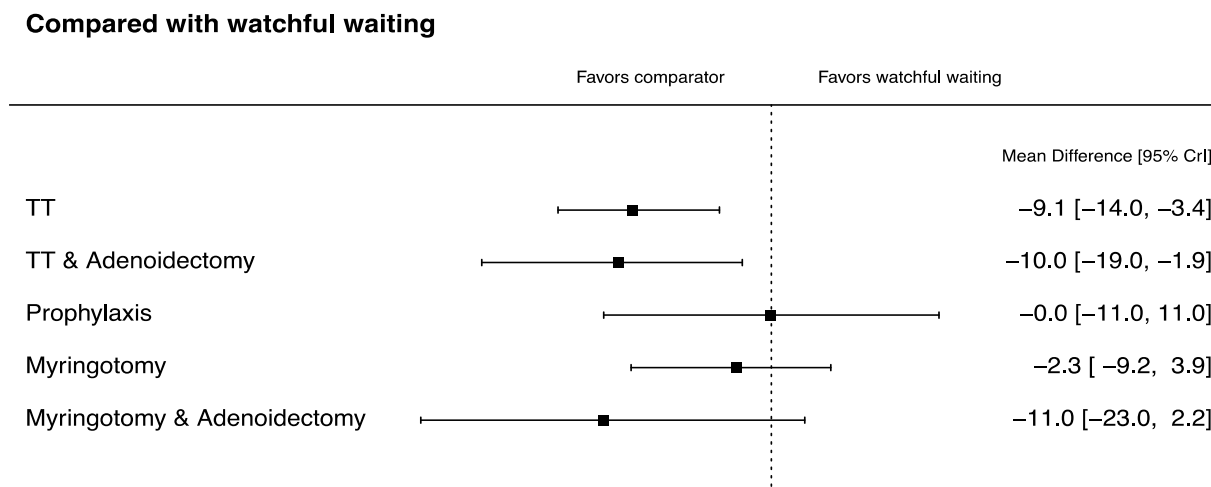
Intervention	1st	2nd	3rd	4th	5th	6th
TT	19	22	56	2	0	0
TT + Adenoidectomy	32	49	15	3	1	0
Myringotomy	1	2	5	59	24	9
Myringotomy + Adenoidectomy	47	24	20	4	2	2
Antibiotic prophylaxis	1	2	3	19	28	46
Watchful waiting	0	0	1	12	44	42

**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.

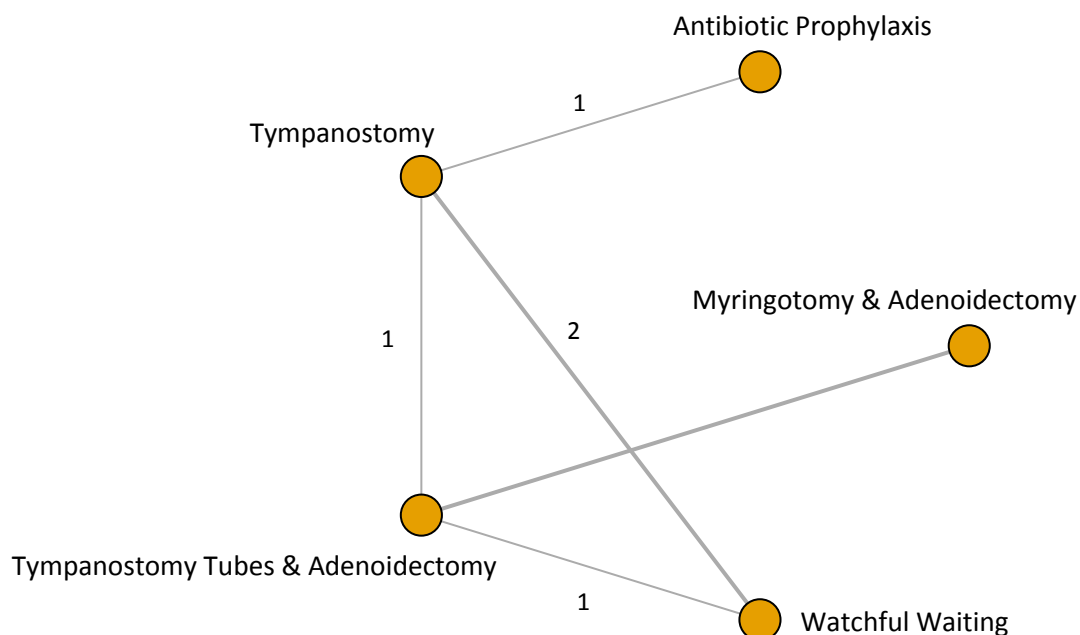
**Figure 7. Early (1 to 3 months) decrease (improvement) in mean hearing thresholds compared with watchful waiting**



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)**

<b>Myringotomy &amp; Adenoidectomy</b>	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)	<b>Prophylaxis</b>	-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)	<b>TT</b>	-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)	<b>TT &amp; Adenoidectomy</b>	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)	<b>Watchful waiting</b>

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**

<b>Intervention</b>	<b>1st</b>	<b>2nd</b>	<b>3rd</b>	<b>4th</b>	<b>5th</b>
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**

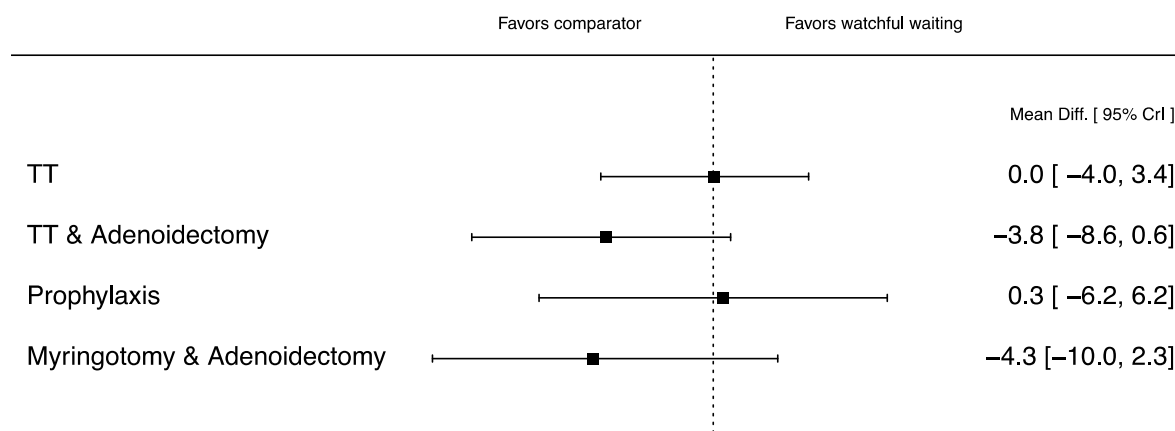
Intervention	Probability (%) of being among the 3 most effective interventions	Probability (%) of being among the 3 least effective interventions
TT	5	95
TT & Adenoidectomy	92	8
Myringotomy & Adenoidectomy	88	12
Antibiotic prophylaxis	10	90
Watchful waiting	4	96

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**

**Compared with watchful waiting**



TT= Tympanostomy tube; CrI= Credibility Interval

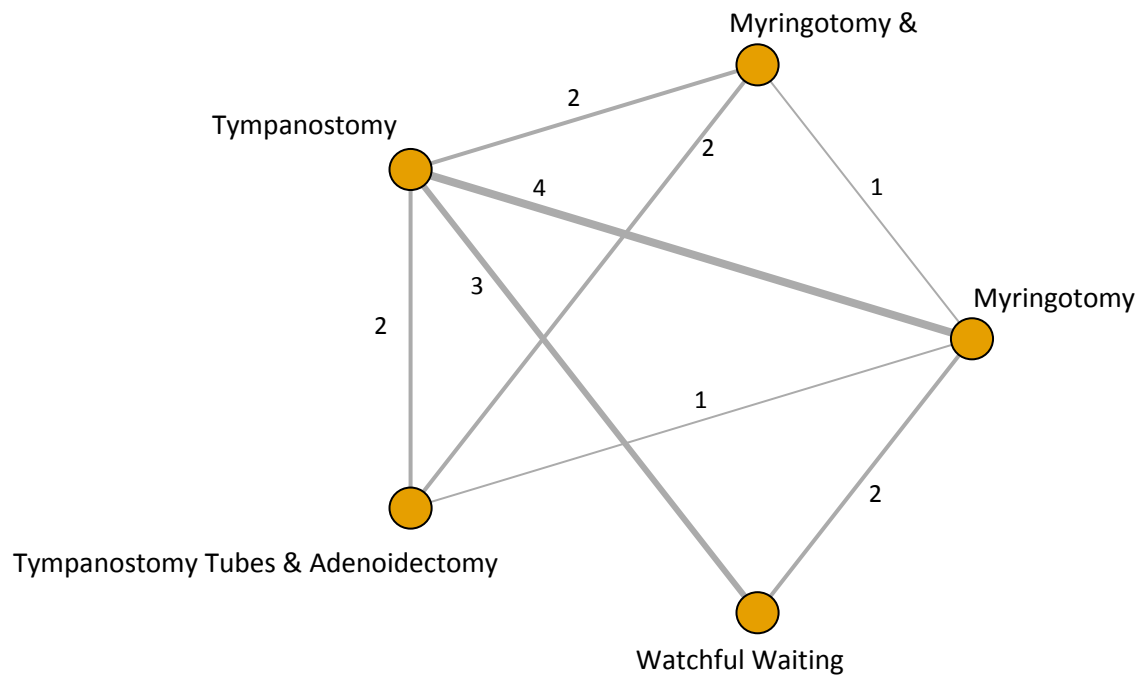
The results for the studies that reported measuring hearing thresholds, but did not report mean hearing thresholds needed for inclusion in the network meta-analysis are summarized below. In the MRC Multicentre Otitis Media Study Group 2004 report outcomes of a speech-in-noise automated toy test (SiN 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.<sup>48</sup> Chaudhuri 2006 reported a comparison of hearing thresholds between groups of children randomized to various medical treatments, placebo, or TT with or without adenoidectomy.<sup>38</sup> D'Eredità 2006 reported that hearing thresholds were normal at one year in both arms of a study comparing laser myringotomy to myringotomy with TT tubes in children, aged 2 to 6 years.<sup>39</sup> 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.<sup>89</sup> Paradise 2001 reported measuring hearing thresholds, but did not report the results for the comparison of hearing thresholds.<sup>52</sup> 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 ( $P=0.03$ ).<sup>61</sup>

## Duration of Effusion

Six RCTs<sup>37, 44, 45, 52, 88</sup> 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, myringotomy with adenoidectomy, TT and adenoidectomy.

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

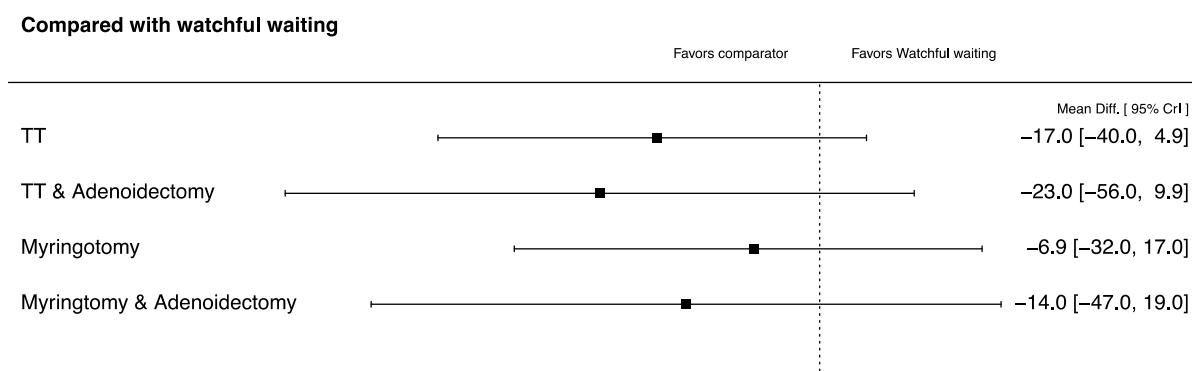


The network plot consists of nodes representing the interventions being compared and edges representing the available direct comparisons. The number of studies that include each comparison is indicated next to each edge (connecting lines with thickness proportional to this number).

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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).<sup>40, 46, 50-54, 56, 58, 62, 69-71, 87</sup> 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.<sup>54</sup> 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.<sup>69</sup> 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.<sup>40</sup>

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.<sup>50-54</sup> 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).<sup>71</sup>

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).<sup>54</sup> Niclasen reported a NRCS of performance on the Strengths and Difficulties Questionnaire (multiple subscales), parent and teacher version. They concluded that their findings suggest an association between 4 or more episodes of early otitis media treated with TT and behavioral and learning difficulties later in childhood.<sup>87</sup> 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,<sup>50-54</sup> and Vlastos 2011 reported on pediatric health related quality

of life.<sup>62</sup> 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) <sup>56</sup>		2 (0)		
Niclasen 2016 NRCS (1568) <sup>87</sup>	3(nr)		12 (nr)	
Rovers 2000 RCT (187) <sup>58</sup>		2 (0)		
Hall 2009 RCT (136) <sup>40</sup>	10 (2)	6 (0)	6 (1)	
Maw 1999 RCT (127) <sup>46</sup>		4 (0)	2 (0)	
Vlastos 2011 RCT (45) <sup>62</sup>				1 (0)
Paradise, 2001, 2003, 2004, 2005, 2007 RCT/NRCS (402/729) <sup>50-54</sup>	15 (2)	18 (4)	14 (2)	4 (0)
Peters 1994 NRCS (188) <sup>69</sup>	15 (1)	5 (0)		
Grievink 1993 NRCS (183) <sup>70</sup>	1 (0)	9 (0)		
Schidler 1997 NRCS (27) <sup>71</sup>		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<sup>90-96</sup> and 2 NRCSs.<sup>8, 93</sup> 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 in 169 patients.<sup>93</sup> Grindler 2014, reported a cross-sectional comparison of quality of life outcomes in 1208 patients.<sup>8</sup>

### Comparators

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

### 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.<sup>90, 92-94</sup> Conversely, Kujala 2012 and Casselbrant 1992 required patients to be free of middle ear effusion at time of assessment for surgery.<sup>91, 95</sup> 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.<sup>95</sup> Comparison groups were dissimilar or the comparability was unclear in most studies.<sup>90, 92, 93</sup> Blinding was partially implemented in only one study.<sup>91</sup> Randomization, group similarity and blinding could not be assessed in Hammarén-Malmi 2005.<sup>94</sup>

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

## 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.<sup>95</sup>

#### 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 ( $P = 0.08$ ).<sup>90</sup>

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 ( $P = 0.001$ ).<sup>91</sup>

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

#### 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.<sup>93</sup>

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,  $P = 1.0$ ).<sup>95</sup>

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.<sup>94</sup>

## **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.<sup>96</sup>

## **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.<sup>8</sup>

## **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.<sup>90</sup> Two studies specifically excluded patients with middle ear effusion at time of surgical evaluation.<sup>91,95</sup>

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.<sup>91</sup>

## 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 <sup>95, 97-99</sup>	NA	NA
Otorrhea	39 <sup>17, 36, 42, 88, 97, 100-133</sup>	20.6 [13.1, 47.3]	10.4 [9.1, 28.2]
Tube Blockage	18 <sup>97, 99, 103, 123, 127, 130-142</sup>	9.0 [ 2.6, 10.7]	4.0 [2.8, 17.1]
Granulation Tissue	12 <sup>36, 106, 109, 110, 118, 127, 130-132, 134, 136, 143</sup>	3.3 [ 2.9, 5.7]	3.9 [1.8, 5.7]
Premature Extrusion	18 <sup>112, 115, 118, 123, 125, 127, 129, 130, 136, 140, 144-151</sup>	13.3 [ 7.1, 47.9]	4.1 [1.6, 14.0]
TT Displacement into middle ear	8 <sup>127, 130, 134, 135, 143, 145, 152, 153</sup>	NA	0.8 [0.7, 0.9]
Persistent Perforation	48 <sup>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</sup>	2.7 [1.8, 6.7]	2.9 [ 2.0, 5.3 ]
Myringosclerosis	22 <sup>36, 52, 61, 74, 122, 130-132, 134, 135, 148, 150, 152, 155, 157, 163, 167-172</sup>	33.5 [5.0, 38.0]	17.1 [6.8, 43.9]
Atrophy, Atelectasis or Retraction	22 <sup>52, 61, 100, 121, 122, 130, 131, 133, 136, 148, 149, 153, 155, 157, 161, 163, 166, 168, 170, 173-175</sup>	13.9 [7.5, 25.9]	14.4 [ 5.0, 32.8]
Cholesteatoma	24 <sup>88, 100, 108, 115, 122, 127, 131-134, 136, 143, 145-147</sup>	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 <sup>99</sup> , 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.<sup>95, 97-99</sup> Of these, three studies<sup>95, 97, 99</sup> reported surgical adverse events including ear canal abrasion, tympanic membrane tear and hemorrhage. The 2002 report by Hoffman<sup>98</sup>, reported perioperative events in 0.81% of 3198 patients. Isaacson, 2008 report no operative deaths in a prospective series of 10,000 tube insertions.<sup>99</sup>

**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<sup>180, 181</sup> and 9 NRCSs<sup>182-190</sup>

### **RCTs**

The RCTs are briefly summarized in Table 12. In the Goldstein 2005 study<sup>180</sup> 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<sup>181</sup> 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. <sup>180</sup>	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. <sup>181</sup>	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 study in 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%<sup>188</sup>) and 23% vs. 18%<sup>190</sup>) 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 more episodes of otorrhea**

Becker 1987 3586818 4/1985-9/1985 U.S. (NRCS) <sup>182</sup>	≥ 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 <sup>183</sup>	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 <sup>184</sup>	6 months	Nonswimming	All Participants	14/41 (34.1)	2.07 (0.78 – 5.50)
		No precautions	All Participants	9/45 (20.0)	[reference]
Francois 1992 1485779 [No dates] France <sup>185</sup>	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 <sup>186</sup>	≥ 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. <sup>187</sup>	1.5 years	Nonswimming	All Participants	7/116 (6.0)	<b>0.34 ( 0.14 – 0.82)</b>
		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 <sup>189</sup>	≥ 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

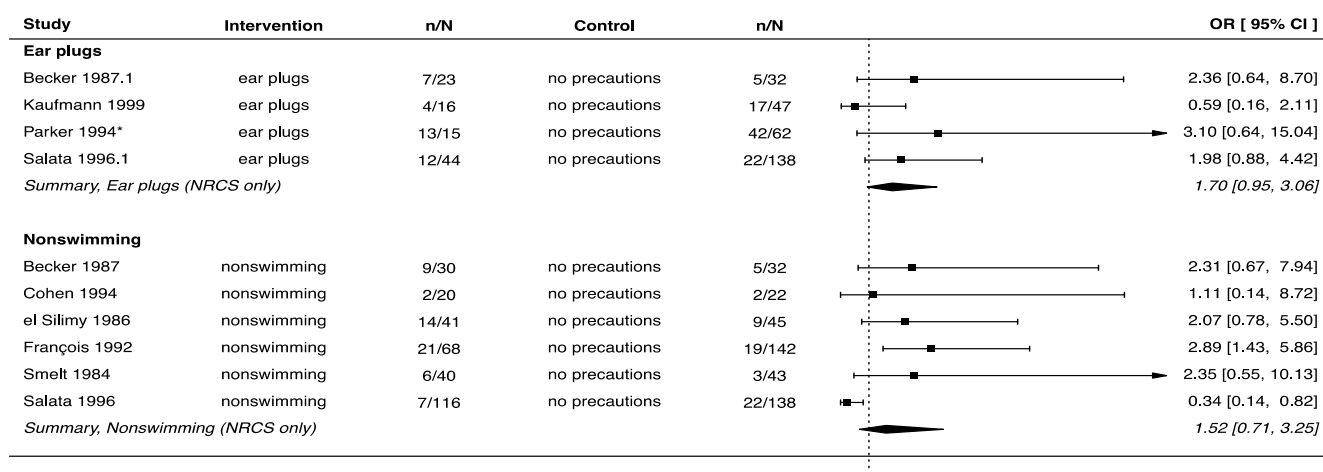
Goldstein 2005 reported a slightly lower adjusted rate of otorrhea randomly assigned to use ear plugs (0.07 episodes/month in intervention group versus 0.10 episodes/month in the control group,  $P=0.05$ ).

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,<sup>19, 139, 142, 190-200</sup> 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.

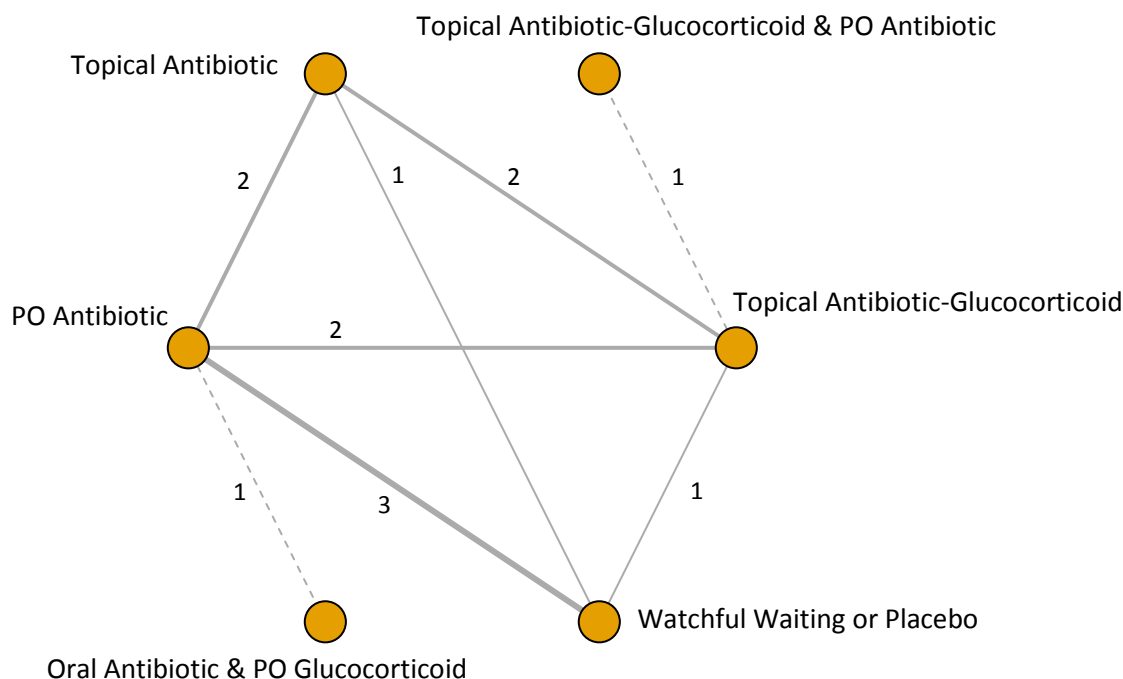
**Table 14. Effectiveness of various interventions to treat TT otorrhea**

Study Year, PMID, Enrollment Period, Country	Intervention Details	Responders	N
Dohar 1999 10326811 U.S. <sup>194</sup>	ofloxacin eardrops	119	141
	unclear - historical practice	140	218
	unclear - current practice	33	47
Dohar 2006 16880248 5/2003-5/2004 U.S. & Finland <sup>142</sup> 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 <sup>197</sup>	hydrocortisone + oxytetracycline + polymyxine	12	15
	hydrocortisone + oxytetracycline + polymyxine & oral amoxicillin +/- clavulanate	19	22
Heslop 2010 20979100 5/2003-5/2007 Chile <sup>198</sup>	ciprofloxacin ear drops	17	22
	oral amoxicillin	6	20
	saline rinse	12	26
Roland 2003 14660913 3/2000-2/2001 U.S. <sup>196</sup>	ciprofloxacin/dexamethasone ear drops	72	87
	ciprofloxacin ear drops	72	80
Roland 2004 14702493 U.S. <sup>139, 191, 201</sup>	ciprofloxacin/dexamethasone ear drops	174	207
	ofloxacin eardrops	153	216
Ruohola 1999 10190921 03/1996-05/1997 Denmark <sup>193</sup>	oral amoxicillin & oral prednisolone	22	23
	oral amoxicillin	24	27
Ruohola 2003 12728089 09/1998-06/1999 Finland <sup>195</sup>	oral amoxicillin-clavulanate	28	34
	oral placebo	13	32
Strachan 2000 10865480 UK <sup>202</sup>	neomycin/polymyxin B/hydrocortisone (drops)	24	29
	neomycin/dexamethasone	19	29
van Dongen 2014 24552319 6/2009-5/2012 Netherlands <sup>19, 199</sup>	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,<sup>199</sup> oral placebo<sup>195</sup> and topical saline wash.<sup>198</sup>

**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<sup>194</sup> 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<sup>202</sup>, 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<sup>193, 197</sup> 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**

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

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

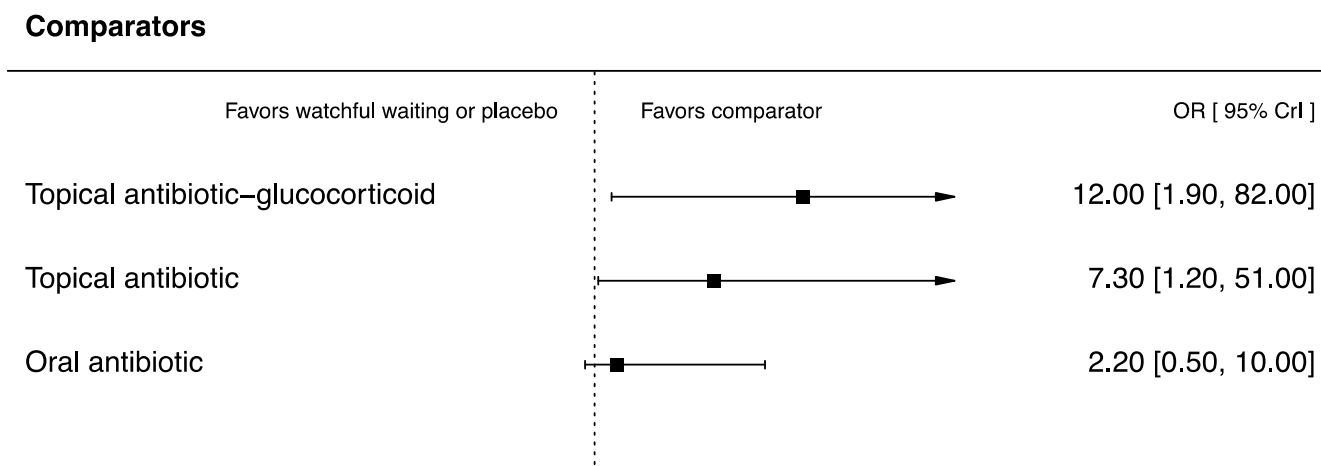
Table 16 lists the probabilities derived from the network meta-analysis that a particular intervention is ranks first to fourth most effective. The probability rankings suggest: 1) treatment strategies that include topical antibiotic drops predominate treatment with oral antibiotics and 2) all active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

<b>Intervention</b>	<b>1st</b>	<b>2nd</b>	<b>3rd</b>	<b>4th</b>
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.

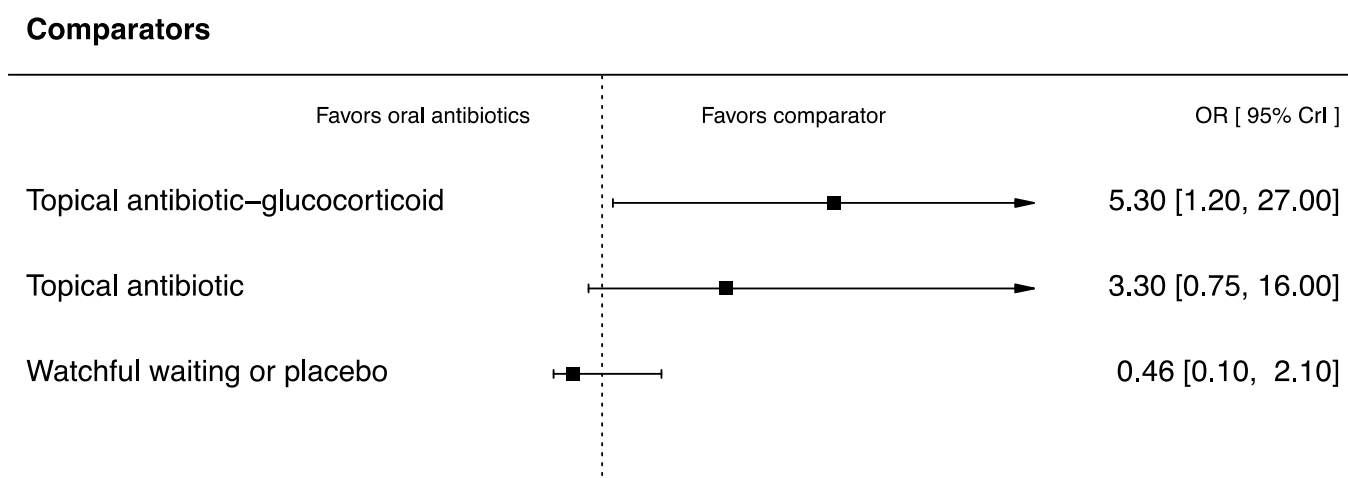
**Figure 14. Relative effectiveness of various interventions compared to watchful waiting or placebo**



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.<sup>199</sup> 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 significant

# 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% CI 12% - 26%; NNT = 6). No significant benefit of adenoidectomy was found in children less than 4 years old.<sup>2</sup>

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.<sup>203</sup>

Quality of life and other patient-centered outcomes (cognitive, language, and behavioral) were reported in eight studies (five RCTs, three NRCSSs, 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.<sup>96</sup>

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.<sup>90</sup> The other two studies specifically excluded patients with middle ear effusion.<sup>91, 95</sup>

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 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% CI: 6% to 18%; NNT = 9].<sup>2</sup>

## 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)]<sup>a</sup> 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)]<sup>b</sup> 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)].<sup>c</sup> The odds ratio for topical antibiotic drops was 3.3 (95% CrI: 0.74 – 16)[NNT 5 (assuming a baseline rate of 0.69)]<sup>d</sup>, although the credible interval includes 1.

<sup>a</sup> 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)

<sup>b</sup> 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)

<sup>c</sup> 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)

<sup>d</sup> 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
<i>Key Question 1</i>								
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) No quantitative synthesis Magnitude of clinically important effects unclear
		TT vs. TT & Adenoidectomy	Moderate to high	Consistent	Imprecise	Direct	Low	3 RCTs 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 Single RCT Magnitude of clinically important effects unclear
		Nonswimming vs. no precautions	High	NA	Imprecise	Direct	Low	No effect Single RCT
	Risk of one or more episodes of otorrhea	Ear plugs vs. no precautions	High	Consistent	Imprecise	Direct	Low	Not effective 4 NRCSS OR 1.7 (CrI: 0.9, 3.1)
		Nonswimming vs. no precautions	High	Mostly consistent	Imprecise	Direct	Low	Not effective 6 NRCSS 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<sup>36, 49</sup> 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 NRCSSs, 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.<sup>204</sup>

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

## 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 is 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.

## References

1. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: Tympanostomy tubes in children. *Otolaryngol Head Neck Surg.* 2013 Jul;149(1 Suppl):S1-35. doi: 10.1177/0194599813487302. PMID: 23818543.
2. Schilder AG, Chonmaitree T, Cripps AW, et al. Otitis media. *Nat Rev Dis Primers.* 2016;2:16063. doi: 10.1038/nrdp.2016.63. PMID: 27604644.
3. Boonacker CW, Rovers MM, Browning GG, et al. Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. *Health Technol Assess.* 2014 Jan;18(5):1-118. doi: 10.3310/hta18050. PMID: 24438691.
4. Rettig E, Tunkel DE. Contemporary concepts in management of acute otitis media in children. *Otolaryngol Clin North Am.* 2014 Oct;47(5):651-72. doi: 10.1016/j.otc.2014.06.006. PMID: 25213276.
5. Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. *Natl Health Stat Report.* 2009 Jan 28(11):1-25. PMID: 19294964.
6. Proceedings from the National Summit on Overuse. 2012. The Joint Commission. [https://www.jointcommission.org/assets/1/6/National\\_Summit\\_Overuse.pdf](https://www.jointcommission.org/assets/1/6/National_Summit_Overuse.pdf). Accessed December 21, 2016.
7. Kleinman LC, Kosecoff J, Dubois RW, et al. The medical appropriateness of tympanostomy tubes proposed for children younger than 16 years in the United States. *JAMA.* 1994 Apr 27;271(16):1250-5. PMID: 7710469.
8. Grindler DJ, Blank SJ, Schulz KA, et al. Impact of Otitis Media Severity on Children's Quality of Life. *Otolaryngol Head Neck Surg.* 2014 Mar 13;151(2):333-40. doi: 10.1177/0194599814525576. PMID: 24627408.
9. Hoffman HJ, Daly KA, Bainbridge KE, et al. Panel 1: Epidemiology, natural history, and risk factors. *Otolaryngol Head Neck Surg.* 2013 Apr;148(4 Suppl):E1-E25. doi: 10.1177/0194599812460984. PMID: 23536527.
10. Croft P, Altman DG, Deeks JJ, et al. The science of clinical practice: disease diagnosis or patient prognosis? Evidence about "what is likely to happen" should shape clinical practice. *BMC Med.* 2015;13:20. doi: 10.1186/s12916-014-0265-4. PMID: 25637245.
11. Paulson LM, Weaver TS, Macarthur CJ. Outcomes of tympanostomy tube placement in children with Down syndrome--a retrospective review. *Int J Pediatr Otorhinolaryngol.* 2014 Feb;78(2):223-6. doi: 10.1016/j.ijporl.2013.10.062. PMID: 24321289.
12. Kuo CL, Tsao YH, Cheng HM, et al. Grommets for otitis media with effusion in children with cleft palate: a systematic review. *Pediatrics.* 2014 Nov;134(5):983-94. doi: 10.1542/peds.2014-0323. PMID: 25287451.
13. Ackerman S, Reilly B, Bernier R. Tympanostomy tube placement in children with autism. *J Dev Behav Pediatr.* 2012 Apr;33(3):252-8. doi: 10.1097/DBP.0b013e31824b9f57. PMID: 22343482.
14. Rosenfeld RM, Kay D. Natural history of untreated otitis media. *Laryngoscope.* 2003 Oct;113(10):1645-57. PMID: 14520089.
15. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics.* 2013 Mar;131(3):e964-99. doi: 10.1542/peds.2012-3488. PMID: 23439909.
16. Tsao GJ, Goode RL. Are water precautions necessary after tympanostomy tube placement? *Laryngoscope.* 2014 Jul;124(7):1513-4. doi: 10.1002/lary.24473. PMID: 24142762.
17. van Dongen TM, van der Heijden GJ, Freling HG, et al. Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors. *PLoS One.* 2013;8(7):e69062. doi: 10.1371/journal.pone.0069062. PMID: 23874870.

18. Casselbrant ML, Kaleida PH, Rockette HE, et al. In reference to What is the role of tympanostomy tubes in the treatment of recurrent acute otitis media? *Laryngoscope*. 2013 Dec;123(12):E127. doi: 10.1002/lary.24142. PMID: 24105683.
19. van Dongen TM, Schilder AG, Venekamp RP, et al. Cost-effectiveness of treatment of acute otorrhea in children with tympanostomy tubes. *Pediatrics*. 2015 May;135(5):e1182-9. doi: 10.1542/peds.2014-3141. PMID: 25896832.
20. Wang JC, Hamood AN, Saadeh C, et al. Strategies to prevent biofilm-based tympanostomy tube infections. *Int J Pediatr Otorhinolaryngol*. 2014 Sep;78(9):1433-8. doi: 10.1016/j.ijporl.2014.05.025. PMID: 25060938.
21. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012.
22. Williams K, Thomson D, Seto I, et al. Standard 6: age groups for pediatric trials. *Pediatrics*. 2012 Jun;129 Suppl 3:S153-60. doi: 10.1542/peds.2012-00551. PMID: 22661762.
23. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. Clinical practice guideline: tympanostomy tubes in children--executive summary. *Otolaryngol Head Neck Surg*. 2013 Jul;149(1):8-16. doi: 10.1177/0194599813490141. PMID: 23818537.
24. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi: 10.1136/bmj.d5928. PMID: 22008217.
25. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. . The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.
26. Normand SL. Meta-analysis: formulating, evaluating, combining, and reporting. *Stat Med*. 1999 Feb 15;18(3):321-59. PMID: 10070677.
27. Team RC. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2016.
28. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software*. 2010;36(3):1-48.
29. van Valkenhoef G, Kuiper J. *gemtc: Network Meta-Analysis Using Bayesian Methods*. 2016.
30. van Valkenhoef G, Lu G, de Brock B, et al. Automating network meta-analysis. *Res Synth Methods*. 2012 December;3(4):285-99.
31. JAGS: A program for analysis of Bayesian graphical models using Gibbs sampling. Proceedings of the 3rd International Workshop on Distributed Statistical Computing ({DSC} 2003), March 20-22, Vienna, Austria. Plummer\_undated-af.
32. Welton NJ, AJ S, Cooper N, et al. *Evidence Synthesis for Decision Making in Healthcare*: Wiley; 2012.
33. Dias S, Welton N, Caldwell D, et al. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in medicine*. 2010;29(7-8):932-44.
34. van Valkenhoef G, Dias S, Ades AE, et al. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Res Synth Methods*. 2016 March;7(1):80-93.
35. Berkman ND, Lohr KN, Ansari M, et al. *AHRQ Methods for Effective Health Care: Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
36. Bernard PA, Stenstrom RJ, Feldman W, et al. Randomized, controlled trial comparing long-term sulfonamide therapy to ventilation tubes for otitis media with effusion. *Pediatrics*. 1991 Aug;88(2):215-22. PMID: 1861917.
37. Casselbrant ML, Mandel EM, Rockette HE, et al. Adenoidectomy for otitis media with effusion in 2-3-year-old children. *Int J Pediatr Otorhinolaryngol*. 2009 Dec;73(12):1718-24. doi: 10.1016/j.ijporl.2009.09.007. PMID: 19819563.
38. Chaudhuri GR, Bandyopadhyay SN, Basu SK. Role of grommet in otitis media with effusion: A necessity or nuisance? A comparative study. *Indian J Otolaryngol Head Neck Surg*. 2006 Jul;58(3):271-3. doi: 10.1007/bf03050837. PMID: 23120310.

39. D'Eredita R, Shah UK. Contact diode laser myringotomy for medium-duration middle ear ventilation in children. *Int J Pediatr Otorhinolaryngol*. 2006 Jun;70(6):1077-80. doi: 10.1016/j.ijporl.2005.11.003. PMID: 16406076.
40. Hall AJ, Maw AR, Steer CD. Developmental outcomes in early compared with delayed surgery for glue ear up to age 7 years: a randomised controlled trial. *Clin Otolaryngol*. 2009 Feb;34(1):12-20. doi: 10.1111/j.1749-4486.2008.01838.x. PMID: 19260880.
41. Hartman M, Rovers MM, Ingels K, et al. Economic evaluation of ventilation tubes in otitis media with effusion. *Arch Otolaryngol Head Neck Surg*. 2001 Dec;127(12):1471-6. PMID: 11735817.
42. Ingels K, Rovers MM, van der Wilt GJ, et al. Ventilation tubes in infants increase the risk of otorrhoea and antibiotic usage. *B-ENT*. 2005;1(4):173-6. PMID: 16429748.
43. Johnston LC, Feldman HM, Paradise JL, et al. Tympanic membrane abnormalities and hearing levels at the ages of 5 and 6 years in relation to persistent otitis media and tympanostomy tube insertion in the first 3 years of life: a prospective study incorporating a randomized clinical trial. *Pediatrics*. 2004 Jul;114(1):e58-67. PMID: 15231974.
44. Mandel EM, Rockette HE, Bluestone CD, et al. Myringotomy with and without tympanostomy tubes for chronic otitis media with effusion. *Arch Otolaryngol Head Neck Surg*. 1989 Oct;115(10):1217-24. PMID: 2789777.
45. Mandel EM, Rockette HE, Bluestone CD, et al. Efficacy of myringotomy with and without tympanostomy tubes for chronic otitis media with effusion. *Pediatr Infect Dis J*. 1992 Apr;11(4):270-7. PMID: 1565550.
46. Maw R, Wilks J, Harvey I, et al. Early surgery compared with watchful waiting for glue ear and effect on language development in preschool children: a randomised trial. *Lancet*. 1999 Mar 20;353(9157):960-3. doi: 10.1016/s0140-6736(98)05295-7. PMID: 10459904.
47. MRC Multicentre Otitis Media Study Group. The role of ventilation tube status in the hearing levels in children managed for bilateral persistent otitis media with effusion. *Clin Otolaryngol Allied Sci*. 2003 Apr;28(2):146-53. PMID: 12680834.
48. MRC Multicentre Otitis Media Study Group. Speech reception in noise: an indicator of benefit from otitis media with effusion surgery. *Clin Otolaryngol Allied Sci*. 2004 Oct;29(5):497-504. doi: 10.1111/j.1365-2273.2004.00843.x. PMID: 15373863.
49. Nguyen LH, Manoukian JJ, Yoskovitch A, et al. Adenoidectomy: selection criteria for surgical cases of otitis media. *Laryngoscope*. 2004 May;114(5):863-6. doi: 10.1097/00005537-200405000-00014. PMID: 15126745.
50. Paradise JL, Campbell TF, Dollaghan CA, et al. Developmental outcomes after early or delayed insertion of tympanostomy tubes. *N Engl J Med*. 2005 Aug 11;353(6):576-86. doi: 10.1056/NEJMoa050406. PMID: 16093466.
51. Paradise JL, Dollaghan CA, Campbell TF, et al. Otitis media and tympanostomy tube insertion during the first three years of life: developmental outcomes at the age of four years. *Pediatrics*. 2003 Aug;112(2):265-77. PMID: 12897272.
52. Paradise JL, Feldman HM, Campbell TF, et al. Effect of early or delayed insertion of tympanostomy tubes for persistent otitis media on developmental outcomes at the age of three years. *N Engl J Med*. 2001 Apr 19;344(16):1179-87. doi: 10.1056/nejm200104193441601. PMID: 11309632.
53. Paradise JL, Feldman HM, Campbell TF, et al. Early versus delayed insertion of tympanostomy tubes for persistent otitis media: developmental outcomes at the age of three years in relation to prerandomization illness patterns and hearing levels. *Pediatr Infect Dis J*. 2003 Apr;22(4):309-14. doi: 10.1097/01.inf.0000059764.77704.55. PMID: 12690269.
54. Paradise JL, Feldman HM, Campbell TF, et al. Tympanostomy tubes and developmental outcomes at 9 to 11 years of age. *N Engl J Med*. 2007 Jan 18;356(3):248-61. doi: 10.1056/NEJMoa062980. PMID: 17229952.

55. Popova D, Varbanova S, Popov TM. Comparison between myringotomy and tympanostomy tubes in combination with adenoidectomy in 3-7-year-old children with otitis media with effusion. *Int J Pediatr Otorhinolaryngol*. 2010 Jul;74(7):777-80. doi: 10.1016/j.ijporl.2010.03.054. PMID: 20399511.
56. Rach GH, Zielhuis GA, van Baarle PW, et al. The effect of treatment with ventilating tubes on language development in preschool children with otitis media with effusion. *Clin Otolaryngol Allied Sci*. 1991 Apr;16(2):128-32. PMID: 2070526.
57. Rovers MM, Krabbe PF, Straatman H, et al. Randomised controlled trial of the effect of ventilation tubes (grommets) on quality of life at age 1-2 years. *Arch Dis Child*. 2001 Jan;84(1):45-9. PMID: 11124783.
58. Rovers MM, Straatman H, Ingels K, et al. The effect of ventilation tubes on language development in infants with otitis media with effusion: A randomized trial. *Pediatrics*. 2000 Sep;106(3):E42. PMID: 10969126.
59. Rovers MM, Straatman H, Ingels K, et al. Generalizability of trial results based on randomized versus nonrandomized allocation of OME infants to ventilation tubes or watchful waiting. *J Clin Epidemiol*. 2001 Aug;54(8):789-94. PMID: 11470387.
60. Rovers MM, Straatman H, Ingels K, et al. The effect of short-term ventilation tubes versus watchful waiting on hearing in young children with persistent otitis media with effusion: a randomized trial. *Ear Hear*. 2001 Jun;22(3):191-9. PMID: 11409855.
61. Velepici M, Starcevic R, Bonifacic M, et al. The clinical status of the eardrum: an inclusion criterion for the treatment of chronic secretory otitis media in children. *Int J Pediatr Otorhinolaryngol*. 2011 May;75(5):686-90. doi: 10.1016/j.ijporl.2011.02.014. PMID: 21397957.
62. Vlastos IM, Houlakis M, Kandiloros D, et al. Adenoidectomy plus tympanostomy tube insertion versus adenoidectomy plus myringotomy in children with obstructive sleep apnoea syndrome. *J Laryngol Otol*. 2011 Mar;125(3):274-8. doi: 10.1017/s0022215110002549. PMID: 21205368.
63. Wilks J, Maw R, Peters TJ, et al. Randomised controlled trial of early surgery versus watchful waiting for glue ear: the effect on behavioural problems in pre-school children. *Clin Otolaryngol Allied Sci*. 2000 Jun;25(3):209-14. PMID: 10944051.
64. Yagi HI. The surgical treatment of secretory otitis media in children. *J Laryngol Otol*. 1977 Mar;91(3):267-70. PMID: 321716.
65. Robson AK, Blanshard JD, Jones K, et al. A conservative approach to the management of otitis media with effusion in cleft palate children. *J Laryngol Otol*. 1992 Sep;106(9):788-92. PMID: 1431515.
66. Hubbard TW, Paradise JL, McWilliams BJ, et al. Consequences of unremitting middle-ear disease in early life. Otologic, audiologic, and developmental findings in children with cleft palate. *N Engl J Med*. 1985 Jun 13;312(24):1529-34. doi: 10.1056/nejm198506133122401. PMID: 4039792.
67. Forquer BD, Linthicum FH, Jr. Middle ear effusion in children: a report of treatment in 500 cases. *West J Med*. 1982 Nov;137(5):370-4. PMID: 6184891.
68. Marshak G, Neriah ZB. Adenoidectomy versus tympanostomy in chronic secretory otitis media. *Ann Otol Rhinol Laryngol Suppl*. 1980 May-Jun;89(3 Pt 2):316-8. PMID: 6778336.
69. Peters SA, Grievink EH, van Bon WH, et al. The effects of early bilateral otitis media with effusion on educational attainment: a prospective cohort study. *J Learn Disabil*. 1994 Feb;27(2):111-21. PMID: 8195687.
70. Grievink EH, Peters SA, van Bon WH, et al. The effects of early bilateral otitis media with effusion on language ability: a prospective cohort study. *J Speech Hear Res*. 1993 Oct;36(5):1004-12. PMID: 8246466.
71. Schilder AG, Hak E, Straatman H, et al. Long-term effects of ventilation tubes for persistent otitis media with effusion in children. *Clin Otolaryngol Allied Sci*. 1997 Oct;22(5):423-9. PMID: 9372253.

72. Coyte PC, Croxford R, McIsaac W, et al. The role of adjuvant adenoidectomy and tonsillectomy in the outcome of the insertion of tympanostomy tubes. *N Engl J Med*. 2001 Apr 19;344(16):1188-95. doi: 10.1056/nejm200104193441602. PMID: 11309633.
73. Xu HF, Xu LR, He Y, et al. [Treatment of cleft palate with secretory otitis media]. *Zhonghua Kou Qiang Yi Xue Za Zhi*. 2003 Jul;38(4):269-70. PMID: 12930655.
74. de Beer BA, Schilder AG, Ingels K, et al. Hearing loss in young adults who had ventilation tube insertion in childhood. *Ann Otol Rhinol Laryngol*. 2004 Jun;113(6):438-44. PMID: 15224825.
75. Stenstrom R, Pless IB, Bernard P. Hearing thresholds and tympanic membrane sequelae in children managed medically or surgically for otitis media with effusion. *Arch Pediatr Adolesc Med*. 2005 Dec;159(12):1151-6. doi: 10.1001/archpedi.159.12.1151. PMID: 16330739.
76. Kadhim AL, Spilsbury K, Semmens JB, et al. Adenoidectomy for middle ear effusion: a study of 50,000 children over 24 years. *Laryngoscope*. 2007 Mar;117(3):427-33. doi: 10.1097/MLG.0b013e31802c938b. PMID: 17279052.
77. Motta G, Esposito E, Motta S, et al. [Acute recurrent pharyngotonsillitis and otitis media]. *Acta Otorhinolaryngol Ital*. 2006 Oct;26(5 Suppl 84):30-55. PMID: 17465378.
78. Reiter R, Haase S, Brosch S. Repaired cleft palate and ventilation tubes and their associations with cholesteatoma in children and adults. *Cleft Palate Craniofac J*. 2009 Nov;46(6):598-602. doi: 10.1597/08-166.1. PMID: 19929085.
79. Kobayashi H, Sakuma T, Yamada N, et al. Clinical outcomes of ventilation tube placement in children with cleft palate. *Int J Pediatr Otorhinolaryngol*. 2012 May;76(5):718-21. doi: 10.1016/j.ijporl.2012.02.027. PMID: 22386274.
80. Wolter NE, Dell SD, James AL, et al. Middle ear ventilation in children with primary ciliary dyskinesia. *Int J Pediatr Otorhinolaryngol*. 2012 Nov;76(11):1565-8. doi: 10.1016/j.ijporl.2012.07.011. PMID: 22883987.
81. Yousaf M, Inayatullah, Khan F. Medical versus surgical management of otitis media with effusion in children. *J Ayub Med Coll Abbottabad*. 2012 Jan-Mar;24(1):83-5. PMID: 23855103.
82. Youssef TF, Ahmed MR. Laser-assisted myringotomy versus conventional myringotomy with ventilation tube insertion in treatment of otitis media with effusion: Long-term follow-up. *Interv Med Appl Sci*. 2013 Mar;5(1):16-20. doi: 10.1556/imas.5.2013.1.3. PMID: 24265883.
83. Tian L, Chen X, Li G. [The clinical curative effect of the low temperature plasma ablation adenoidectomy and tympanic membrane indwelling catheter in parallel or not used on childhood patients with secretory otitis media]. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi*. 2015 Mar;29(5):415-7. PMID: 26103659.
84. Li S, Zhang H, Wei Y, et al. [Clinical comparative study on the treatment characteristics of secretory otitis media between cleft and non-cleft palate patients]. *Hua Xi Kou Qiang Yi Xue Za Zhi*. 2015 Jun;33(3):259-62. PMID: 26281253.
85. Hu S, Patel NA, Shinhar S. Follow-up audiometry after bilateral myringotomy and tympanostomy tube insertion. *Int J Pediatr Otorhinolaryngol*. 2015 Dec;79(12):2068-71. doi: 10.1016/j.ijporl.2015.09.015. PMID: 26429601.
86. Kuscu O, Gunaydin RO, Icen M, et al. The effect of early routine grommet insertion on management of otitis media with effusion in children with cleft palate. *J Craniomaxillofac Surg*. 2015 Dec;43(10):2112-5. doi: 10.1016/j.jcms.2015.09.008. PMID: 26545930.
87. Niclasen J, Obel C, Homoe P, et al. Associations between otitis media and child behavioural and learning difficulties: Results from a Danish cohort. *Int J Pediatr Otorhinolaryngol*. 2016 May;84:12-20. doi: 10.1016/j.ijporl.2016.02.017. PMID: 27063746.
88. Gates GA, Avery CA, Prihoda TJ, et al. Effectiveness of adenoidectomy and tympanostomy tubes in the treatment of chronic otitis media with effusion. *N Engl J Med*. 1987 Dec 3;317(23):1444-51. doi: 10.1056/nejm198712033172305. PMID: 3683478.

89. Gates GA, Wachtendorf C, Hearne EM, et al. Treatment of chronic otitis media with effusion: results of tympanostomy tubes. *Am J Otolaryngol*. 1985 May-Jun;6(3):249-53. PMID: 4040338.
90. Gonzalez C, Arnold JE, Woody EA, et al. Prevention of recurrent acute otitis media: chemoprophylaxis versus tympanostomy tubes. *Laryngoscope*. 1986 Dec;96(12):1330-4. PMID: 3537596.
91. Casselbrant ML, Kaleida PH, Rockette HE, et al. Efficacy of antimicrobial prophylaxis and of tympanostomy tube insertion for prevention of recurrent acute otitis media: results of a randomized clinical trial. *Pediatr Infect Dis J*. 1992 Apr;11(4):278-86. PMID: 1565551.
92. El-Sayed Y. Treatment of recurrent acute otitis media chemoprophylaxis versus ventilation tubes. *Australian Journal of Otolaryngology*. 1996;2(4):352-5.
93. Mattila PS, Joki-Erkila VP, Kilpi T, et al. Prevention of otitis media by adenoidectomy in children younger than 2 years. *Arch Otolaryngol Head Neck Surg*. 2003 Feb;129(2):163-8. PMID: 12578443.
94. Hammaren-Malmi S, Saxen H, Tarkkanen J, et al. Adenoidectomy does not significantly reduce the incidence of otitis media in conjunction with the insertion of tympanostomy tubes in children who are younger than 4 years: a randomized trial. *Pediatrics*. 2005 Jul;116(1):185-9. doi: 10.1542/peds.2004-2253. PMID: 15995051.
95. Kujala T, Alho OP, Luotonen J, et al. Tympanostomy with and without adenoidectomy for the prevention of recurrences of acute otitis media: a randomized controlled trial. *Pediatr Infect Dis J*. 2012 Jun;31(6):565-9. doi: 10.1097/INF.0b013e318255ddde. PMID: 22466327.
96. Kujala T, Alho OP, Kristo A, et al. Quality of life after surgery for recurrent otitis media in a randomized controlled trial. *Pediatr Infect Dis J*. 2014 Jul;33(7):715-9. doi: 10.1097/inf.0000000000000265. PMID: 24445832.
97. Brodsky L, Brookhauser P, Chait D, et al. Office-based insertion of pressure equalization tubes: the role of laser-assisted tympanic membrane fenestration. *Laryngoscope*. 1999 Dec;109(12):2009-14. doi: 10.1097/00005537-199912000-00022. PMID: 10591365.
98. Hoffmann KK, Thompson GK, Burke BL, et al. Anesthetic complications of tympanostomy tube placement in children. *Arch Otolaryngol Head Neck Surg*. 2002 Sep;128(9):1040-3. PMID: 12220208.
99. Isaacson G. Six Sigma tympanostomy tube insertion: achieving the highest safety levels during residency training. *Otolaryngol Head Neck Surg*. 2008 Sep;139(3):353-7. doi: 10.1016/j.otohns.2008.06.012. PMID: 18722211.
100. Hörmann K, Roehrs M. [Middle-ear findings in young cleft lip and palate children. Comparison of two treatment clinics]. *Dtsch Z Mund Kiefer Gesichtschir*. 1991 Mar-Apr;15(2):149-52. PMID: 1816937.
101. Suetake M, Kobayashi T, Takasaka T, et al. Is change in middle ear air volume following ventilation tube insertion a reliable prognostic indicator? *Acta Otolaryngol Suppl*. 1990;471:73-80. PMID: 2239252.
102. Gates GA, Avery CA, Cooper JC, Jr., et al. Chronic secretory otitis media: effects of surgical management. *Ann Otol Rhinol Laryngol Suppl*. 1989 Jan;138:2-32. PMID: 2492178.
103. Weigel MT, Parker MY, Goldsmith MM, et al. A prospective randomized study of four commonly used tympanostomy tubes. *Laryngoscope*. 1989 Mar;99(3):252-6. doi: 10.1288/00005537-198903000-00003. PMID: 2645490.
104. Gates GA, Avery C, Prihoda TJ, et al. Delayed onset post-tympanotomy otorrhea. *Otolaryngol Head Neck Surg*. 1988 Feb;98(2):111-5. PMID: 3128752.
105. Debruyne F, Jorissen M, Poelmans J. Otorrhea during transtympanic ventilation. *Am J Otol*. 1988 Jul;9(4):316-7. PMID: 3177616.
106. Tavin ME, Gordon M, Ruben RJ. Hearing results with the use of different tympanostomy tubes: a prospective study. *Int J Pediatr Otorhinolaryngol*. 1988 Feb;15(1):39-50. PMID: 3372141.

107. Debruyne F, Jorissen M, Poelmans J. [Follow-up of trans-tympanum tubes]. *Acta Otorhinolaryngol Belg*. 1986;40(4):666-77. PMID: 3799183.
108. Rothera MP, Grant HR. Long-term ventilation of the middle ear using the Goode T-tube. *J Laryngol Otol*. 1985 Apr;99(4):335-7. PMID: 4040147.
109. Levinson SR, Gill AJ, Teich L. Semipermeable membrane tubes: a prospective study. *Otolaryngol Head Neck Surg*. 1982 Sep-Oct;90(5):622-8. PMID: 6819525.
110. Plotkin RP. Middle ear ventilation with the Castelli membrane tube. *Laryngoscope*. 1981 Jul;91(7):1173-5. PMID: 7195446.
111. Mandel EM, Casselbrant ML, Kurs-Lasky M. Acute otorrhea: bacteriology of a common complication of tympanostomy tubes. *Ann Otol Rhinol Laryngol*. 1994 Sep;103(9):713-8. PMID: 8085732.
112. Brown JA. Management of ventilation tubes: preventing premature extrusion. *J S C Med Assoc*. 1993 Sep;89(9):427-30. PMID: 8231117.
113. Debruyne F, Degroote M. One-year follow-up after tympanostomy tube insertion for recurrent acute otitis media. *ORL J Otorhinolaryngol Relat Spec*. 1993 Jul-Aug;55(4):226-9. PMID: 8336923.
114. Owen MJ, Norcross-Nechay K, Howie VM. Brainstem auditory evoked potentials in young children before and after tympanostomy tube placement. *Int J Pediatr Otorhinolaryngol*. 1993 Jan;25(1-3):105-17. PMID: 8436453.
115. Heaton JM, Mills RP. Otorrhea via ventilation tubes in adults and children. *Clin Otolaryngol Allied Sci*. 1993 Dec;18(6):496-9. PMID: 8877228.
116. Siddiqui N, Toynton S, Mangat KS. Results of middle ear ventilation with 'Mangat' T-tubes. *Int J Pediatr Otorhinolaryngol*. 1997 Jun 20;40(2-3):91-6. PMID: 9225174.
117. Golz A, Netzer A, Joachims HZ, et al. Ventilation tubes and persisting tympanic membrane perforations. *Otolaryngol Head Neck Surg*. 1999 Apr;120(4):524-7. PMID: 10187945.
118. Valtonen H, Qvarnberg Y, Nuutinen J. Tympanostomy in young children with recurrent otitis media. A long-term follow-up study. *J Laryngol Otol*. 1999 Mar;113(3):207-11. PMID: 10435125.
119. Rosenfeld RM, Bhaya MH, Bower CM, et al. Impact of tympanostomy tubes on child quality of life. *Arch Otolaryngol Head Neck Surg*. 2000 May;126(5):585-92. PMID: 10807325.
120. Ah-Tye C, Paradise JL, Colborn DK. Otorrhea in young children after tympanostomy-tube placement for persistent middle-ear effusion: prevalence, incidence, and duration. *Pediatrics*. 2001 Jun;107(6):1251-8. PMID: 11389239.
121. Valtonen H, Dietz A, Qvarnberg Y. Long-term clinical, audiologic, and radiologic outcomes in palate cleft children treated with early tympanostomy for otitis media with effusion: a controlled prospective study. *Laryngoscope*. 2005 Aug;115(8):1512-6. doi: 10.1097/01.mlg.0000172207.59888.a2. PMID: 16094135.
122. Pereira MB, Pereira DR, Costa SS. Tympanostomy tube sequelae in children with otitis media with effusion: a three-year follow-up study. *Braz J Otorhinolaryngol*. 2005 Jul-Aug;71(4):415-20. doi: /S0034-72992005000400003. PMID: 16446953.
123. Spielmann PM, McKee H, Adamson RM, et al. Follow up after middle-ear ventilation tube insertion: what is needed and when? *J Laryngol Otol*. 2008 Jun;122(6):580-3. doi: 10.1017/s0022215107001168. PMID: 18047760.
124. O'Reilly RC, He Z, Bloedon E, et al. The role of extraesophageal reflux in otitis media in infants and children. *Laryngoscope*. 2008 Jul;118(7 Part 2 Suppl 116):1-9. doi: 10.1097/MLG.0b013e31817924a3. PMID: 18594333.
125. Ida JB, Worley NK, Amedee RG. Gold laser adenoidectomy: long-term safety and efficacy results. *Int J Pediatr Otorhinolaryngol*. 2009 Jun;73(6):829-31. doi: 10.1016/j.ijporl.2009.02.020. PMID: 19324425.
126. Jung H, Lee SK, Cha SH, et al. Current bacteriology of chronic otitis media with effusion: high rate of nosocomial infection and decreased antibiotic sensitivity. *J Infect*. 2009 Nov;59(5):308-16. doi: 10.1016/j.jinf.2009.08.013. PMID: 19715725.

127. Kinnari TJ, Aarnisalo AA, Rihkanen H, et al. Can head position after anesthesia cause occlusion of the tympanostomy tube? *J Otolaryngol Head Neck Surg.* 2010 Feb;39(1):1-4. PMID: 20122337.
128. Marzouk HA, Nathawad R, Hammerschlag MR, et al. Methicillin-resistant *Staphylococcus aureus* colonization in otitis-prone children. *Arch Otolaryngol Head Neck Surg.* 2011 Dec;137(12):1217-22. doi: 10.1001/archoto.2011.192. PMID: 22183900.
129. Tuli BS, Parmar TL, Singh B. Evaluation of tympanostomy tubes in middle ear affections. *Indian J Otolaryngol Head Neck Surg.* 2001 Jul;53(3):217-20. doi: 10.1007/bf03028558. PMID: 23119801.
130. Saki N, Nikakhlagh S, Salehe F, et al. Incidence of Complications Developed after the Insertion of Ventilation Tube in Children under 6 years old in 2008-2009. *Iran J Otorhinolaryngol.* 2012 Winter;24(66):15-8. PMID: 24303379.
131. Smillie I, Robertson S, Yule A, et al. Complications of ventilation tube insertion in children with and without cleft palate: a nested case-control comparison. *JAMA Otolaryngol Head Neck Surg.* 2014 Oct;140(10):940-3. doi: 10.1001/jamaoto.2014.1657. PMID: 25171763.
132. Luo HN, Ma SJ, Sheng Y, et al. Pepsin deteriorates prognosis of children with otitis media with effusion who undergo myringotomy or tympanostomy tube insertion. *Int J Pediatr Otorhinolaryngol.* 2014 Dec;78(12):2250-4. doi: 10.1016/j.ijporl.2014.10.026. PMID: 25465449.
133. Powell J, Powell S, Lennon M, et al. Paediatric ventilation tube insertion: our experience of seventy-five children in audiology-led follow-up. *Clin Otolaryngol.* 2015 Aug;40(4):385-9. doi: 10.1111/coa.12380. PMID: 25598389.
134. Birck HG, Mravec JJ. Myringostomy for middle ear effusions. Results of a two-year study. *Ann Otol Rhinol Laryngol.* 1976 Mar-Apr;85(2 Suppl 25 Pt 2):263-7. PMID: 1267356.
135. Mackenzie IJ. Factors affecting the extrusion rates of ventilation tubes. *J R Soc Med.* 1984 Sep;77(9):751-3. PMID: 6541254.
136. Eliachar I, Joachims HZ, Goldsher M, et al. Assessment of long-term middle ear ventilation. *Acta Otolaryngol.* 1983 Jul-Aug;96(1-2):105-12. PMID: 6613541.
137. Jamal TS. Avoidance of postoperative blockage of ventilation tubes. *Laryngoscope.* 1995 Aug;105(8 Pt 1):833-4. doi: 10.1288/00005537-199508000-00012. PMID: 7543180.
138. Walker P. Ventilation tube duration versus site of placement. *Aust N Z J Surg.* 1997 Aug;67(8):571-2. PMID: 9287928.
139. Roland PS, Kreisler LS, Reese B, et al. Topical ciprofloxacin/dexamethasone otic suspension is superior to ofloxacin otic solution in the treatment of children with acute otitis media with otorrhea through tympanostomy tubes. *Pediatrics.* 2004 Jan;113(1 Pt 1):e40-6. PMID: 14702493.
140. Wallace HC, Newbegin CJ. Does ENT outpatient review at 1-week post ventilation tube insertion improve outcome at 1 month in paediatric patients? *Clin Otolaryngol Allied Sci.* 2004 Dec;29(6):595-7. doi: 10.1111/j.1365-2273.2004.00869.x. PMID: 15533143.
141. Allen J, Morton RP, Ahmad Z. Early post-operative morbidity after tympanostomy tube insertion. *J Laryngol Otol.* 2005 Sep;119(9):699-703. PMID: 16156910.
142. Dohar J, Giles W, Roland P, et al. Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea through tympanostomy tubes. *Pediatrics.* 2006 Sep;118(3):e561-9. doi: 10.1542/peds.2005-2033. PMID: 16880248.
143. Muenker G. Results after treatment of otitis media with effusion. *Ann Otol Rhinol Laryngol Suppl.* 1980 May-Jun;89(3 Pt 2):308-11. PMID: 6778334.
144. van Baarle PW, Wentges RT. Extrusion of transtympanic ventilating tubes, relative to the site of insertion. *ORL J Otorhinolaryngol Relat Spec.* 1975;37(1):35-40. PMID: 1169745.
145. Kokko E, Palva T. Clinical results and complications of tympanostomy. *Ann Otol Rhinol Laryngol.* 1976 Mar-Apr;85(2 Suppl 25 Pt 2):277-9. PMID: 1267359.

146. Paradise JL, Bluestone CD, Rogers KD, et al. Efficacy of adenoidectomy for recurrent otitis media in children previously treated with tympanostomy-tube placement. Results of parallel randomized and nonrandomized trials. *JAMA*. 1990 Apr 18;263(15):2066-73. PMID: 2181158.
147. MacKinnon DM. The sequel to myringotomy for exudative otitis media. *J Laryngol Otol*. 1971 Aug;85(8):773-94. PMID: 4105168.
148. Daly KA, Hunter LL, Lindgren BR, et al. Chronic otitis media with effusion sequelae in children treated with tubes. *Arch Otolaryngol Head Neck Surg*. 2003 May;129(5):517-22. doi: 10.1001/archotol.129.5.517. PMID: 12759263.
149. Praveen CV, Terry RM. Does passive smoking affect the outcome of grommet insertion in children? *J Laryngol Otol*. 2005 Jun;119(6):448-54. doi: 10.1258/0022215054273197. PMID: 15992470.
150. Khan F, Asif M, Farooqi GH, et al. Management outcome of secretory otitis media. *J Ayub Med Coll Abbottabad*. 2006 Jan-Mar;18(1):55-8. PMID: 16773972.
151. Hammaren-Malmi S, Saxen H, Tarkkanen J, et al. Passive smoking after tympanostomy and risk of recurrent acute otitis media. *Int J Pediatr Otorhinolaryngol*. 2007 Aug;71(8):1305-10. doi: 10.1016/j.ijporl.2007.05.010. PMID: 17582514.
152. Fiebach A, Matschke RG. [Duration and complications following grommet insertion in childhood]. *HNO*. 1987 Feb;35(2):61-6. PMID: 3570884.
153. Fior R, Veljak C. Late results and complications of tympanostomy tube insertion for prophylaxis of recurrent purulent otitis media in pediatric age. *Int J Pediatr Otorhinolaryngol*. 1984 Dec;8(2):139-46. PMID: 6526581.
154. Van Cauwenberge P, Cauwe F, Kluyskens P. The long-term results of the treatment with transtympanic ventilation tubes in children with chronic secretory otitis media. *Int J Pediatr Otorhinolaryngol*. 1979 Sep;1(2):109-16. PMID: 576016.
155. Tos M, Poulsen G. Secretory otitis media. Late results of treatment with grommets. *Arch Otolaryngol*. 1976 Nov;102(11):672-5. PMID: 985199.
156. Costa OA, Balieiro RO. Secretory otitis media in Brazilian children. *Scand Audiol Suppl*. 1986;26:93-4. PMID: 3472336.
157. Barfoed C, Rosborg J. Secretory otitis media. Long-term observations after treatment with grommets. *Arch Otolaryngol*. 1980 Sep;106(9):553-6. PMID: 7190819.
158. Levine S, Daly K, Giebink GS. Tympanic membrane perforations and tympanostomy tubes. *Ann Otol Rhinol Laryngol Suppl*. 1994 May;163:27-30. PMID: 8179266.
159. Hampton SM, Adams DA. Perforation rates after ventilation tube insertion: does the positioning of the tube matter? *Clin Otolaryngol Allied Sci*. 1996 Dec;21(6):548-9. PMID: 9118580.
160. Postma DS, Poole MD, Wu SM, et al. The impact of day care on ventilation tube insertion. *Int J Pediatr Otorhinolaryngol*. 1997 Sep 18;41(3):253-62. PMID: 9350484.
161. Valtonen HJ, Qvarnberg YH, Nuutinen J. Otological and audiological outcomes five years after tympanostomy in early childhood. *Laryngoscope*. 2002 Apr;112(4):669-75. doi: 10.1097/00005537-200204000-00014. PMID: 12150521.
162. Valtonen H, Tuomilehto H, Qvarnberg Y, et al. A 14-year prospective follow-up study of children treated early in life with tympanostomy tubes: Part 1: Clinical outcomes. *Arch Otolaryngol Head Neck Surg*. 2005 Apr;131(4):293-8. doi: 10.1001/archotol.131.4.293. PMID: 15837895.
163. De Beer BA, Schilder AG, Zielhuis GA, et al. Natural course of tympanic membrane pathology related to otitis media and ventilation tubes between ages 8 and 18 years. *Otol Neurotol*. 2005 Sep;26(5):1016-21. PMID: 16151352.
164. Carignan M, Dorion D, Stephenson MF, et al. First myringotomy with insertion of a modified Goode T-Tube: changing the perforation paradigm. *J Otolaryngol*. 2006 Oct;35(5):287-91. PMID: 17049144.
165. Florentzson R, Finizia C. Transmyringal ventilation tube treatment: a 10-year cohort study. *Int J Pediatr Otorhinolaryngol*. 2012 Aug;76(8):1117-22. doi: 10.1016/j.ijporl.2012.04.013. PMID: 22648089.

166. O'Neil MB, Cassidy LD, Link TR, et al. Tracking tympanostomy tube outcomes in pediatric patients with otitis media using an electronic database. *Int J Pediatr Otorhinolaryngol*. 2015 Aug;79(8):1275-8. doi: 10.1016/j.ijporl.2015.05.029. PMID: 26115935.
167. Gundersen T, Tonning FM. Ventilating tubes in the middle ear. *Arch Otolaryngol*. 1976 Apr;102(4):198-9. PMID: 1267702.
168. Tos M, Stangerup SE, Larsen P. Dynamics of eardrum changes following secretory otitis. A prospective study. *Arch Otolaryngol Head Neck Surg*. 1987 Apr;113(4):380-5. PMID: 3814387.
169. Slack RW, Maw AR, Capper JW, et al. Prospective study of tympanosclerosis developing after grommet insertion. *J Laryngol Otol*. 1984 Aug;98(8):771-4. PMID: 6470572.
170. Daly KA, Hunter LL, Levine SC, et al. Relationships between otitis media sequelae and age. *Laryngoscope*. 1998 Sep;108(9):1306-10. PMID: 9738746.
171. Koc A, Uneri C. Sex distribution in children with tympanosclerosis after insertion of a tympanostomy tube. *Eur Arch Otorhinolaryngol*. 2001 Jan;258(1):16-9. PMID: 11271428.
172. Friedman EM, Sprecher RC, Simon S, et al. Quantitation and prevalence of tympanosclerosis in a pediatric otolaryngology clinic. *Int J Pediatr Otorhinolaryngol*. 2001 Sep 28;60(3):205-11. PMID: 11551611.
173. Bonding P, Lorenzen E. Chronic secretory otitis media--long-term results after treatment with grommets. *ORL J Otorhinolaryngol Relat Spec*. 1974;36(4):227-35. PMID: 4215997.
174. Bonding P, Lorenzen E. Cicatricial changes of the eardrum after treatment with grommets. *Acta Otolaryngol*. 1973 Apr;75(4):275-6. PMID: 4702615.
175. Li Y, Hunter LL, Margolis RH, et al. Prospective study of tympanic membrane retraction, hearing loss, and multifrequency tympanometry. *Otolaryngol Head Neck Surg*. 1999 Nov;121(5):514-22. PMID: 10547462.
176. Tos M, Poulsen G. Attic retractions following secretory otitis. *Acta Otolaryngol*. 1980 May-Jun;89(5-6):479-86. PMID: 7192477.
177. Golz A, Goldenberg D, Netzer A, et al. Cholesteatomas associated with ventilation tube insertion. *Arch Otolaryngol Head Neck Surg*. 1999 Jul;125(7):754-7. PMID: 10406312.
178. Spilsbury K, Ha JF, Semmens JB, et al. Cholesteatoma in cleft lip and palate: a population-based follow-up study of children after ventilation tubes. *Laryngoscope*. 2013 Aug;123(8):2024-9. doi: 10.1002/lary.23753. PMID: 23737350.
179. Djurhuus BD, Christensen K, Skytthe A, et al. The impact of ventilation tubes in otitis media on the risk of cholesteatoma on a national level. *Int J Pediatr Otorhinolaryngol*. 2015 Apr;79(4):605-9. doi: 10.1016/j.ijporl.2015.02.005. PMID: 25724629.
180. Goldstein NA, Mandel EM, Kurs-Lasky M, et al. Water precautions and tympanostomy tubes: a randomized, controlled trial. *Laryngoscope*. 2005 Feb;115(2):324-30. doi: 10.1097/01.mlg.0000154742.33067.fb. PMID: 15689760.
181. Parker GS, Tami TA, Maddox MR, et al. The effect of water exposure after tympanostomy tube insertion. *Am J Otolaryngol*. 1994 May-Jun;15(3):193-6. PMID: 8024107.
182. Becker GD, Eckberg TJ, Goldware RR. Swimming and tympanostomy tubes: a prospective study. *Laryngoscope*. 1987 Jun;97(6):740-1. PMID: 3586818.
183. Cohen HA, Kauschansky A, Ashkenasi A, et al. Swimming and grommets. *J Fam Pract*. 1994 Jan;38(1):30-2. PMID: 8289048.
184. el Silimy O, Bradley PJ. Bacteriological aspects of swimming with grommets. *Clin Otolaryngol Allied Sci*. 1986 Oct;11(5):323-7. PMID: 3780019.
185. Francois M, Jaquemin P, Margo JN, et al. [Swimming and ventilating tubes. Results of a multicenter study]. *Ann Pediatr (Paris)*. 1992 Dec;39(10):627-9. PMID: 1485779.
186. Kaufmann TU, Veraguth D, Linder TE. [Water precautions after insertion of a tympanostomy tube: necessary or obsolete?]. *Schweiz Med Wochenschr*. 1999 Oct 9;129(40):1450-5. PMID: 10546304.
187. Salata JA, Derkay CS. Water precautions in children with tympanostomy tubes. *Arch Otolaryngol Head Neck Surg*. 1996 Mar;122(3):276-80. PMID: 8607955.

188. Sharma PD. Swimming with grommets. *Scand Audiol Suppl.* 1986;26:89-91. PMID: 3472335.
189. Smelt GJ, Yeoh LH. Swimming and grommets. *J Laryngol Otol.* 1984 Mar;98(3):243-5. PMID: 6538215.
190. Konradsson K, Ortegren U. [Transmyringal ventilation tubes: postoperative restrictions and early complications]. *Lakartidningen.* 1986 Oct 15;83(42):3514-7. PMID: 3784716.
191. Waycaster C, Cockrum P, Reese B, et al. Treatment of Acute Otitis Media in Children with Tympanostomy Tubes: A Caregiver's Perspective. *Pharmacy and Therapeutics.* 2004;29(11):721-30.
192. 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.
193. Ruohola A, Heikkinen T, Jero J, et al. Oral prednisolone is an effective adjuvant therapy for acute otitis media with discharge through tympanostomy tubes. *J Pediatr.* 1999 Apr;134(4):459-63. PMID: 10190921.
194. Dohar JE, Garner ET, Nielsen RW, et al. Topical ofloxacin treatment of otorrhea in children with tympanostomy tubes. *Arch Otolaryngol Head Neck Surg.* 1999 May;125(5):537-45. PMID: 10326811.
195. Ruohola A, Heikkinen T, Meurman O, et al. Antibiotic treatment of acute otorrhea through tympanostomy tube: randomized double-blind placebo-controlled study with daily follow-up. *Pediatrics.* 2003 May;111(5 Pt 1):1061-7. PMID: 12728089.
196. Roland PS, Anon JB, Moe RD, et al. Topical ciprofloxacin/dexamethasone is superior to ciprofloxacin alone in pediatric patients with acute otitis media and otorrhea through tympanostomy tubes. *Laryngoscope.* 2003 Dec;113(12):2116-22. doi: 10.1097/00005537-200312000-00011. PMID: 14660913.
197. Granath A, Rynnel-Dagoo B, Backheden M, et al. Tube associated otorrhea in children with recurrent acute otitis media; results of a prospective randomized study on bacteriology and topical treatment with or without systemic antibiotics. *Int J Pediatr Otorhinolaryngol.* 2008 Aug;72(8):1225-33. doi: 10.1016/j.ijporl.2008.04.015. PMID: 18565598.
198. 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.
199. 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/NEJMoal301630. PMID: 24552319.
200. van Dongen TM, Venekamp RP, Wensing AM, et al. Acute otorrhea in children with tympanostomy tubes: prevalence of bacteria and viruses in the post-pneumococcal conjugate vaccine era. *Pediatr Infect Dis J.* 2015 Apr;34(4):355-60. doi: 10.1097/inf.0000000000000595. PMID: 25764097.
201. Roland PS, Dohar JE, Lanier BJ, et al. Topical ciprofloxacin/dexamethasone otic suspension is superior to ofloxacin otic solution in the treatment of granulation tissue in children with acute otitis media with otorrhea through tympanostomy tubes. *Otolaryngol Head Neck Surg.* 2004 Jun;130(6):736-41. doi: 10.1016/j.otohns.2004.02.037. PMID: 15195060.
202. Strachan D, Clarke SE, England RJ. The effectiveness of topical treatment in discharging ears with in-dwelling ventilation tubes. *Rev Laryngol Otol Rhinol (Bord).* 2000;121(1):27-9. PMID: 10865480.
203. Rovers MM, Black N, Browning GG, et al. Grommets in otitis media with effusion: an individual patient data meta-analysis. *Arch Dis Child.* 2005 May;90(5):480-5. doi: 10.1136/ad.2004.059444. PMID: 15851429.
204. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. *Otolaryngol Head Neck Surg.* 2001 Apr;124(4):374-80. PMID: 11283489.

205. Idicula WK, Juncisek JA, Cass ND, et al.  
Identification of biofilms in post-tympanostomy  
tube otorrhea. *Laryngoscope*.  
2016 Aug;126(8):1946-51. doi:  
10.1002/lary.25826. PMID: 27426942.

## **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  
inflamm\* 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 Chevetton 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 patients	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 Schröder	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) eustachian 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 Bezuhy	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 transmyringal 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 secretory 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 Repogle	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 otitis 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 Otolaryngology, 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

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		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 Kalcioğlu 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 Pardo 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 Gábríel	[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 Chodynicky 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'Neil 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 otorinolaringologij	Reviewed in abstract only
21166142	Elzbieta Hassmann-Poznańska and Artur Goździewski and Małgorzata Piszcz and Hanna Zajackiewicz and Bożena 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 ear 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	Przegląd 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 Bożena 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 6 months 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, Johnston2 004 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 (sensorineural loss) or defects in their speech-producing apparatus (e.g. cleft palate), neurological 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								
Veletic 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 Netherlands	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 26281253 a 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 26281253 b 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 ( $\geq 2$ episodes in previous 12 months), with OME or AOM. Underwent adenoidectomy; Recurrent febrile episodes related to adenotonsillar inflammation ( $\geq 2$ episodes in previous 12 months), with OME or AOM. Underwent adenoidectomy	.		2-11	excluded other craniofacial anomalies, genetic syndromes	minimum 104
Reiter 2009	NRCS, retrospect	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**

<b>Author Year PMID Years of recruitment Country</b>	<b>Design</b>	<b>Number of participant s</b>	<b>Age Range (y)</b>	<b>Inclusion criteria</b>	<b>Exclusion criteria</b>
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 participant s	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/plann ed duration (weeks)
Becker 1987 3586818 4/1985- 9/1985 U.S.	NRCS, prospectiv e		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, prospectiv e	3, 12	Underwent plastic ventillation tube insertion because of recurrent otitis media or serious otitis media complicated by impaired hearing	78-130

Author Year PMID Date Country	Study design	Age range (years)	Inclusion criteria	No. assessments/plann ed 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 otitis 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)
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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 otorrhea 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 pain 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 +/- adenoidectomy (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

<b>Study</b>	<b>Arm (Description)</b>	<b>Antibiotic name, dose, duration</b>	<b>Diagnostic criteria for AOM</b>	<b>Management of acute infections</b>	<b>Tube type</b>
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 intervention)	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  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, Johnston20 04 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 intervention)	.			
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, Entemed 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 09/1982- 08/1983 Netherlands					
Schilder 1997 9372253 09/1982- 08/1983 Netherlands	control (no TT)	.			
Stenstrom 2005 16330739 1985-1989 Canada	TT (Tympanostomy tubes)	.			50 (83%) of 60 patients received T-type VTs
Stenstrom 2005 16330739 1985-1989 Canada	Control (medical treatment (low-dose sulfisoxazole for 6 months)	.			
Veletic 2011 21397957 2004-2009 Croatia	TT AND adenoidectomy	.			
Veletic 2011 21397957 2004-2009 Croatia	Adenoidectomy (Adenoidectomy only)	.			
Vlastos 2011 21205368 5/2007- 5/2008 Greece	TT AND adenoidectomy	.			Shepard type
Vlastos 2011	Myringotomy AND adenoidectomy	.			

<b>Study</b>	<b>Arm (Description)</b>	<b>Antibiotic name, dose, duration</b>	<b>Diagnostic criteria for AOM</b>	<b>Management of acute infections</b>	<b>Tube type</b>
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 +/- adenoidectomy	.			
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	
Konr�dsson 1986 3784716 6/1983-11/1983 Sweden	no precautions	
Konr�dsson 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/l ow SES n/N (%)	Cigarette smoke exposure n/N (%)	Daycar e 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]						16296/267 14 (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/l ow SES n/N (%)	Cigarette smoke exposure n/N (%)	Daycar e 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/l ow SES n/N (%)	Cigarette smoke exposure n/N (%)	Daycar e n/N (%)
26429601											
Hubbard 1985 4039792	Early TT										
Hubbard 1985 4039793	Late TT										
Kadhim 2007 17279052	TT (Tympanostom y 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/l ow SES n/N (%)	Cigarette smoke exposure n/N (%)	Daycar e 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)	120/12 0 (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)	121/12 3 (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)	110/11 0 (100)
Niclasen-2016- 27063746	No TT					>= 4		288/569 (50.6)		Maternal: 250/569 (44.0); paternal	0-3 years 521/56 9

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 (%)	Daycar e 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/l ow SES n/N (%)	Cigarette smoke exposure n/N (%)	Daycar e 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/l ow SES n/N (%)	Cigarette smoke exposure n/N (%)	Daycar e 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)
Veletic 2011 21397957	TT AND adenoidectomy	5.56									
Veletic 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 +/- adenoidectomy										
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 (amoxicillin)	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 (%)
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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 placebo	[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
Veletic 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
Hammarén-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							Unclear		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
Kuşçu-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 definition 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 described	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 instructions to avoid swimming	Unclear	Yes	11%	No	Yes	No	No	Unclear	No		No	No	Yes	Yes	No

Salata 1996 8607955	Yes	Consecutive or obviously representative series of cases*	parent selection	received different prophylaxis	Written self report or medical record only	Yes	unknown relative non- response rate	Not Applicable	No	No	No	Yes	Yes	Yes	Yes	Yes	unclear - high dropo- ut	Yes	Yes
Sharma 1986 3472335	Yes	Parental choice	Parental choice	Children 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 Applicable	No	No	Unclear	Not Applicable	No	No	No	No	No	No	No
Dohar 1999 10326811	Yes	Consecutive or obviously representative series of cases*	Hospital controls	historical and concurrent with the same dx	Secure record (eg surgical records)*	Yes	Same rate for both groups*	Not Applicable	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**

<i>Study author, years</i>	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
<i>Paradise, 2001, 2003, 2004, 2005, 2007</i>	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

<i>Study author, years</i>	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 Phonological 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 Phonological 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 withheld	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 - impulsivity 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					

<i>Study author, years</i>	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	nr	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	nr	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-Kollektiv 1816937 Germany	prosp nrcs	[cleft palate - University of Hamburg]		X					X		X	X	
Hormann -Iowa-Kollektiv 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, Entemed 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 initiation of symptoms]				X			X	X	X		
Paradise 11309632 US	prosp rct (1991-1995)	Armstrong [TT early treatment; underwent TT insertion at initiation 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 sulfate-hydrocortisone otic drops]		X									
Postma 9350484 US	prosp cohort (1988-1991)	Armstrong grommet 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	nr	T tube, Paparella TT [TT: no ear drops]											X
Rakover 9176804 Israel	nr	T tube, Paparella TT [TT with ear drops (preventive dexamethasone, neomycin and polymyxin 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 nr	Reuter bobbin tubes [underwent Laser Office Ventilation of Ears with Insertion of Tubes (LOVE IT)]		X									
Siegel 12161732 US	prosp nr	Reuter bobbin tubes [underwent standard cold surgical myringotomy and tube placement (M&T)]		X									
Slack 6470572 UK	prosp cohort	Shepard grommet								X			
Smillie 25171763	nr	[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	nr cs (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 Australia	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]											
Velepik 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 unequivocally present in external auditory canal, regardless of whether a tube was present or not, not occluding 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 unequivocally present in external auditory canal, regardless of whether a tube was present or not, not occluding 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 nrct	[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, Entemed 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	%AOM [%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	%AOM [%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 nracs (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	nracs (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 Extrusion
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 Extrusion
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 ncrrs	[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 perforation
Paradise 11309632 US	prosp rct (1991-1995)	Armstrong [TT early treatment; underwent TT insertion at initiation 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	nracs (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%	
Velep 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 nrns (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	nracs (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
Velepici 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 nracs	[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 quadrant 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 nracs	[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 initiation 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	nracs (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
Velepici 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. Cholesteatoma**

Author PMID Country	Design (recruitment period)	Tube Type [arm desc.]	Age (SD) [min, max]	% male	%rAOM [%COME]	Followup	N [ears]	% Cholesteatoma	def_cholesteatoma
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	nracs (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

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

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

with  $k = 1, \dots, K$  indexing the  $K$  studies, and  $j = 1, 2, \dots$  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.  $\mathbf{T}_k = (T_{k1}, \dots, T_{k,N-1})'$  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

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

where  $\mathbf{\Omega}$  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  $\mathbf{T} = (T_1, \dots, T_{N-1})'$  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,

$$\mathbf{T} \sim N(\mathbf{0}, c\mathbf{I}) \text{ and}$$

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

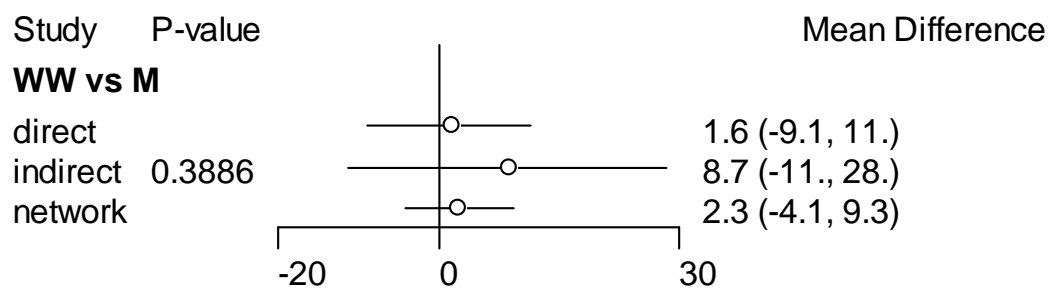
where  $\mathbf{0}$  is a column vector of zeros,  $\mathbf{I}$  a conformal identity matrix and  $c$  and  $m$  scaling factors that are set to 15 and 5 times the range of observed effects, respectively.

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.

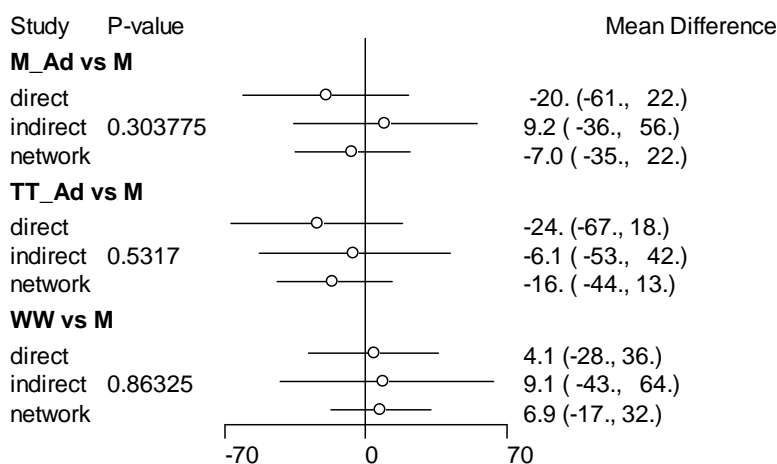
**Appendix Figure I1. Inconsistency analysis results for KQ1 – early hearing levels**



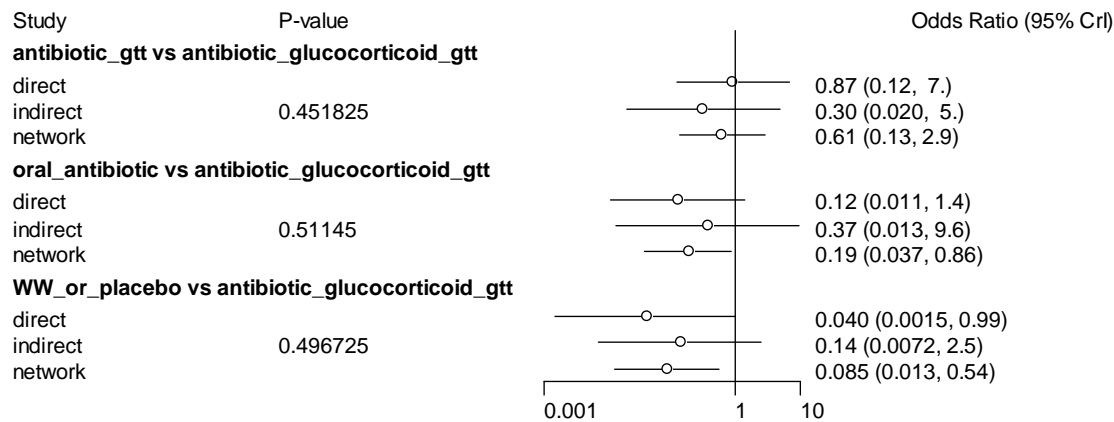
## KQ 1: Late Hearing Levels

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

