

Draft Comparative Effectiveness Review

Number xx

Tympanostomy Tubes in Children with Otitis Media

Prepared for:

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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.

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

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

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

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.

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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 does not necessarily represent the views of individual reviewers.

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Tympanostomy Tubes in Children with Otitis Media

Structured Abstract

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

Data sources. We conducted literature searches in MEDLINE®, the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, EMBASE®, and CINAHL®. Additionally, we perused the reference lists of published relevant clinical practice guidelines, 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 was 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 10,129 citations, of which 184 articles are included in the report. 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, but there is no evidence of a sustained benefit. A period of watchful waiting does not worsen language, cognition, behavior, or quality of life. The current evidence base provides little guidance for the treatment of children with conditions such as cleft palate, Down syndrome, or other neurobehavioral disabilities. Children with recurrent AOM may have fewer episodes after TT placement, but the evidence base is severely limited and it is unclear whether quality of life outcomes are improved. The benefits of TT placement must be weighed against a variety of adverse events. There is no compelling evidence for the children with TT to avoid swimming or bathing or use ear plugs or bathing caps. Should otorrhea develop, the evidence supports treatment with a topical antibiotic-glucocorticoid antibiotic or antibiotic drops. Antibiotic-glucocorticoid drops appear to be superior to watchful waiting and more effective than oral antibiotics for treatment of otorrhea.

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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. OME is defined as chronic OME, if effusion persists for 3 months or longer.¹ Acute otitis media and chronic OME have shared causes. Children with chronic OME are prone to recurrent AOM episodes, and after an AOM episode all children have OME for some time.² Chronic OME can result in hearing deficits, which may 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.³

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

Myringotomy with tympanostomy tube (TT) placement is the most common ambulatory surgery performed on children in the United States, with almost 700,000 procedures performed yearly at an estimated annual cost of \$1.8 billion.⁵ 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.⁶

The AAO-HNS CPG deems 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. In addition, TT placement is associated with complications, such as acute otorrhea.⁷ 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.⁸ However, the otorrhea is sometimes chronic, associated with a foul odor, fever, or pain, and it may negatively affect quality of life. Treatment is aimed at eradicating bacterial infection, using antibiotic eardrops with or without glucocorticoids (to reduce symptoms).⁹

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.

The 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?

- 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?

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? What factors (such as age, age of onset, number of recurrences, presence of persistent middle ear effusion, comorbidities, and 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, the 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 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)

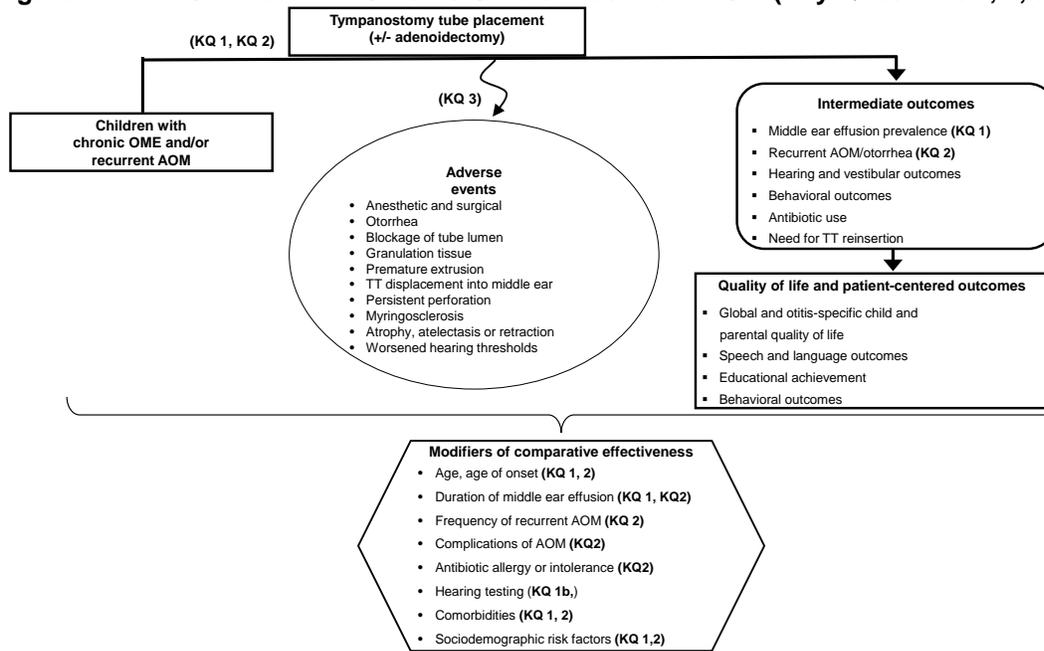


Figure B. Need for Water Precautions in Children with TT (Key Question 4)

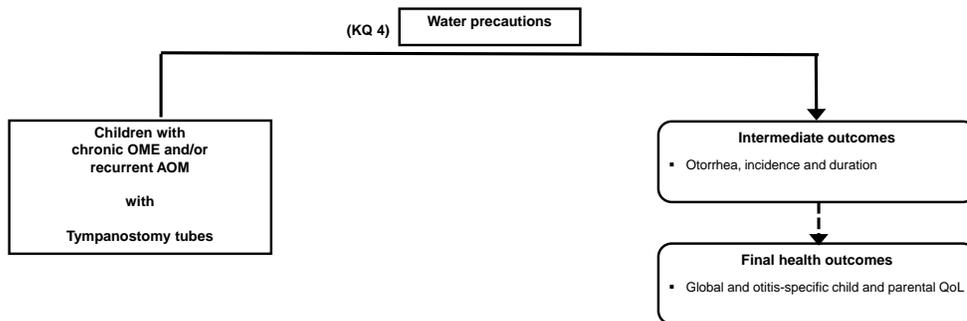
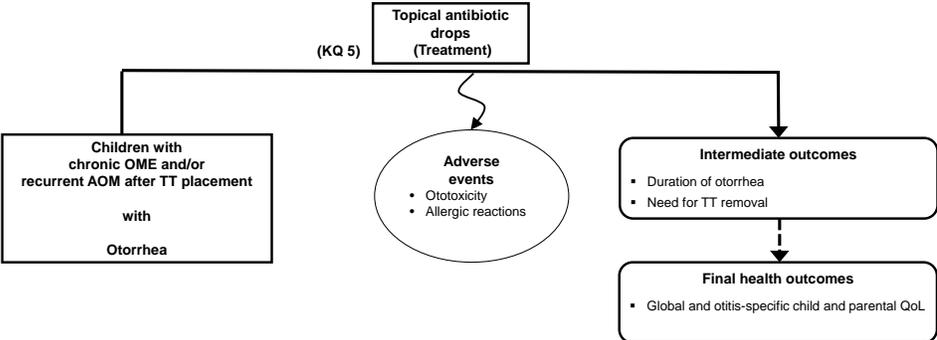


Figure C. Treatment of Otorrhea in Children with TT (Key Question 5)



Methods

The Brown Evidence-based Practice Center (EPC) conducted the 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.¹⁰ The PROSPERO protocol registration number is CRD42015029623.

Eligibility Criteria

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

Populations

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

For KQ 1, we included studies of children with chronic OME. We preferred the standard definition of effusion that persists for at least three months,¹ but included results based on studies' alternative definitions if our preferred one was not reported. We excluded children with chronic suppurative otitis media.

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

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

Interventions/Exposures

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

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

KQ 5 compares ototopical preparations, and includes FDA approved products (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 levels (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, 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 and population based retrospective single group studies (registry studies) with at least 1000 subjects.

Searching for the Evidence

We conducted literature searches of all studies in MEDLINE®, the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, EMBASE®, and CINAHL® databases

(details in Appendix A of the full report). 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://srdhr.ahrq.gov>).

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.¹¹ For observational studies, we used relevant questions from the Newcastle Ottawa Scale.¹²

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 level). 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 (SOE)

We graded the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence.¹³ Each strength-of-evidence dimensional rating is summarized in the “Summary of Evidence Reviewed” table (Table E).

Assessing Applicability

We assessed the applicability within and across studies with reference to children in the populations of interest (chronic OME, recurrent AOM and children with TT), and whether interventions and comparators are used in current practice.

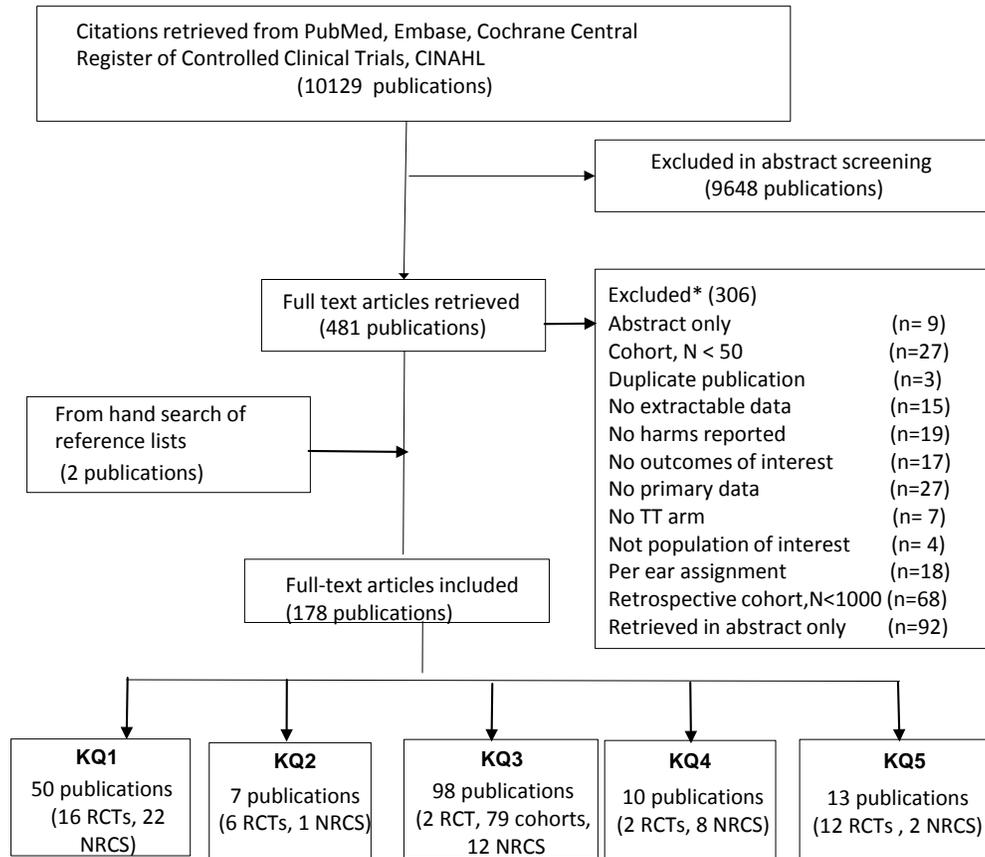
Results

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 = non-randomized comparative trial; RCT = randomized controlled trial; Some publications reported data from the same study. 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 50 publications (reporting results of 16 RCTs and 22 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). Three of these RCTs enrolled patients with recurrent acute otitis media or chronic middle ear effusion.¹⁴⁻¹⁶

Hearing levels were measured in 16 RCTs. In 10 of these, mean hearing levels were reported by arm at various time points. For the network meta-analysis, we classified hearing levels obtained at one to three months as “early”. Similarly, hearing levels 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 levels at 1 to 3 months.

Figure E. Network Graph of Comparators for Early (1 to 3 Month) Hearing Levels

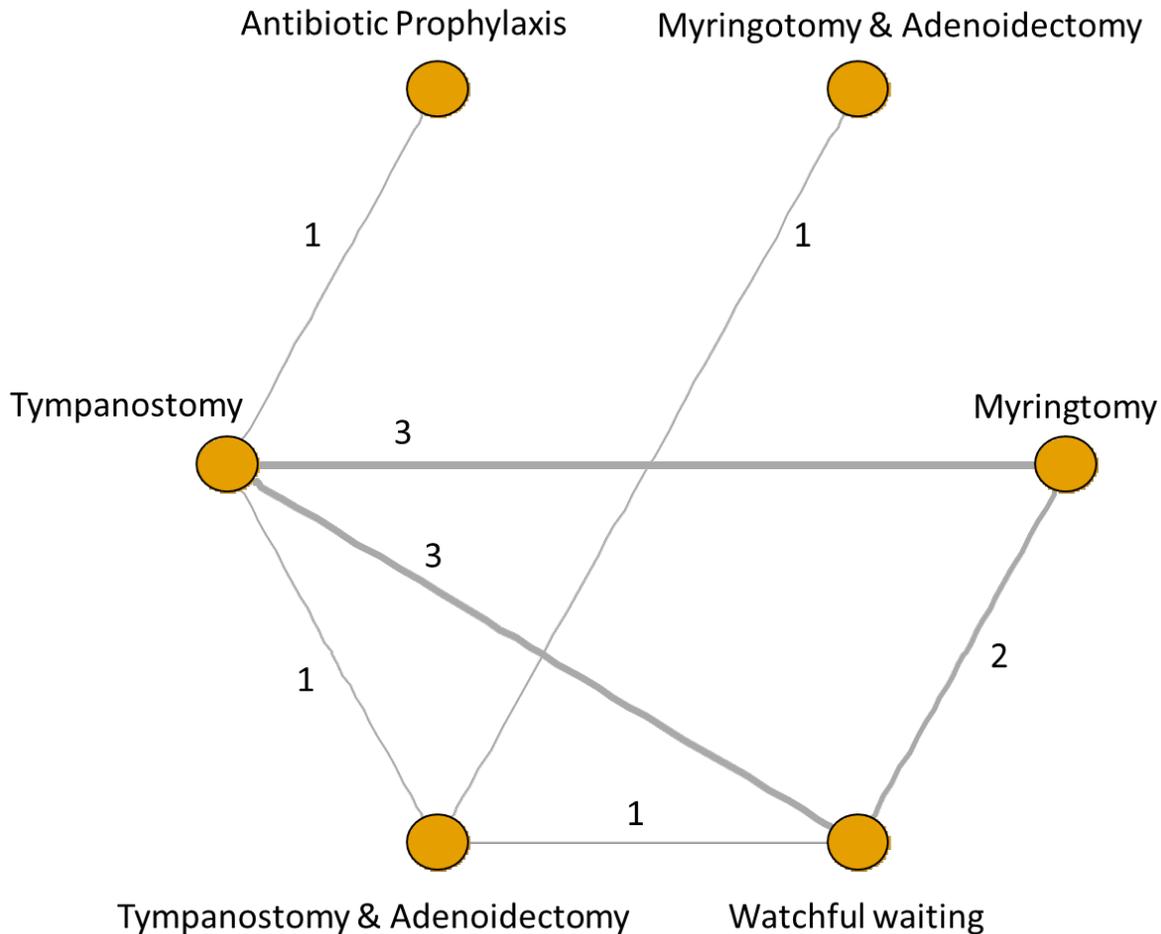
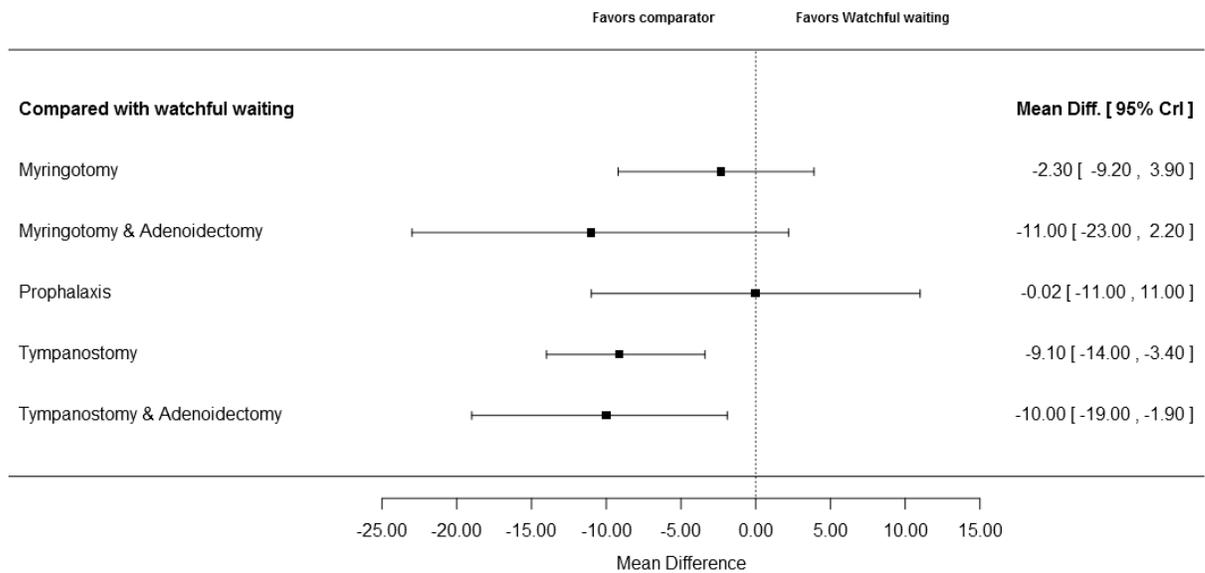


Figure F illustrates the effectiveness of various interventions at 1 to 3 months, compared with watchful waiting. Mean hearing levels improved (decreased) by average of 9.1 dB following TT, and by 10 dB following TT with adenoidectomy. Credible intervals for these effects exclude zero. The credible intervals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



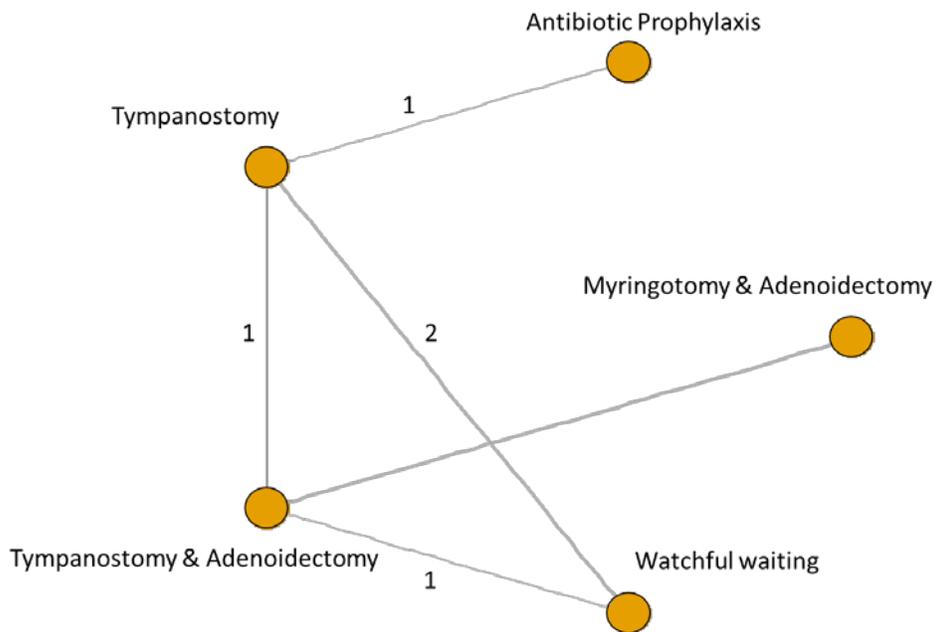
As shown in Table A, the strategies with the highest probability of being among the three most effective interventions with respect to early improvements in hearing levels were TT, TT with adenoidectomy, and myringotomy with adenoidectomy.

Table A. Probabilities (%) That an Intervention is Among the Three Most Effective with Respect to Early Hearing Levels

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

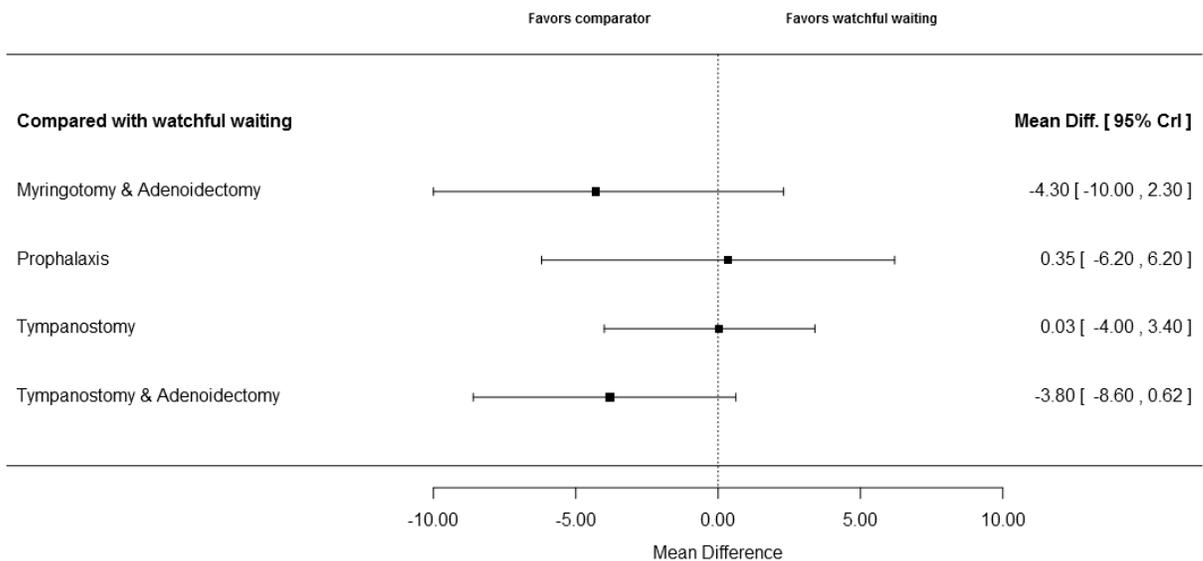
Five RCTs reported hearing levels at 12 to 24 months. Figure G shows the topology of the network of comparisons at this time interval.

Figure G. Network Graph of Comparators for Late (12-24 month) Hearing Levels



As shown in Figure H, by 12 to 24 months, the mean difference in hearing levels for TT alone, compared to watchful waiting was 0 dB (95% CI -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 – 24 Month) Decrease (Improvement) in Mean Hearing Levels Compared with Watchful Waiting



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 levels. TT alone, antibiotic prophylaxis, and watchful waiting were among the three least effective ones.

Table B. Probabilities (%) That an Intervention is Among the Two Most Effective with Respect to Late Hearing Levels

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 levels, but did not report mean hearing levels are summarized in the full report.

Non-Randomized 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.¹⁷ Three studies (two in cleft palate^{18, 19} and one in primary ciliary dyskinesia¹⁷) compared TT placement with nonsurgical treatment, while one study compared early versus delayed TT in different settings.²⁰ Two studies assessed the effects of TT and cleft repairing versus cleft repairing alone.^{21, 22} Hearing levels measured as pure tone average were reported in four studies.^{17, 19, 20, 22} 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.^{17, 19} TT in addition to cleft repair improved hearing levels with unknown significance.²² The improvement by early TT compared to delayed procedures in patients with cleft palate was marginally significant.²⁰ The rate of normal hearing, defined as hearing threshold < 20 dB bilaterally, was significantly higher in TT than control (P <0.05)²¹

Quality of life and patient-centered outcomes: Eight studies (five RCTs, three NRCS, and one that combined both designs) in 12 papers reported on 119 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. 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,²³⁻²⁷ and Vlastos reported on pediatric health related quality of life.²⁸ Neither found any significant differences. Full details for all outcomes are in Appendix G of the full report.

Key Question 2

We identified six studies in seven publications. A total 1049 patients were randomized, with an additional 169 patients enrolled in an NRCS whose treatment assignment was determined by parental choice.²⁹ Three RCTs³⁰⁻³² compared TT placement with daily oral antibiotic prophylaxis. Two of these studies included a comparison with placebo^{30, 31} and the third compared TT placement with no treatment.³³ The effectiveness of TT alone versus TT with adenoidectomy was evaluable in three studies.^{15, 29, 33} These studies had moderate or high risk of bias and were not clearly reported. .

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.³⁰

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 ($P < 0.001$). They report 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 also significantly associated with higher rates of recurrent AOM.³¹

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.³³

TT Versus Antibiotic Prophylaxis

Gonzalez 1986 reported that 55 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 ($P = 0.08$).³⁰ 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 ($P = 0.001$).³¹ El-Sayed found no difference in the treatment outcomes of children treated with trimethoprim/sulfamethoxazole compared to children treated with TT ($P = 0.37$).³²

TT Versus TT and Adenoideotomy

An RCT by Mattila 2003 found no difference in cumulative hazard of recurrent AOM or in efficacy in children who underwent TT with adenoideotomy compared with TT alone.²⁹ Kujala 2014 reported no significant difference between the TT with adenoideotomy and TT only groups in the number of failures (absolute difference -5% [95% CI -16 to 6]; P = 0.37), time to failure (P = 0.29), first AOM episode (P = 0.6), or proportion of children with no AOM episodes (absolute difference 1%, CI -13 to 15, P = 1.0).³³ A subsequent 2005 RCT by the same group also found no differences in the mean number of otitis media episodes overall or in the subgroup of children with recurrent AOM at enrollment.¹⁵

Quality of Life Outcomes

Although Kujala 2014 found that insertion of TT tubes, without or without adenoideotomy, significantly reduced the risk of recurrent AOM, a subsequent publication from the same trial examining quality of life outcomes found no differences in overall ear-related quality of life (Otitis Media-6 questionnaire [OM-6]), the subscales of caregiver concern, emotional distress, physical suffering, activity limitations, hearing loss, or speech impairment between surgically treated and no surgery groups.³⁴

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.³

Risk Factors

No study evaluated whether age, age of onset, number of recurrences, comorbidities, history of complications of acute otitis media, antibiotic allergy or intolerance, or other sociodemographic risk factors modify the effectiveness of TT placement for recurrent AOM.

There are no prospective 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 reported that the number of infections per child during 6 month followup and the number of patients who had no further episodes of AOM was significantly better (P < 0.05) in children with OME than in those without middle ear effusion.³⁰ The other two studies specifically excluded patients with middle ear effusion at the time of surgical evaluation.^{31,33}

Key Question 3

We extracted data on the occurrence of 11 adverse events from 76 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, cholesteotoma and long term hearing loss. The number of publications reporting each event, and the median (with 25th and 75th 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	Number of Publications	Patients: Median Percent (25 th , 75 th)	Ears: Median Percent (25%, 75th%)
Perioperative Complications	3	0.81 (intraoperative events)	1.04 (canal abrasion); 0.01 (tear of TT)
Otorrhea	47	20.6 [12, 38]	10.5 [7.5, 15.5]
Tube Blockage	20	7.8 [0, 13]	6.5 [2.8, 37.3]
Granulation Tissue	12	1.7 [0, 3.4]	2.1 [1.5, 4.2]
Premature Extrusion	20	9.6 [4, 37.9]	5.0 [1.8, 39.4]
TT Displacement in middle ear	8	0.5 [0.4, 1.2]	0.8 [0.7, 0.9]
Persistent Perforation	48	2.8 [1.8, 6.7]	2.4 [1.3, 4.6]
Myringosclerosis	24	18.9 [3.3, 55.9]	11.3 [5.3, 49.8]
Atrophy, Atelectasis or Retraction	22	12.5 [6.4, 20.3]	18.2 [4.4, 40.1]
Cholesteotoma	23	0.8 [0, 1.9]	0.7 [0, 4.98]
Hearing Loss	13	9 [0.6, 24.7]	14.4 [6.7, 56.1]

See Appendix I of the full report for adverse event details by study, as well Appendix C in the full report 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 nine studies, two RCTs and seven 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.

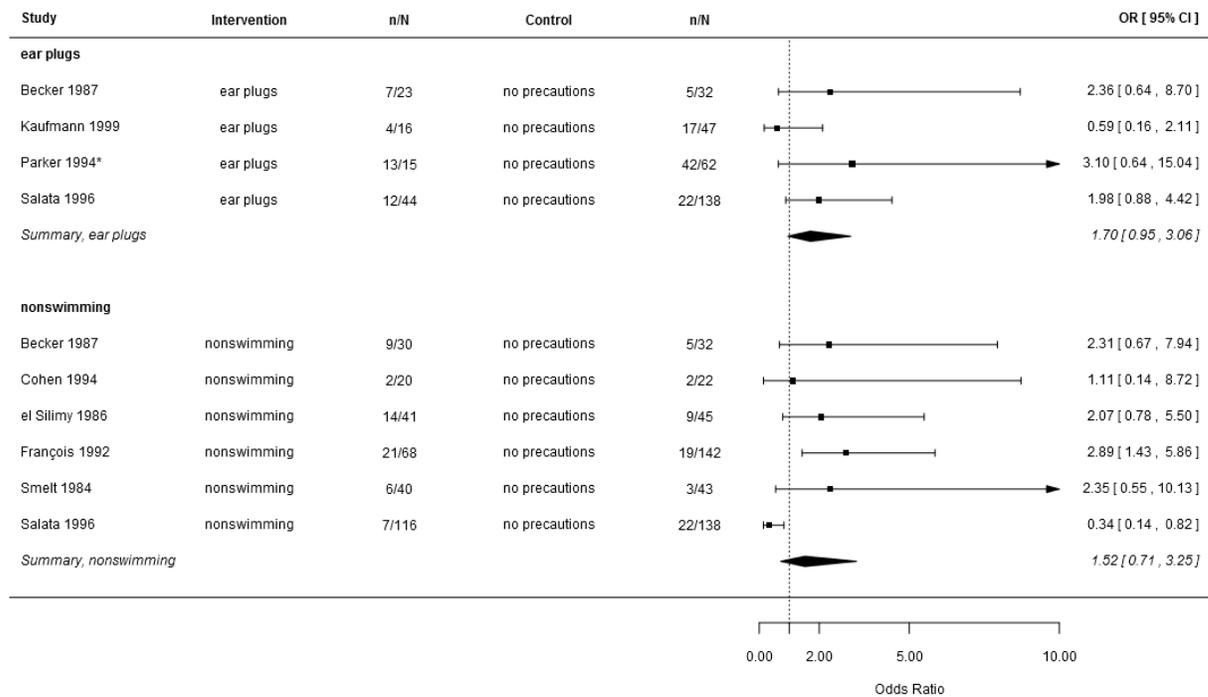
Outcomes

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.³⁵ Parker 1994 reported identical mean otorrhea rates in nonswimmers and swimmers.³⁶ The forest plot shown in Figure I, summarizes the results. Random effects meta-analysis was used to pool the individual odds-ratios 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).

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.

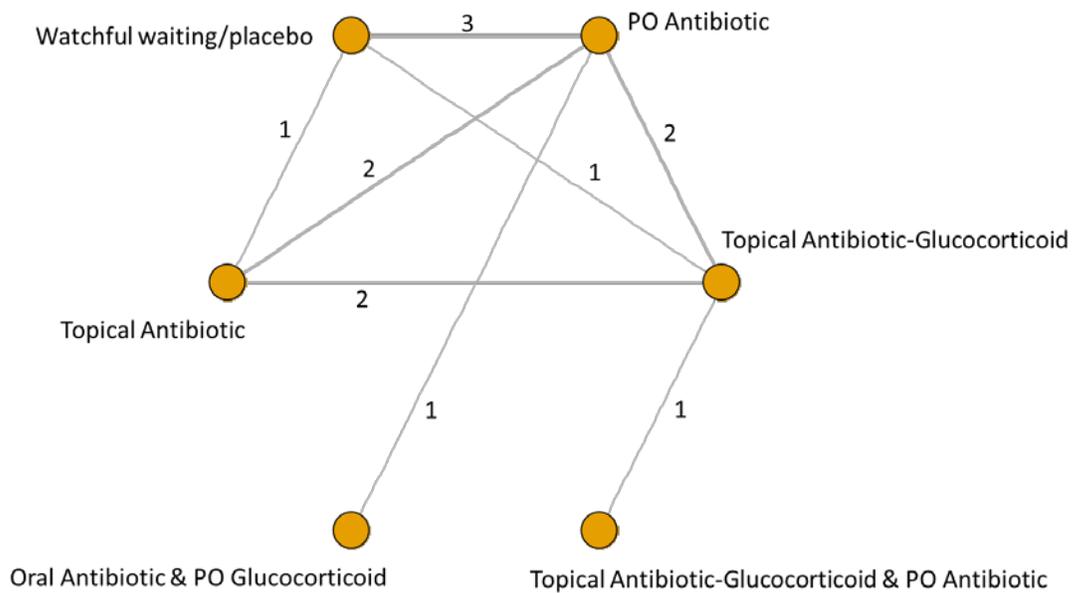
Figure I. NRCSs Only, **Children with ≥ 1 Episodes of Otorrhea**



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. 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. The network of available comparisons is shown in Figure J below.

Figure J. Network Graph of Comparators for TT Otorrhea.



Outcomes

Clinical Cure

Ten 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).

For the 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 D, treatment strategies that include topical antibiotic-glucocorticoid drops predominate over oral antibiotics and watchful waiting or placebo.

Table D. Probabilities (%) That an Intervention is Among the Three Most Effective with Respect to Clinical Resolution of Otorrhea

Intervention	Probability (%) of being among the 3 most effective interventions	Probability (%) of being among the 3 least effective interventions
Antibiotic-glucocorticoid drop	92	8
Antibiotic-glucocorticoid drop & Oral antibiotic	80	20
Antibiotic drop	64	36
Oral antibiotic	5	95
Oral antibiotic & Oral glucocorticoid	58	42
Watchful waiting or Placebo	2	98

The plots show that topical antibiotic-glucocorticoid and antibiotic-only drops are superior to watchful waiting (Figure K). When compared to oral antibiotics, topical antibiotic-glucocorticoid preparations are superior to oral antibiotics (Figure L).

Figure K. Relative Effectiveness of Interventions Compared to Watchful Waiting or Placebo Therapy

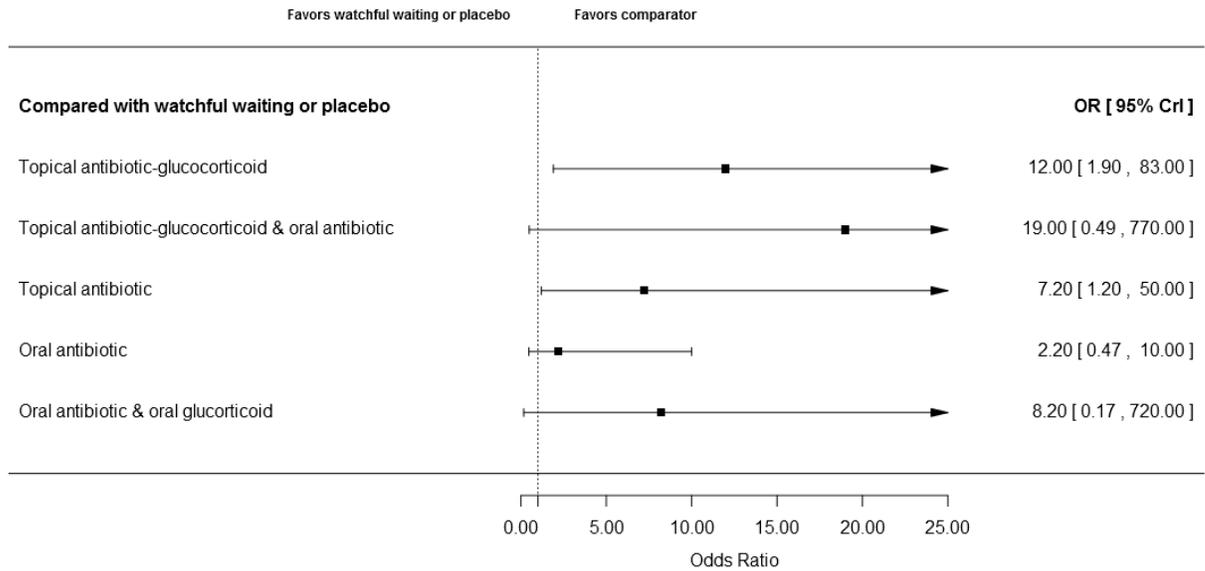
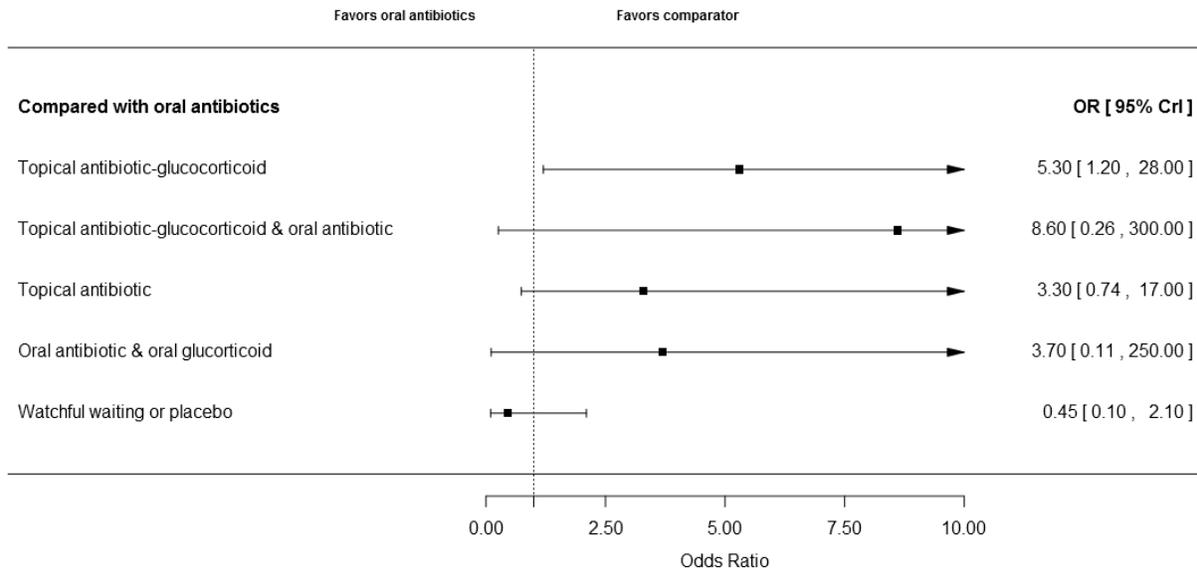


Figure L. Relative Effectiveness of Interventions Compared to Treatment with Oral Antibiotics



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. Parent reported child health-related quality of life was good throughout and showed no difference in change over time within or between arms. Confidence intervals were relatively wide.³⁷

Discussion

Overall summary and Strength of Evidence

Our systematic review of 184 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, 32 publications reported results of 22 RCTs. Given the functional importance of hearing, we chose hearing levels as our primary intermediate outcome for meta-analysis. At one to three months after TT placement, and compared to watchful waiting, mean hearing levels after TT placement with or without adenoidectomy improved by approximately 10 dB. Myringotomy with adenoidectomy yielded nonsignificant improvements in early hearing results versus watchful waiting. By 12 to 24 months, none of the interventions had different outcomes than watchful waiting. 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.

We conclude that TT placement results in improved average hearing levels during early followup of 1 to 3 months after surgery, but these improvements are not sustained at 1 to 2 year followup. 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

The very limited available evidence suggests that, compared to no TT placement, 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.³⁰ 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 cholesteotoma, 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.^{35, 36} One RCT reported a slightly higher average rate of otorrhea (after adjusting for compliance) in children who did not wear ear plugs.³⁵ A second RCT, with high risk of bias, found a statistically nonsignificant difference in the odds ratio in nonswimmers versus swimmers.³⁶ 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

Ten RCTs were included in a network meta-analysis of the comparative effectiveness of various treatments for TT otorrhea.^{37, 45-52}

The common outcome evaluated was absence of otorrhea after completion of treatment. Compared to watchful waiting or placebo, topical antibiotics and topical antibiotic-glucocorticoid preparations are clearly effective, with odds ratios of 12 and 7.2, respectively. Other therapies may be effective, but the credible intervals include the null effect. Risk of bias was rated moderate overall.

Table E. Summary of Conclusions and Associated Strength of Evidence Dispositions

Conclusion	Strength of Evidence	Comments
<i>Key Question 1- effectiveness of TT in children with chronic otitis media with effusion</i>		
Treatment with TT results in short term improvements in hearing levels , compared to Watchful waiting	Moderate	Network metaanalysis -9.1 (CrI: -14.0, -3.4) dB at 1 to 3 months
Improvements in hearing levels are not sustained at 12 to 24 months.	Moderate	Network meta-analysis 0.03 (CrI: -4.0, 3.4) dB at 12 to 24 months
Concurrent Adenoidectomy with TT may be associated with longer term improvements in hearing levels	[Insufficient]	Network meta-analysis -3.8 (CrI: -8.6, 0.62) at 12-24 months
Periods of watchful waiting do not result in consistently worse cognitive, language, behavioral or quality of life outcomes in children without comorbidities.	Low	Limited number of studies (less than 9, out of a total 68), each using different outcome definitions No quantitative synthesis done
The efficacy of TT may be modified by baseline hearing levels	[Insufficient]	
TT efficacy may vary across populations by risk factors such as age, gender, age of onset and other sociodemographic factors	[Insufficient]	
<i>Key Question 2 - Comparative effectiveness of TT in recurrent acute otitis media</i>		
Treat with TT results in fewer episodes of recurrent acute otitis media compared to Watchful waiting	Low	Limited number of studies (3), multiple different outcome definitions, Cannot assess effect modification by factors
The effect of middle ear effusion on efficacy of TT placement to reduced recurrent AOM is unclear	[Insufficient]	Limited number of RCTs (1), post-hoc subgroup analysis
Concurrent Adenoidectomy with TT does not result in fewer episodes of recurrent acute otitis media	Low	Limited number of RCTs (3)
Treatment with TT may not improve quality of life	Low	Limited number of RCTs (1) No quantitative synthesis done
<i>Key Question 4 – Effectiveness of ear plugs or avoidance of swimming</i>		
Ear plugs or avoidance of swimming may not reduce the risk of otorrhea after swimming	Low	Limited number of studies (2 RCTs,
<i>Key Question 5 – Effectiveness of topical antibiotic drops vs. systemic antibiotics or watchful waiting</i>		
Topical antibiotic-glucocorticoid drops superior to oral antibiotics in achieving clinical cure	Moderate	Network meta-analysis OR: 5.3 (CrI: 1.2, 28.0)
Topical antibiotic drops may be superior to oral antibiotics in achieving clinical cure	[Insufficient]	Network meta-analysis OR: 3.3 (CrI: 0.74, 17.0)
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, 83) [antibiotic-glucocorticoid] OR: 7.2 (CrI: 1.2, 50.0) [antibiotic only]

CrI = credible interval; DA = decision analysis; SMD = standardized mean difference; WMD = weighted mean difference.

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.

The majority of trials utilized similar inclusion criteria and subgroup analysis of higher or lower risk groups is sparse. With the exception of two older trials^{14, 16} that included children with chronic 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. In studies with complete followup, the intervention itself is subject to natural attrition due to extrusion of the TT over time, which complicates the interpretation of intention-to-treat comparisons.

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. Future trials would benefit from standardization and consistent definition of adverse events. Bacterial cultures performed in the research may assist in differentiating infections due to organisms associated with AOM from superinfections or colonization with other organisms.

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 levels suggests the possibility of a more sustained improvement in hearing levels 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 with specific conditions, such as cleft palate, Down syndrome, or other neurobehavioral disabilities.

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 with a topical antibiotic or antibiotic-glucocorticoid drop. Both are more likely to result in clinical cure than watchful waiting. Antibiotic-glucocorticoid drops are superior to watchful waiting and are more effective than oral antibiotics with respect to treatment of otorrhea.

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Introduction

Background and Objectives

Uncertainty about the effectiveness of tympanostomy tubes (TT) for children with otitis media, indications for tympanostomy in children, effectiveness of antibiotics for children with tube otorrhea, and the need for prophylactic water precaution devices prompted AHRQ 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. OME is defined as chronic OME, if effusion persists for 3 months or longer.¹ Acute otitis media and chronic OME have shared causes. Children with chronic OME are prone to recurrent AOM episodes, and after an AOM episode all children have OME for some time.² Myringotomy with TT placement is the most common ambulatory surgery performed on children in the United States, with almost 700,000 procedures performed yearly at an estimated annual cost of \$1.8 billion.³ The proceedings of the National Summit on Overuse, convened in 2012, reported that TT surgeries increased from just under 500,000 in 1996 to more than 650,000 in 2006, according to the National Center for Health Statistics. Based on a sample of continually enrolled children into a treatment pathways database and a Medicaid database, 2.5 percent of all U.S. children 2 years old and older had TT inserted in 2010.^{4,6} A 1994 study reported indications for TT placement in children: 30 percent were for chronic OME, 24 percent for recurrent AOM, and 46 percent of surgical candidates had both recurrent AOM and chronic OME.⁷

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

Because recurrent AOM and chronic OME have shared causes, and, for many patients, represent a continuum, it may be important to consider children's risk of these conditions, and risk of important outcomes under various treatments for these conditions, when researching or planning children'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, and may be preferable to algorithms that use a single threshold for duration or frequency of a diagnosis.¹⁰

Along these lines we note that certain children, including those with Down syndrome and cleft palate, have a very high risk for middle ear disease. In a retrospective review of patients with Down syndrome, the authors found that the majority of patients required two or more sets of tubes during their childhood.¹¹ Due to the effects of palatal dysfunction on Eustachian tube

function, children with cleft palate also have a high incidence of OME and associated hearing loss.¹² The American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) clinical practice guideline (CPG) identifies a subpopulation of children who may be at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors.¹ The inclination to treat OME more aggressively in these children is reflected in a study that found that approximately 1 in 6 children with autism spectrum disorder underwent TT placement.¹³

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

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

Acute otorrhea is common after TT placement.¹⁷ Postoperative otorrhea (up to 30 days after surgery) is common and reflects, in part, underlying (preoperative) middle ear glandular changes and inflammation. Some otorrhea is to be expected, since the role of the tube is to ventilate the middle ear. Episodes of otorrhea that reflect acute bacterial infection may be otherwise asymptomatic and less troublesome than AOM episodes in children with intact eardrums.¹⁸ However, the otorrhea is sometimes chronic, associated with a foul odor, fever, or pain, and it may negatively affect quality of life. Treatment is aimed at eradicating bacterial infection, using antibiotic eardrops with or without glucocorticoids (to reduce symptoms).¹⁹ A number of subgroups of acute otorrhea exist, including: 1) otorrhea in the immediate postoperative period, 2) otorrhea caused by the same pathogens as AOM, including *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, and 3) otorrhea resulting from superinfection with *Staphylococcus aureus*, including methicillin resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas* associated with biofilms.²⁰

The objectives for the systematic review are to synthesize information on the effectiveness of TT in children with chronic otitis media with effusion and recurrent acute otitis media, summarize the frequency of adverse effects and/or complications associated with TT placement, and 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

The Key Questions

With input from clinical experts during Topic Refinement, and from the Public, during a public review period, we developed the following 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?

- 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?

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? What factors (such as age, age of onset, number of recurrences, presence of persistent middle ear effusion, comorbidities, and sociodemographic risk factors, history of complications of acute otitis media, antibiotic allergy or intolerance) identify children who are most 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)

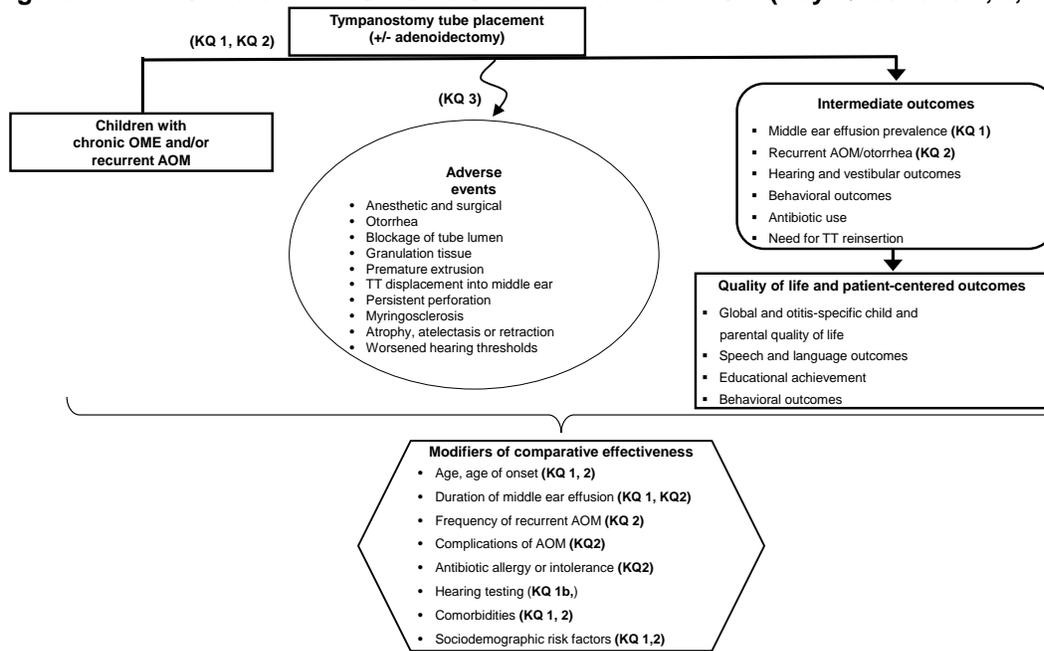


Figure 2. Need for Water Precautions in Children with TT (Key Question 4)

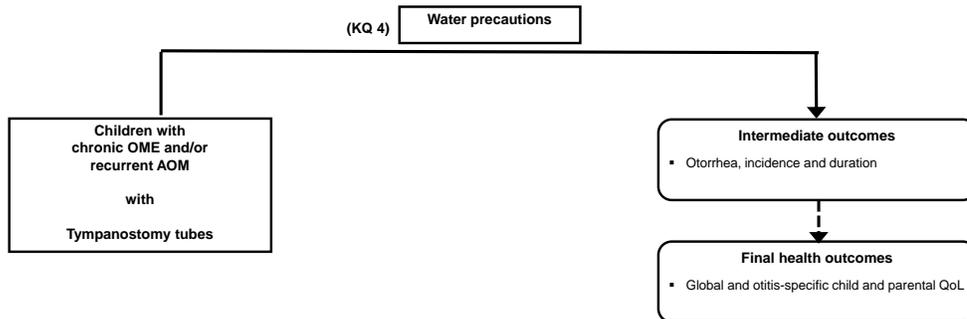
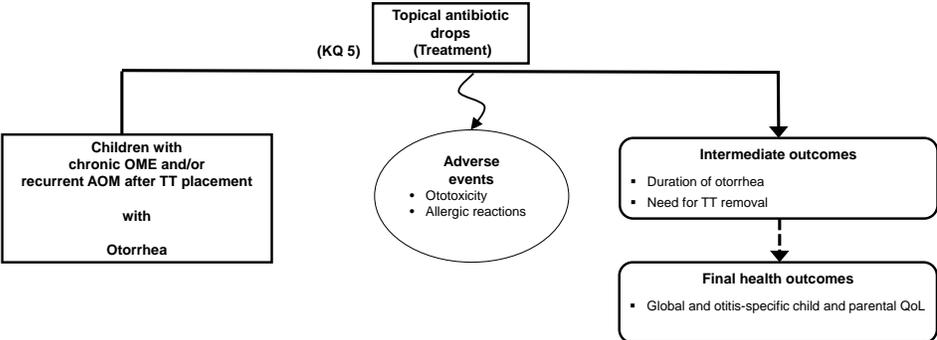


Figure 3. Treatment of Otorrhea in Children with TT (Key Question 5)



Methods

The Brown Evidence-based Practice Center (EPC) conducted the 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.²¹ The PROSPERO protocol registration number is CRD42015029623.

Eligibility Criteria

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

Populations

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

For KQ 1, we included studies of children with chronic OME. We preferred the standard definition of effusion that persists for at least 3 months,¹ but also included results based on studies' alternative definitions, if our preferred one was not reported. We excluded children with chronic suppurative otitis media.

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

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

Interventions/Exposures

For KQs 1, 2, and 3 we considered all studies that included 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 distinguish 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.

KQ 5 compares otological preparations, and includes 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 levels (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 considered 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 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).

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

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 single group studies enrolling at least 50 subjects and population based retrospective single-group studies (registry studies) with ≥ 1000 subjects.

Evidence Identification

We conducted literature searches of all studies in MEDLINE®, both the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, EMBASE®, and CINAHL® (from inception) to identify primary research studies meeting our criteria. We used the search strategies in Appendix A. The 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.

We searched Devices@FDA.gov at www.accessdata.fda.gov/scripts/cdrh/devicesatfda/ for the classification product code “ETD” (TT). This returned 109 records, all of which are deemed to be substantially equivalent to previous devices (indicating there are no new data that the FDA considered) or have original approvals that predate the electronic records and require either contacting the manufacturer for information or requesting it from the FDA.

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 also searched the Clinicaltrials.gov and FDA Web sites. All articles identified through these sources were screened for eligibility using the same criteria as was used for articles identified through literature searches. Peer and public review will provide an additional opportunity for the TEP and other experts in the field to ensure that no key publications have been missed. The search will be updated upon submission of the draft report for peer and public review.

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. 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. During double-screening, we resolved conflicts as a group. 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 will include 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 tool²⁴, which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we used relevant questions from the Newcastle Ottawa Scale.²⁵ The methodological attributes of studies and comments on study execution and outcome measurement that pertain to specific outcomes within a study were considered when determining the overall strength of evidence for conclusions related to those outcomes, as is standard practice.

Data Synthesis

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

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

Specific methods and metrics (summary measures) meta-analyzed were chosen based on available, reported study data. When available, these were summarized as odds ratios of categorical outcomes and net change of continuous outcomes (e.g., mean hearing level).

For KQ 4, we conducted random effects meta-analyses of nonrandomized comparative studies that were sufficiently similar in population, interventions, and outcomes. We used typical models that assume that study-specific latent treatment effects are normally distributed across studies²⁶, and estimated them by maximizing the restricted likelihood in a generalized linear mixed model, using the R²⁷ package *metafor*.²⁸

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

For network meta-analyses, we used a hierarchical model with a within-study level and a between-studies level that models responses at the arm level, and nests arms within studies. We did two sets of analyses, one assuming consistency of treatment effects and one examining this assumption. The models are shown in Appendix J. 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 sampler³¹, using initial values drawn randomly from the marginal distributions of the priors of respective parameters. We fit four MCMC chains. After a burn in of 5000 iterations, we monitored convergence of random effects means and variances automatically, by checking every 10000 iterations whether the Gelman Rubin diagnostic was less than 1.05 with 95% probability for all monitored parameters. After convergence was reached, an extra 10000 iterations were run. All models converged quickly, within 10000 iterations. Model fit was assessed by comparing the posterior mean of the residual deviance to the number of data points.³² The ratio of residual deviance to number of data points ranged from 0.97 to 1.06, suggesting adequate model fit.

For each analysis, we empirically assessed if the network meta-analysis consistency assumption was violated by comparing the direct and indirect evidence using a node-splitting approach. We separately parameterized the direct and indirect effects, and compared the estimates of the two.^{33,34} These analyses were not suggestive of inconsistency, but in small networks, like the ones in this report, 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 J).

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 (SOE)

We graded the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence.³⁵ We assessed the strength of evidence for each outcome. Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we will 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. The data sources, basic study characteristics, and each strength-of-evidence dimensional rating is summarized in the “Summary of Evidence Reviewed” table (Table 18) detailing our reasoning for arriving at the overall strength of evidence rating.

Assessing Applicability

We assessed the applicability within and across studies with reference to children in the populations of interest (chronic OME, recurrent AOM, and children with TT), and whether interventions and comparators are used in current practice.

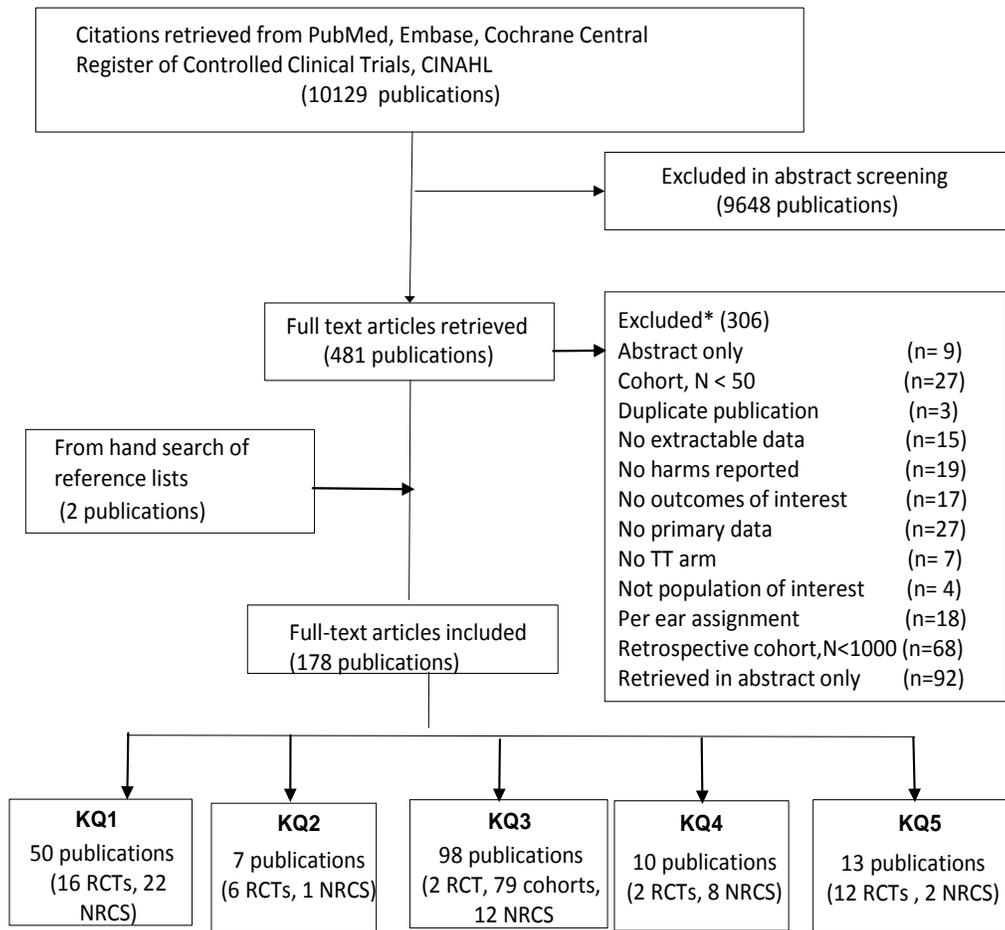
Results

The literature search yielded 10,129 citations (Figure 4). We identified 481 of these as potentially relevant full-text studies. These were retrieved for further evaluation. Overall, 306 full text articles did not meet eligibility criteria (see Appendix B for a list of rejected articles along with reasons for rejection); thus 178 articles are included in this report. Searching the FDA database, clinicaltrials.gov, the WHO International Clinical Trials Registry Platform, and conference proceedings, 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=98) related to KQ 3. These included prospective surgical case series that followed 50 or more children after TT placement or large (≥ 1000 subject) registry based retrospective cohorts. There is a relative paucity of studies available to other the main effectiveness KQs.

We entered results for quality of life outcomes into a highly summarized table, which does not provide all reported data. In these tables, for each test (or scale or subscale, etc.) we report which interventions statistically significantly favored the patient (e.g., resulted in better quality of life). If neither intervention was favored, we report no further data. If one intervention was statistically significantly better than another, we report the net (or final) difference for the test (or subscale), its estimated 95% CI and P value, and the “worst” and “best” possible score for the test.

Figure 4. Literature Flow Diagram



CINAHL = Cumulative Index to Nursing and Allied Health Literature; KQ = Key Question; NRCS = non-randomized comparative trial; RCT = randomized controlled trial; some publications reported data from the same study. 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?

Description of Eligible Studies

We identified 50 publications, representing 16 RCTs^{4, 36-49} and 22 NRCSs, that assessed the effectiveness of TT in children with chronic middle ear effusion.

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).^{4, 36-49} Sample sizes ranged between 23 and 491. Most trials enrolled a majority of boys. The proportion of male children ranged from 48 to 82 percent. Most studies enrolled children with persistent middle ear effusion in one or both ears for periods of 2 to 6 months. Two studies included at least some patients with recurrent AOM with or without persistent middle ear effusion.^{36, 44} 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).

Table 1. Summary of RCTs

Study Year [PMID] Country	Inclusion Criteria	Age (years)	Enrollment period	Comparators (N)	Hearing (measurement time in months)	MEE (followup in months)
Bernard 1991 1861917 Canada ³⁶	MEE > 3 months in at least one ear	2.5 to 7	NR	Sulfisoxazole (65) vs. TT (60)	Mean HL (0,2,4,6,12,18)	NR
Casselbrant 2009 19819563 1997-2005 U.S. ³⁷	bilateral MEE >= 3 mo, unilateral MEE >= 6 mo	2.0 to 3.9	1997- 2005	TT (32) vs. TT & adenoidectomy (32) vs Myringotomy & Adenoidectomy (34)	Study entry only	Percent time with MEE (18, 36)
Chaudhuri 2006 23120310 India ³⁸	Unclear	0 to 12	NR	Antibiotic prophylaxis (25) vs. Oral steroid (25) vs. Placebo (25) vs. TT +/- adenoidectomy (25)		Composite cure (appearance, audiometry, tympanography)
D'Eredità 2006 16406076 Italy ³⁹	OME >= 3 mo	2 to 6	1/2001- 1/2003	TT (15) vs. Myringotomy (15)	Hearing levels normal in all children in both groups at 1-year	Duration of middle ear ventilation
Gates 1987 3683478 U.S. ⁴⁰	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. ⁴¹	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. ⁴¹	MEE >= 2 mo	7 mo to 12	09/1979- 09/1984	TT (11) vs. Myringotomy (12)		
Mandel 1992 1565550 U.S. ⁴²	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 ⁴³	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) 22443163 UK ⁴⁴	bilateral OME & better ear HL >= 20 dB for 3 mo	3.25 to 6.75	4/1994- 1/1998	TT (126) vs. TT & adenoidectomy (128) vs. Watchful waiting (122)	HL (0,3,6,9,12,15,18,21,24)	
Nguyen 2004 15126745 Canada ⁴⁴	recurrent OM with > 3 episodes in 6 mo or 4 in 12 mo, persistent OME > 3 months, or HL >	1.5 to 18	01/1998- 01/2003	TT (16) vs. TT & adenoidectomy (18)	Included in composite outcome	Included in composite outcome

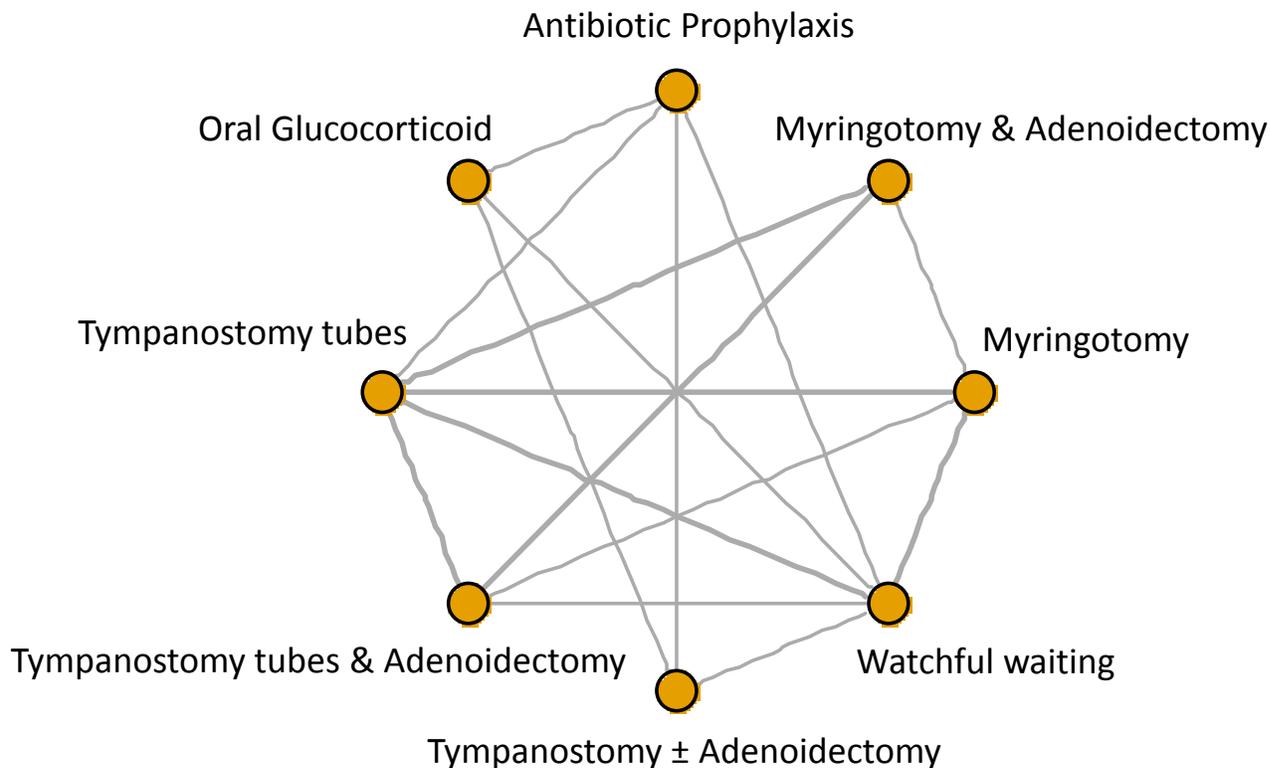
	30 dB					
Paradise 2001 11309632 U.S. ⁴⁵	bilateral MEE >= 3 mo, unilateral MEE >= 135 days)	< 3	6/1991- 12/1995	TT (216) vs. Watchful Waiting (213)	NR	Percent time with effusion (6,12,18,24)
Popova 2010 20399511 Bulgaria ⁴⁶	bilateral MEE >= 3 mo & HL > 20 dB	3 to 7	2007- 2009	TT (42) vs. Myringotomy AND Adenoidectomy (36)	HL (0,1,6,12)	Number with recurrence
Rach 1991 2070526 Netherlands ⁴⁷	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 ⁴⁸	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)
Vlastos 2011 21205368 Greece ⁴⁹	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 levels (time in months), OME: Otitis Media with effusion, MEE: Middle ear effusion, NR: not reported, mo: months

Figure 5 describes which interventions have been compared head to head in the 16 eligible RCTs for any outcome. The 16 RCTs evaluated multiple interventions (TT, TT with adenoidectomy, myringotomy with adenoidectomy, myringotomy alone, oral antibiotic prophylaxis and watchful waiting). Ten studies compared pairs of interventions, 4 compared triplets, and 2 compared quadruplets. Sixteen comparisons were observed, out of 28 that are possible among 8 treatments.

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 1999⁴³ and Gates 1987⁴⁰, trials had unclear (did not report) or had high risk of bias for lack of blinding of outcome assessors. The details of random sequence generation were unclear in the majority of studies (unclear risk of bias). Randomization sequence generation was adequately described in four RCTs.^{4, 40, 45, 49} 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 which 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.⁴⁷ All studies had at least some incomplete outcome data for some subjects. The proportion of subjects with missing data increased in studies with longer term followup. The TARGET study employed missing data imputation to limit attrition bias.⁴ Most studies report an intention to treat analysis. However, in many studies, there was a high rate of crossover to surgical interventions (TT, adenoidectomy or both).

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.

Description of Nonrandomized Comparative Studies

Of the NRCSs, seven were prospective.⁵⁰⁻⁵⁶ All the NRCSs were variably subjected to risk of bias. Only five studies^{50, 52-54, 57} included consecutive or obviously representative cases for the intervention group, of which three^{50, 52, 57} recruited the control group from community-based settings as opposed to hospital-based ones. Treatment was reliably ascertained (e.g. based on a surgical record) in only two studies,^{57, 58} despite the same methods applied across groups in most other studies. Attrition was not of great concern in most retrospective studies, while the dropout rate was higher than 20% in four prospective studies^{50, 52, 53, 56} Blinding was either not implemented or not able to be assessed in all the studies. Potential confounders were appropriately adjusted for in only five studies.^{50, 51, 53, 59, 60} Of the five studies with results of multivariable analysis, two^{50, 53} compared TT placement with control (medical treatment or no treatment), while one⁵¹ compared early TT in a university center versus delayed procedures in a hospital center. The other two studies assessed the effects of adenoideotomy.^{59, 60}

Table 2. Summary of NRCSS

Study, Year, PMID, country	Enrollment period	Comparators (N)	Special populations	Covariate Adjusted	Outcome
Retrospective studies					
Coyte 2001 11309633 Canada	1992-1997	TT (10602) & adenoidectomy vs. TT (26714)	Adenoidectomy, tonsillectomy or both	Yes	Need for further surgery
Forquer 1982 6184891 U.S.	NR	TT (177) vs. medical treatment & delayed TT (170) vs. medical treatment (153)		No	Hearing level; Middle ear effusion
Kadhim 2007 17279052 Australia	1981-2004	TT (36532) vs. TT & adenoidectomy (7534)		Yes	Need for further surgery
Kobayashi 2012 22386274 Japan	1996-1999	Early TT (82) vs. late TT (bilateral: 6 mo, unilateral: 3 mo) (100)	Cleft palate	No	Need for further surgery
Kremer 1979 456299 Israel	1966-1974	TT & myringotomy+/-adenoidectomy (151) vs. myringotomy+/-adenoidectomy (101)		No	
Marshak 1980 6778336 Israel	NR	TT (29) vs. myringotomy & adenoidectomy (29)		No	Middle ear effusion
Motta 2006 17465378 Italy	1/1/2001-12/31/2001	TT & adenoidectomy (34) vs. adenoidectomy (40)		No	Middle ear effusion
Navarro 1997 9382253 Netherlands	9/1982-8/1983	TT (29) vs. control (34)		No	Hearing level; Middle ear effusion
Reiter 2009 19929085 Germany	NR	TT & palate cleft repair (50) vs. palate cleft repair (66)	Cleft palate	No	Hearing level
Robson 1992 1431515 UK	1976-1988	TT (38) vs. control (32)	Cleft palate	No	Hearing level; Middle ear effusion
Wolter 2012 22883987 Canada	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	9/1997-5/2000	TT & palate cleft repair (31) vs. palate cleft repair (31)	Cleft palate	No	Hearing level
Youssef 2013 24265883 Egypt	3/2007-1/2009	TT & myringotomy +/- adenoidectomy (86) vs. laser myringotomy +/- adenoidectomy (86)		No	Middle ear effusion
Prospective studies					
Hubbard 1985 4039792 U.S.	1/1979	Early TT (24) vs. late TT (24)	Cleft palate	No	Hearing level
Stenstrom 2005 16330739 Canada	1985-1989	TT (38) vs. sulfisoxazole (27)		No	Long term hearing levels
Velepich 2011 21397957 Croatia	2004-2009	TT & myringotomy (59 ears) vs. adenoidectomy (102 ears)		No	Hearing levels
Yagi 1977 321716 Sudan	NR	TT & myringotomy & adenoidectomy (100) vs. adenoidectomy (100)		No	Middle ear effusion
Yousaf 2012 23855103 Pakistan	6/2008-12/2011	TT (44) vs. myringotomy (26)		No	Middle ear effusion

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

Hearing Outcomes: RCTs

Hearing levels (in dB) were measured in a total of 10 RCTs at various time points, allowing estimation of comparative effects between interventions. Six RCTs reported hearing levels at 1 to 3 months (classified as “early”).^{4, 36, 41, 42, 46} Five RCTs reported hearing levels at 12 to 24 months (classified as “late”).^{4, 36, 46, 48, 49} 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 levels.⁴¹ Patients with no significant hearing loss (≤ 20 dB bilaterally or ≤ 40 dB unilaterally) were randomized to watchful waiting, myringotomy or TT. A second group of 23 patients 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 levels 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 mo) Comparisons for Hearing Levels

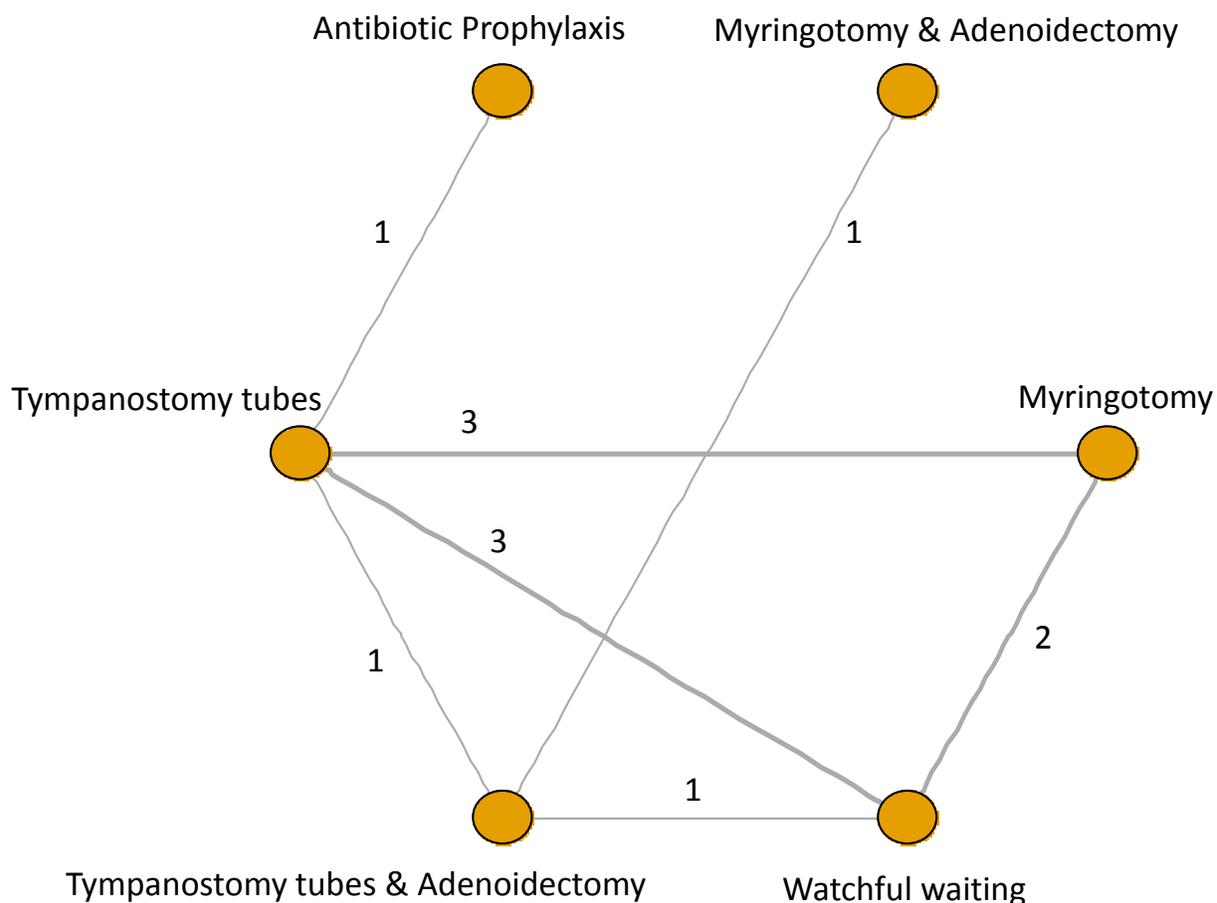


Table 3 shows combined direct and indirect data from the network meta-analysis for early hearing levels for all possible comparisons between the treatments. Bearing in mind that a difference in hearing levels of 10 dB is likely clinically important, it appears that interventions that ventilate the middle ear (TT and TT and adenoideotomy) improved hearing levels by -9.1 dB and -10.5 dB respectively, with 95% credible intervals that exclude a null effect in the 1 to 3 month time frame.

Table 3. Differences in Early Hearing Levels (in dB, 1-3 months)

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

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

Table 4 lists the probabilities that an intervention is the first, second, etc., most effective with respect to early hearing levels. 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 (%) That an Intervention Ranks as the *i*-th Most Effective with Respect to Early Hearing Levels

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 (%) that an Intervention is Among the Three Most Effective with Respect to Early Hearing Levels

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 levels 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 Levels Compared with Watchful Waiting

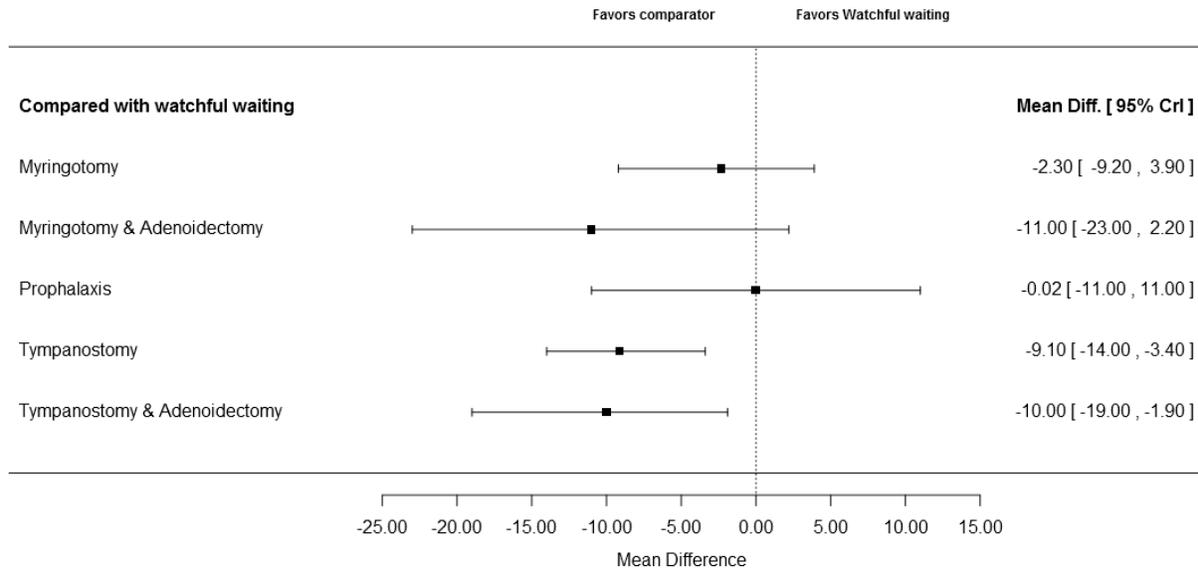


Figure 8 shows the topology of the network for late (12 to 24 month) hearing levels. Data from two head-to-head trials comparing TT with watchful waiting are shown in Figure 9.

Figure 8. Network Diagram of Late (12-24 month) Comparisons for Hearing Levels

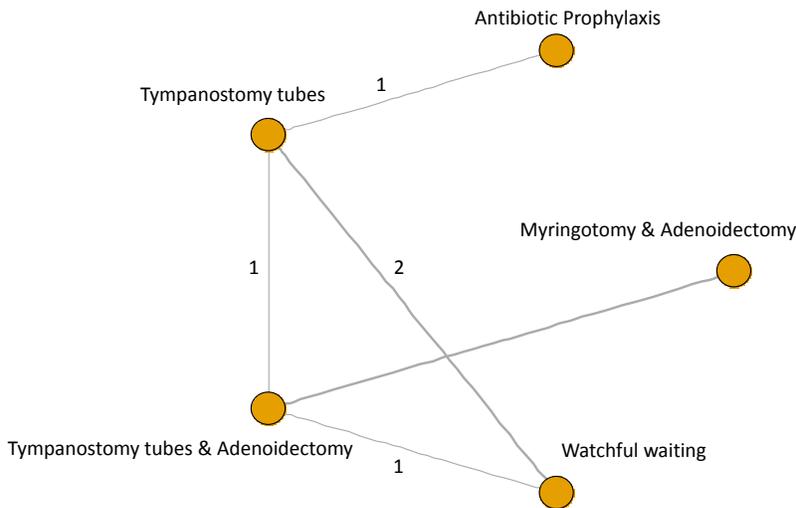


Table 6 shows combined direct and indirect data from the network meta-analysis for late hearing levels for all possible comparisons between the treatments. Bearing in mind that a difference in hearing levels of 10 dB is likely clinically important, none of the point estimates for

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 adenoideotomy (TT with adenoideotomy) may be more effective than watchful waiting.

Table 6. Differences in Late Hearing Levels (in dB, 1-3 months)

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

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

Table 7 lists the probabilities that an intervention is the first and second most effective with respect to early hearing levels. 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 least time interval, interventions that include adenoideotomy now 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 (%) that an Intervention Ranks as the *i*-th Most Effective with Respect to Late Hearing Levels

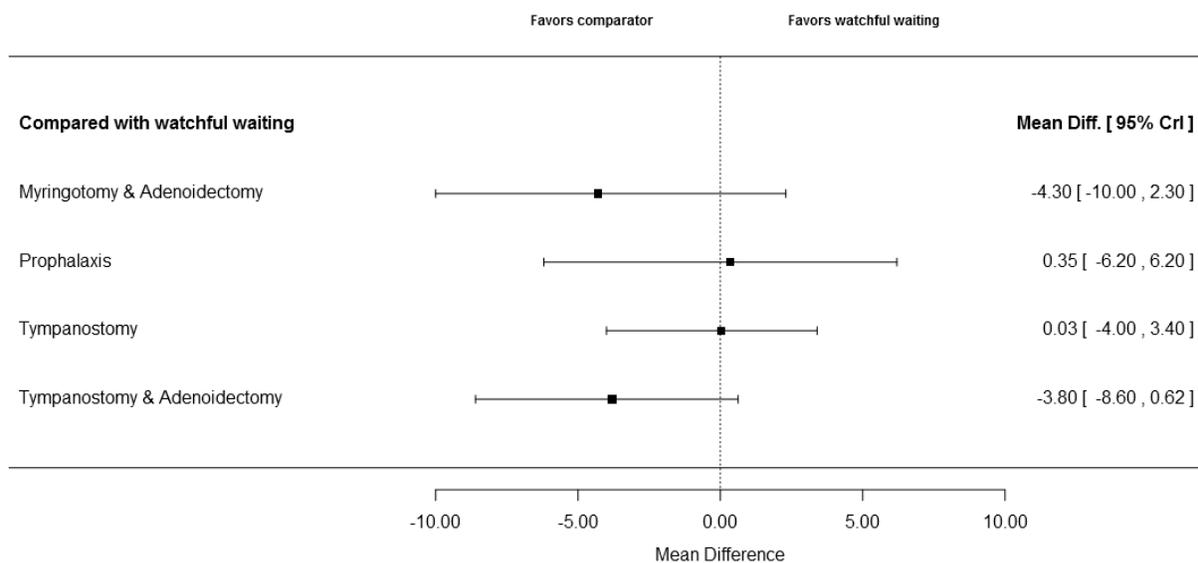
Intervention	1st	2nd	3rd	4th	5th
TT	1	4	27	48	21
TT + Adenoideotomy	33	59	5	2	1
Myringotomy + Adenoideotomy	59	29	6	3	3
Antibiotic prophylaxis	6	5	26	18	46
Watchful waiting	1	3	37	29	30

Table 8. Probabilities (%) that an Intervention is Among the Two Most Effective with Respect to Late Hearing Levels

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

As shown in Figure 9, by 12 to 24 months, the mean difference in hearing levels for TT alone, compared to watchful waiting is now centered on zero. At this time point, the interventions that include adenoideotomy (TT with adenoideotomy and myringotomy with adenoideotomy) are now most likely to be effective. The myringotomy with adenoideotomy, and TT with adenoideotomy comparisons also overlap zero, but the 95 percent credible intervals are relatively wide and are consistent with the possibility of added effectiveness of adenoideotomy.

Figure 9. Late (12 – 24 month) Decrease (Improvement) in Mean Hearing Levels Compared with Watchful Waiting



The results for the studies that reported measuring hearing levels, but did not report mean hearing levels needed for inclusion in the network meta-analysis are summarized below. The MRC Multicentre Otitis Media Study Group 2004 report outcomes for speech reception in noise. This study allocated children to receive TT with or without adenoideotomy or to medical management only and included 47 of 68 children enrolled in the TARGET trial. They reported a significant interaction between baseline performance, such that children with poor baseline performance had greater relative improvements speech-in-noise perception after surgery.⁶¹ Chaudhuri 2006 reported a comparison of hearing levels between groups of children randomized to various medical treatments, placebo or TT with or without adenoideotomy.³⁸ D'Eredità 2006 reported that hearing levels 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.³⁹ Gates 1985 reported a trial of children 4-8 years of age (54 week followup) 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 adenoideotomy, TT, and adenoideotomy 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.⁶² Paradise 2001 reports measuring hearing levels, but did not report the results for the comparison of hearing levels.⁴⁵

Hearing Outcomes: Non-Randomized Controlled Studies

Hearing levels measured as pure tone average were reported in two studies.^{50, 51} Average hearing threshold was significantly lower in TT than in non-surgical control ($P < 0.001$) and was marginally significantly lower in early TT ($P = 0.05$ for ears with better hearing and 0.06 for ears with worse hearing). Tube replacement was reported in two studies.^{59, 60} The rate of reinsertion was significantly decreased by adenoidectomy in addition to TT (RR=0.5, 95% CI: 0.5 to 0.6 in Coyte 2001; RR=0.61, 95% CI 0.52 to 0.72 in Kadhim 2007).

Six studies reported results in the populations with co-morbidities of interest, including cleft palate/lip^{51, 58, 63-65} and primary ciliary dyskinesia.⁶⁶ Three studies (two in cleft palate^{63, 64}, one in primary ciliary dyskinesia) compared TT placement with non-surgical treatment, while one study compared early versus delayed TT in different settings.⁵¹ Two studies assessed the effects of TT and cleft repairing versus cleft repairing alone.^{58, 65} Hearing levels measured as pure tone average were reported in four studies.^{51, 64-66} In patients with cleft palate/lip and primary ciliary dyskinesia, respectively, average hearing threshold was lower in TT than non-surgical control, though not statistically significant.^{64, 66} TT in addition to cleft repair improved hearing levels with unknown significance.⁶⁵ The improvement by early TT compared to delayed procedures in patients with cleft palate was marginally significant.⁵¹ The rate of normal hearing, defined as hearing threshold < 20 dB bilaterally, was significantly higher in TT than control ($P < 0.05$)⁵⁸

Duration of Effusion

Six RCTs 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

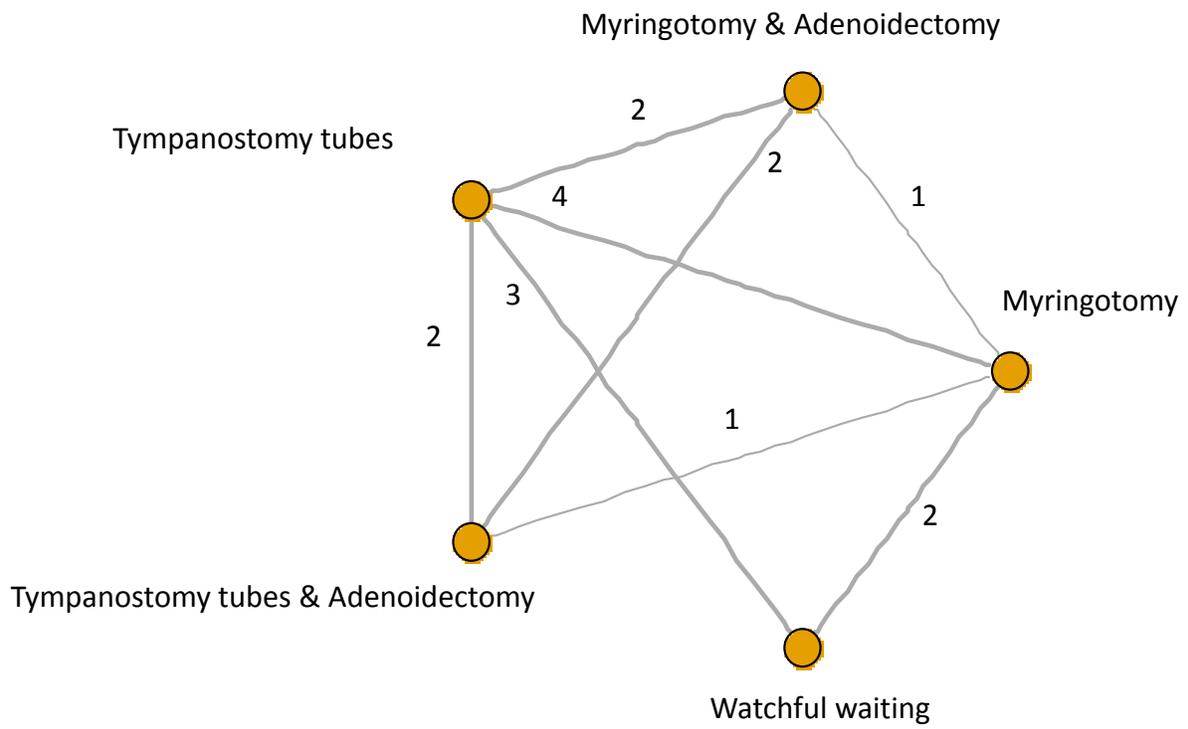
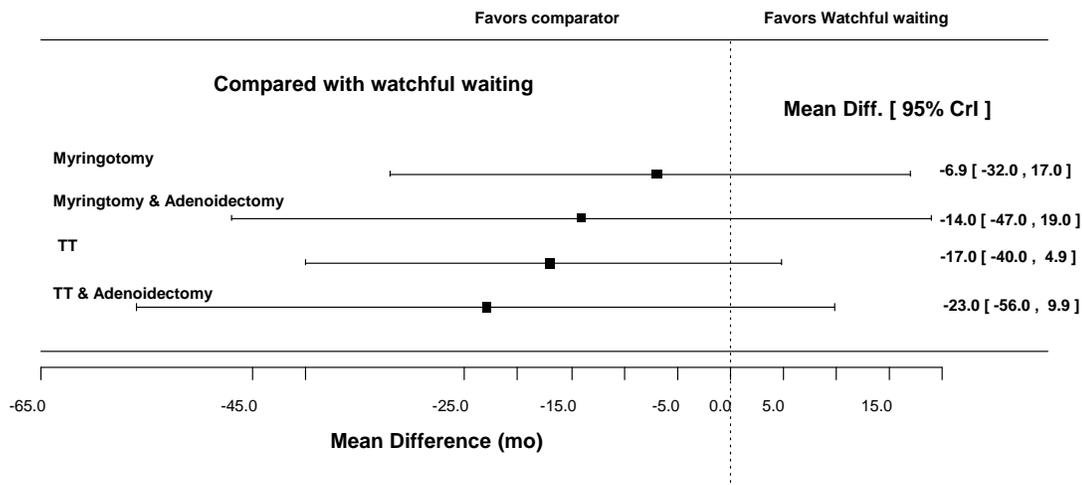


Figure 11 shows a trend toward greater effectiveness for TT with adenoideotomy than TT alone. However, credible intervals are wide and cannot exclude a null effect for all interventions.

Figure 11. Decrease (improvement) in Mean Duration of Middle Ear Effusion Compared with Watchful Waiting



As summarized in Table 9, TT and adenoideotomy 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 (%) 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 + Adenoideotomy	79	21
Myringotomy + Adenoideotomy	12	88
Antibiotic prophylaxis	41	59
Watchful waiting	6	94

Quality of Life and Patient-Centered Outcomes

Eight studies (5 RCTs, 3 NRCS, and one that combined both designs) in 12 papers reported on 119 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).^{43, 45, 47-50, 52, 67-72} The results varied in magnitude and direction, even across subscales of the same test.

Four studies reported on 40 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.⁷⁰ 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.⁵² 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.⁷²

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 timepoints, 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 was 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.^{45, 67-70} In a small study of 27 children, Schilder 1997 found a significant difference in two language measure outcomes, but not on the three others. In word forms production, the tubes group performed significantly better (mean difference 26.4, SD 0.92), as well as in the auditory discrimination measure (mean difference 0.08, SD 0.03).⁷¹

Three of the eight studies reported on 22 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)⁷⁰

Only two studies reported on quality of life outcomes: Paradise reported on measures of parental stress at various ages,^{45, 67-70} and Vlastos 2011 reported on pediatric health related quality of life.⁴⁹ 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) ⁴⁷		2 (0)		
Rovers 2000 RCT (187) ⁴⁸		2 (0)		
Hall 2009 RCT (136) ⁷²	10 (2)	6 (0)	6 (1)	
Maw 1999 RCT (127) ⁴³		4 (0)	2 (0)	
Vlastos 2011 RCT (45) ⁴⁹				1 (0)
Paradise, 2001, 2003, 2004, 2005, 2007 RCT/NRCS (402/729) ^{45, 67-70}	15 (2)	18 (4)	14 (2)	4 (0)
Peters 1994 NRCS (188) ⁵²	15 (1)	5 (0)		
Grievink 1993 NRCS (183) ⁵⁰	1 (0)	9 (0)		
Schidler 1997 NRCS (27) ⁷¹		5 (2)		

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?

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

Description of Comparative Studies

We identified 7 publications, reporting on 6 RCTs.⁷³⁻⁷⁹ A total 1049 patients were randomized, with an additional 169 patients enrolled in Mattila 2003, whose treatment assignment was determined by parental choice and therefore categorized as an NRCS.⁷⁶ Grindler 2014, reported a cross-sectional comparison of quality of life outcomes in 1208 patients.⁸

Comparators

Three RCTs⁷³⁻⁷⁵ compared TT placement with daily oral antibiotic prophylaxis. Two of these studies included a comparison with placebo,^{73,74} and Kujala 2012 compared TT placement with no treatment.⁷⁸ The effectiveness of TT alone vs TT with adenoidectomy was evaluable in three studies.⁷⁶⁻⁷⁸

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 and Mattila 2003 did not exclude patients with otitis media with effusion. Conversely, Kujala 2012 and Casselbrant 1992 required patients to be free of middle ear effusion at time of assessment for surgery.

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.⁷⁸ Comparison groups were dissimilar or the comparability was unclear in most studies.^{73,75,76} Blinding was partially implemented in only one study.⁷⁴ Randomization, group similarity and blinding could not be assessed in Hammarén-Malmi, 2005.⁷⁷

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

Outcomes

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 by 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 ($p=0.006$). They report a post-hoc subgroup comparison of children who had middle ear effusion upon entering the study 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.

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 ($P<0.001$). They report conclusions from a multivariable Poisson model concluding 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.⁷⁴

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.⁷⁸

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 ($P = 0.08$).⁷³

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 ($P = 0.001$).⁷⁴

El-Sayed found no difference in the treatment outcomes of children treated with trimethoprim/sulfamethoxazole compared to children treated with TT ($P = 0.37$).⁷⁵

These limited findings in the current era are uncertain, given increases in bacterial resistance rates.

TT Versus TT and Adenoideotomy

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 adenoideotomy compared with TT alone.⁷⁶

In the Kujala 2012 study,⁷⁸ there was no significant difference in the TT with adenoideotomy 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 by the same group, 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.⁷⁷

Quality of Life Outcomes

Although Kujala 2012, found that insertion of TT tubes, without or without adenoideotomy, significantly reduced the risk of recurrent AOM, a subsequent publication of quality of life outcomes from this trial (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.⁷⁹

A cross sectional study reported by 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.⁸

Risk Factors

No study evaluated whether age, age of onset, number of recurrences, comorbidities, history of complications of acute otitis media, antibiotic allergy or intolerance or other sociodemographic risk factors modify the effectiveness of TT placement for recurrent AOM.

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. They report that the number of infections per child during 6 month followup and the number of patients who had no further episodes of AOM was significantly better (P < 0.05) in children with OME than in those without middle ear effusion.⁷³ The other two studies specifically excluded patients with middle ear effusion at time of surgical evaluation.^{73, 74, 78}

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 data on the occurrence of 11 adverse events from 76 cohorts and from RCTs and NRCSSs 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, cholesteotoma, and long term hearing loss. The number of publications reporting each event and the median (with 25th and 75th percentiles) percent of patients and ears are summarized in Table 11. For detailed descriptions of adverse event details by study, see Appendix I. For study specific details including design, recruitment period, tube type(s) used, age, proportion with recurrent AOM, followup time, and study specific definitions, see Appendix C.

Table 11. Median Percentage of Patients and Ears with Adverse Events Associated with TT Placement

Adverse Event	No. of Publications	Patients: Median Percent [25%, 75th%]	Ears: Median Percent (25%, 75th%)
Perioperative Complications	3 ⁸⁰⁻⁸²	0.81 (intraoperative events)	1.04 (canal abrasion); 0.01 (tear of TT)
Otorrhea	47 ^{17, 39, 40, 80, 83-125}	20.6 [12, 38]	10.5 [7.5, 15.5]
Tube Blockage	20 ^{80, 82, 84, 88, 101, 108, 109, 113, 116, 117, 123-132}	7.8 [0, 13]	6.5 [2.8, 37.3]
Granulation Tissue	12 ^{45, 100, 101, 107, 113, 116, 119, 122, 126, 128, 130, 133}	1.7 [0, 3.4]	2.1 [1.5, 4.2]
Premature Extrusion	20 ^{75, 85, 88, 95, 97, 113, 117, 120, 122, 124, 128, 130, 134-141}	9.6 [4, 37.9]	5.0 [1.8, 39.4]
TT Displacement in middle ear	8 ^{40, 113, 126, 131, 133, 137, 142, 143}	0.5 [0.4, 1.2]	0.8 [0.7, 0.9]
Persistent Perforation	48 ^{39, 40, 45, 54, 85, 89, 90, 93, 96, 106, 107, 109, 112-114, 116, 118, 120-123, 125, 126, 128, 130, 131, 133, 134, 136-138, 141-157}	2.8 [1.8, 6.7]	2.4 [1.3, 4.6]
Myringosclerosis	24 ^{45, 53, 54, 88, 101, 106, 113, 116, 126, 131, 134, 136, 142, 145, 147, 148, 153, 154, 158-163}	18.9 [3.3, 55.9]	11.3 [5.3, 49.8]
Atrophy, Atelectasis or Retraction	22 ^{45, 54, 96, 106, 109, 113, 116, 121, 128, 134, 140, 143, 148, 153-156, 158, 163-166}	12.5 [6.4, 20.3]	18.2 [4.4, 40.1]
Cholesteotoma	23 ^{40, 95, 96, 101, 106, 109, 112, 116, 126, 128, 133, 137-139, 153, 155, 160, 163, 165, 167-170}	0.8 [0, 1.9]	0.7 [0, 4.98]
Hearing Loss	13 ^{53, 82, 85, 105, 117, 120, 131, 134, 146, 154, 158, 160, 171}	9 [0.6, 24.7]	14.4 [6.7, 56.1]

In general, the study specific definitions of adverse events are 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 cholesteotoma, are likely confounded by the severity of preexisting and ongoing middle ear disease. TT displacement into the middle ear space is an exception, as this event is unambiguous.

Key Question 4

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

Description of Comparative Studies

We identified nine studies, two RCTs^{172, 173} and seven NRCSs¹⁷⁴⁻¹⁸⁰ (see Table 12). Study arms comparing ear plugs versus no precautions enrolled a total of 549 patients, 172 in an RCT and 377 in NRCSs. A second group of studies included arms comparing occurrence of otorrhea in nonswimming versus no precautions group. Of these, 92 patients were enrolled in an RCT and 767 in NRCSs.

The studies 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.

We found only two RCTs. Goldstein 2005 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. Parker 1994 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), intention-to-treat analysis (15/45 assigned to nonswimming group self-selected to swim and analyzed separately), 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 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) in children who did. They reported a statistically significant difference ($P = 0.05$) in a Poisson regression model adjusting for compliance. Parker 1994 reported identical mean otorrhea rates in nonswimmers and swimmers.

All studies reported the number of children with more than one episode of otorrhea in each arm. For this outcome, 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).

All studies reported the number of patients in each arm who experienced at least one episode of otorrhea. Details are shown in Table 14. Goldstein 2005 also reported this information for a subgroup of children with 125 or more instances of water exposure.

No studies assessed quality of life outcome measures.

Table 12. Number of Children with ≥ 1 Episodes of Otorrhea, Comparative Studies of Water Precautions Versus no Precautions

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. (RCT) ¹⁷²	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 with \geq 125 instances of water exposure	29/39 (74.3)	2.69 (0.95 – 7.64)
		No precautions	children with \geq 125 instances of water exposure	14/27 (51.8)	[reference]
Parker 1994 8024107 12/1989-2/1991 U.S. (RCT) ¹⁷³	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]
Becker 1987 3586818 4/1985-9/1985 U.S. (NRCS) ¹⁷⁴	≥ 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 (NRCS) ¹⁷⁵	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 (NRCS) ¹⁷⁶	6 months	Nonswimming	All Participants	14/41 (34.1)	2.07 (0.78 – 5.50)
		No precautions	All Participants	9/45 (20.0)	[reference]
Francois1992 1485779 [No dates] France (NRCS) ¹⁷⁷	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 (NRCS) ¹⁷⁸	≥ 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. (NRCS) ‡ ¹⁷⁹	1.5 years	Nonswimming	All Participants	7/116 (6.0)	0.34 (0.14 – 0.82)
		Ear plugs	All Participants	12/44 (27.3)	1.92 (0.88 – 4.42)
		Ear drops	All Participants	23/101 (22.8)	1.55 (0.81 – 2.98)
		No precautions	All Participants	22/138 (15.9)	[reference]
Smelt 1984 653821 [No dates] UK (NRCS) ¹⁸⁰	≥ 2 months	Nonswimming	All Participants	6/40 (15.0)	2.35 (0.55 – 10.12)
		No precautions	All Participants	3/43 (7.0)	[reference]

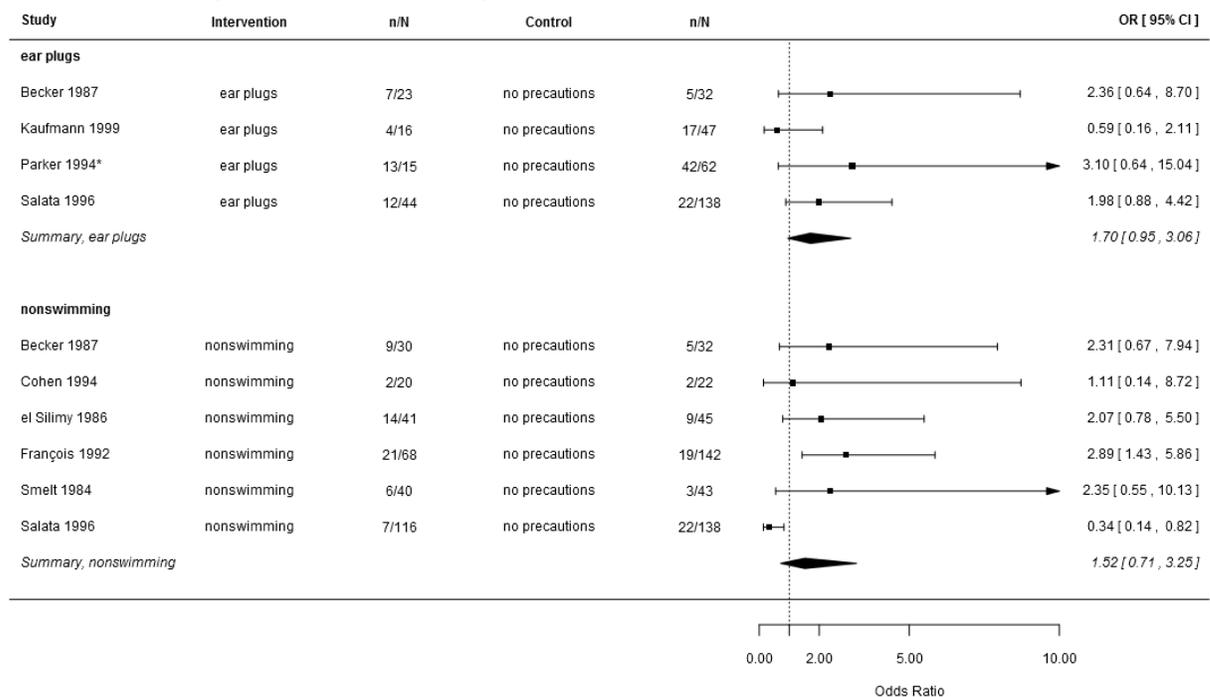
95% Confidence intervals that do not overlap one (no difference) are shown in bold font; †Randomized to the nonswimming group, but self-selected to swim using ear precautions (e.g., ear plugs, wax, cotton with petroleum jelly); ‡ Otorrhea related to bathing and swimming combined; §No restrictions on swimming. Advised not to dive or swim deeply underwater.

The forest plot shown in Figure 12 summarizes these results. Random effects meta-analysis was used to pool the individual odds-ratios 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 1.7 (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 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 trend in the NRCSs which favors 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).

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 appear to reduce the risk of swimming-related otorrhea.

Figure 12. NRCSs Only, Children with ≥ 1 Episodes of Otorrhea



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 that the ascertainment of outcomes is more complete in RCTs than in NRCSs.

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?

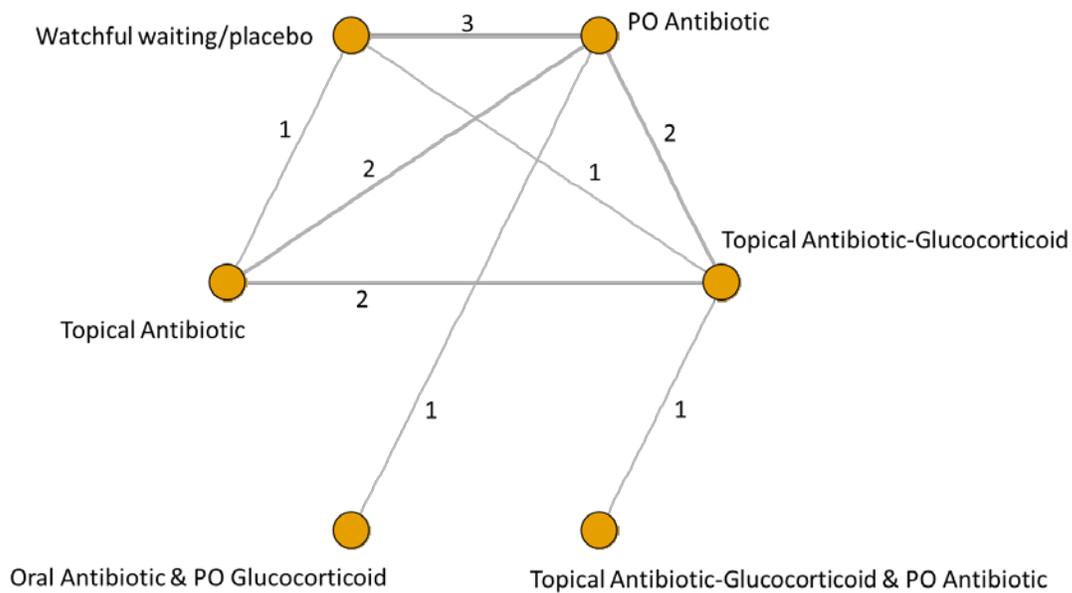
We identified 12 papers^{19, 127, 181-190}, representing 11 studies (10 RCTs and 1 NRCS), with a total of 1811 patients analyzed (1405 in RCTs and 406 in the NRCS) that assessed the effectiveness of various interventions to treat TT otorrhea. These studies, with arm details, are listed in Table 13. Risk of confounding bias was low, given that studies' for allocation sequence was generated with modern methods and was concealed. However, eight of 10 studies had high risk of bias due to open label design, which precluded blinding of personnel and care providers.

Table 13. Effectiveness of Various Interventions to Treat TT Otorrhea

Study Year, PMID Enrollment Period, Country	Intervention Details	Responders	N
van Dongen 2014, 24552319 25896832 6/2009-5/2012, Netherlands ^{19, 181}	hydrocortisone–bacitracin–colistin eardrops	72	76
	oral amoxicillin–clavulanate	43	77
	initial observation	34	75
Goldblatt 1998, 10190709 [no dates], U.S. ¹⁸²	ofloxacin eardrops	107	140
	oral amoxicillin–clavulanate	101	146
Heslop 2010, 20979100 5/2003-5/2007, Chile ¹⁸³	ciprofloxacin ear drops	17	22
	oral amoxicillin	6	20
	saline rinse	12	26
Ruohola 1999, 10190921 03/1996-05/1997, Denmark ¹⁸⁴	oral amoxicillin & oral prednisolone	22	23
	oral amoxicillin	24	27
Ruohola 2003, 12728089 09/1998-06/1999, Finland ¹⁸⁵	oral amoxicillin–clavulanate	28	34
	oral placebo	13	32
Dohar 1999, 10326811 [no dates], U.S. ¹⁸⁶	ofloxacin eardrops	119	141
	unclear - historical practice	140	218
	unclear - current practice	33	47
Dohar 2006, 16880248 5/2003-5/2004, U.S. & Finland ¹²⁷	ciprofloxacin/dexamethasone ear drops	33	39
	oral amoxicillin–clavulanate	24	41
Granath 2008, 18565598 2/1998-12/2002, Sweden ¹⁸⁷	hydrocortisone + oxytetracycline + polymyxine	12	15
	hydrocortisone + oxytetracycline + polymyxine ear drops & oral amoxicillin +/- clavulanate	19	22
Roland 2003, 14660913 3/2000-2/2001, U.S. ¹⁸⁸	ciprofloxacin/dexamethasone ear drops	72	87
	ciprofloxacin ear drops	72	80
Roland 2004, 14702493 [no dates], U.S. ¹⁸⁹	ciprofloxacin/dexamethasone ear drops	174	207
	ofloxacin eardrops	153	216
Strachan 2000, 10865480 [no dates], UK ¹⁹⁰	neomycin/polymyxin B/hydrocortisone (drops)	24	29
	neomycin/dexamethasone (spray)	19	29

The studies reported multiple comparisons, summarized in Figure 13, including oral antibiotics (amoxicillin and amoxicillin/clavulanate), various antibiotic drops and various antibiotic-glucocorticoid drops, oral corticosteroids, and combinations. Several studies had a watchful waiting or placebo arm.

Figure 13. Network of Treatment Comparisons



Outcomes

Clinical Cure

Ten 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 10 studies as the test of cure (range 7 to 20 days after initiation of treatment).^{127, 181-185, 187-189}

Two studies were excluded from our meta-analysis. Dohar 1999 reported clinical cure in 84.6 percent of 143 patients treated with topical ofloxacin in a prospective single arm trial, 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).¹⁸⁶ However, the specific treatments used in the historical practice group and concurrent practice group were not reported. The second excluded study, Strachan 2000, compared an antibiotic-glucocorticoid topical drop containing neomycin sulfate, polymyxin B sulfate and hydrocortisone with a topical spray formulation containing neomycin sulfate and dexamethasone.¹⁹⁰

The relative effects of various are shown in Table 14. Treatment strategies that include topical antibiotic-glucocorticoid drops predominate over oral antibiotics and watchful waiting or placebo. Table 15 lists the probabilities that a particular intervention is ranks first to sixth most effective. Table 16 aggregates these probabilities, and summarizes the probability that a given intervention in among the three most effective, and conversely the three least effective. Treatment strategies that include topical antibiotic-glucocorticoid drops predominate over oral antibiotics and watchful waiting or placebo.

Table 14. Network Meta-analysis of Interventions for Otorrhea

Antibiotic-glucocorticoid drop	0.4 (-2.7, 3.6)	-0.5 (-2.0, 1.1)	-1.7 (-3.3,-0.1)	-0.3 (-4.2, 4.1)	-2.4 (-4.4, -0.6)
-0.4 (-3.6, 2.7)	Antibiotic-glucocorticoid drop with oral antibiotic	-0.9 (-4.4, 2.6)	-2.1 (-5.7, 1.4)	-0.8 (-5.8, 4.7)	-2.9 (-6.6, 0.7)
0.5 (-1.1, 2.0)	0.9 (-2.6, 4.4)	Antibiotic drop	-1.2 (-2.8, 0.3)	0.1 (-3.7, 4.6)	-2.0 (-3.9, -0.2)
1.7 (0.1, 3.3)	2.1 (-1.4, 5.7)	1.2 (-0.3, 2.8)	Oral antibiotic	1.3 (-2.2, 5.6)	-0.8 (-2.3, 0.8)
0.3 (-4.1, 4.2)	0.8 (-4.7, 5.8)	-0.1 (-4.6, 3.7)	-1.3 (-5.6, 2.2)	Oral antibiotic with oral glucocorticoid	-2.1 (-6.6, 1.7)
2.4 (0.6, 4.3)	2.9 (-0.7, 6.6)	2.0 (0.2, 3.9)	0.8 (-0.8, 2.3)	2.1 (-1.7, 6.6)	Watchful waiting or placebo

Differences in Log Odds Ratios with 95% Credible Intervals for clinical cure of otorrhea among the 6 treatments category 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. Negative numbers imply better outcomes for the first.

Table 15. Probabilities (%) that an Intervention Ranks as the *i*-th Most Effective with Respect to Clinical Resolution of Otorrhea

Intervention	1st	2nd	3rd	4th	5th	6th
Antibiotic-glucocorticoid drop	17	45	30	7	1	0
Antibiotic-glucocorticoid drop with oral antibiotic	47	20	13	11	5	4
Antibiotic drop	6	19	39	32	3	1
Oral antibiotic	0	1	4	25	62	8
Oral antibiotic with oral glucocorticoid	29	16	13	20	11	11
Watchful waiting or placebo	0	0	1	5	18	75

Table 16. Probabilities (%) that an Intervention is Among the Three Most Effective with Respect to Clinical Resolution of Otorrhea

Intervention	Probability (%) of being among the 3 most effective interventions	Probability (%) of being among the 3 least effective interventions
Antibiotic-glucocorticoid drop	92	8
Antibiotic-glucocorticoid drop with oral antibiotic	80	20
Antibiotic drop	64	36
Oral antibiotic	5	95
Oral antibiotic with oral glucocorticoid	58	42
Watchful waiting or placebo	2	98

As illustrated in Figure 14, both topical antibiotic-glucocorticoid and antibiotic drops are superior to watchful waiting. When compared to oral antibiotics, topical antibiotic-glucocorticoid preparations are superior to oral antibiotics (Figure 15).

Figure 14. Relative Effectiveness of Interventions Compared to Watchful Waiting or Placebo Therapy

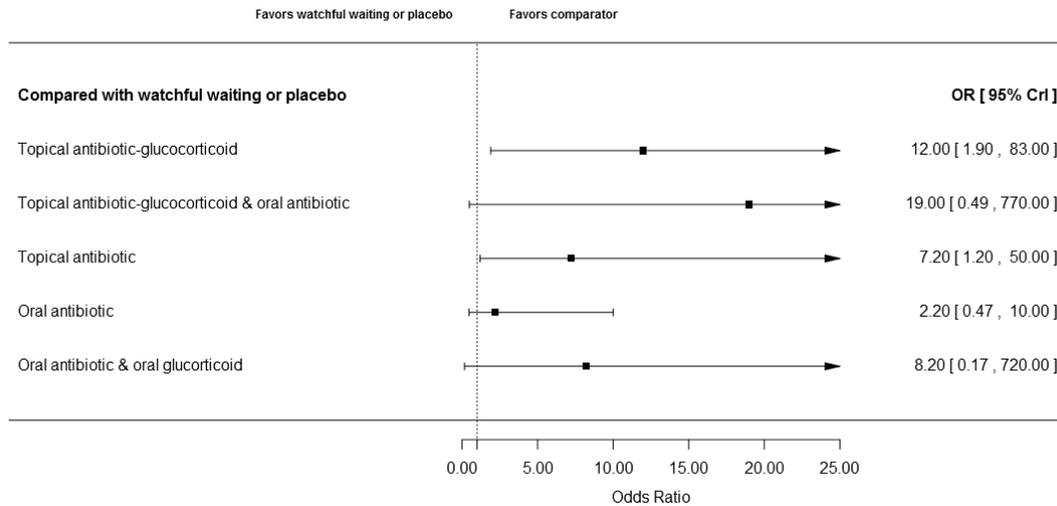
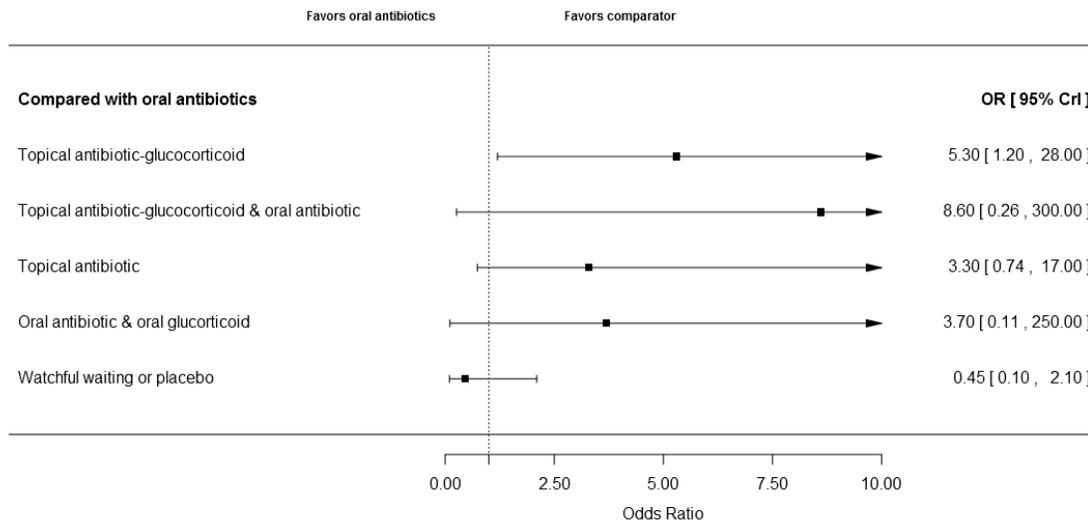


Figure 15. Relative Effectiveness of Various Interventions Compared to Treatment with Oral Antibiotics



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. Parent-reported child health related quality of life was good throughout and showed no difference in change over time within or between arms. Confidence intervals were relatively wide, and encompassed zero.¹⁸¹ 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 Donden 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	Quality of life (CHO-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

Discussion

Overall summary and Strength of Evidence

Our systematic review of 184 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. Given the functional importance of hearing, we chose hearing levels as our primary intermediate outcome for meta-analysis.

Hearing levels were obtained in 16 RCTs, and in 10 trials they were reported by arm at various time points. At early followup times (defined as 1 to 3 months after TT placement), mean hearing levels after TT placement improved (decreased) by an average of 9.1 dB (95% CrI -14 to -3.4), compared to watchful waiting. A similar improvement was seen for children treated with TT and adenoidectomy. On average, these children improved by 10 dB (95% CrI -19 to -1.9). No significant change in hearing levels was noted after treatment with myringotomy alone or with oral antibiotic prophylaxis. A trend was noted for myringotomy with adenoidectomy, but credible intervals are wide and include the null effect. By 12 to 24 months, none of the interventions demonstrated an average treatment effect. The point estimates for the groups treated with adenoidectomy and myringotomy, with or without TT are consistent with small improvements, but the credible intervals include the null effect. Data were very sparse with respect to which factors might predict those children more likely to benefit from TT.

Quality of life and other patient-centered outcomes (cognitive, language, and behavioral) were reported in eight studies (five RCTs, three NRCS, 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 levels 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.⁷⁹

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.⁷³ The other two studies specifically excluded patients with middle ear effusion.^{74, 78} Three RCTs consistently found no difference in recurrent episodes of AOM when comparing TT versus TT and adenoidectomy.

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 cholesteotoma, are likely confounded by the severity of preexisting and ongoing middle ear disease. TT displacement into the middle ear space is unambiguous.

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 higher average rate of otorrhea

(after adjusting for compliance) in children who did not wear ear plugs. The unadjusted odds ratio of having more than one episode 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

Nine RCTs were included in a network meta-analysis of the comparative effectiveness of various treatments for TT otorrhea. The common outcome evaluated was absence of otorrhea after completion of treatment. Compared to watchful waiting or placebo, topical antibiotics and topical antibiotic-glucocorticoid preparations have odds ratios of 12 and 7.2, respectively with credible intervals that exclude the null effect i.e., exclude 1. Other therapies may be effective, but the credible intervals include the null effect. When compared to treatment with an oral antibiotic, the topical antibiotic-glucocorticoid has demonstrated higher effectiveness, odds ratio 5.3 (95% CrI: 1.2 to 28). For other therapies, the credible intervals are wide and include the null effect.

An overall summary of main conclusions with an assessment of the strength of evidence is summarized in Table 18. Appendix H includes detailed information on strength of evidence assessments.

Table 18. Summary of Conclusions and Associated Strength of Evidence Dispositions

Conclusion	Strength of Evidence	Comments
<i>Key Question 1 - effectiveness of TT in children with chronic otitis media with effusion</i>		
Treatment with TT results in short term improvements in hearing levels , compared to Watchful waiting	Moderate	Network meta-analysis -9.1 (CrI: -14.0, -3.4) dB at 1 to 3 months
Improvements in hearing levels are not sustained at 12 to 24 months.	Moderate	Network meta-analysis 0.03 (CrI: -4.0, 3.4)
Concurrent Adenoidectomy with TT may be associated with longer term improvements in hearing levels	[Insufficient]	Network meta-analysis -3.8 (CrI: -8.6, 0.62) at 12-24 months
Periods of watchful waiting do not result in consistently worse cognitive, language, behavioral or quality of life outcomes in children without comorbidities.	Low	Limited number of studies (less than 9, out of a total 68), each using different outcome definitions No quantitative synthesis done
The efficacy of TT may be modified by baseline hearing levels	[Insufficient]	
TT efficacy may vary across populations by risk factors such as age, gender, age of onset and other sociodemographic factors	[Insufficient]	
<i>Key Question 2 - Comparative effectiveness of TT in recurrent acute otitis media</i>		
Treatment with TT results in fewer episodes of recurrent acute otitis media compared to Watchful waiting	Low	Limited number of studies (3), multiple different outcome definitions, Cannot assess effect modification by factors
The effect of middle ear effusion on efficacy of TT placement to reduced recurrent AOM is unclear	[Insufficient]	Limited number of RCTs (1), post-hoc subgroup analysis
Concurrent Adenoidectomy with TT does not result in fewer episodes of recurrent acute otitis media	Low	Limited number of RCTs (3)
Treatment with TT may not improve quality of life	Low	Limited number of RCTs (1) No quantitative synthesis done

<i>Key Question 4 – Effectiveness of ear plugs or avoidance of swimming</i>		
Ear plugs or avoidance of swimming may not reduce the risk of otorrhea after swimming	Low	Limited number of studies (2 RCTs,
<i>Key Question 5 – Effectiveness of topical antibiotic drops vs. systemic antibiotics or watchful waiting</i>		
Topical antibiotic-glucocorticoid drops superior to oral antibiotics in achieving clinical cure	Moderate	Network meta-analysis OR: 5.3 (CrI: 1.2, 28.0)
Topical antibiotic drops superior to oral antibiotics in achieving clinical cure	[Insufficient]	Network meta-analysis OR: 3.3 (CrI: 0.74, 17.0)
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, 83) [antibiotic-glucocorticoid] OR: 7.2 (CrI: 1.2, 50.0) [antibiotic only]

CrI = credible interval; DA = decision analysis; SMD = standardized mean difference; WMD = weighted mean difference.

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.

With the exception of two trials^{36, 44} 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. With the exception of a few NRCS, 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. In studies with complete followup, the intervention itself is subject to natural attrition because of extrusion of the TT over time, which complicates intention to treat comparisons.

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.

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 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, that is 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. Future trials would benefit from standardization and consistent definition of adverse events. Bacterial cultures performed in the research may assist in differentiating infections due to organisms associated with AOM from superinfections or colonization with other organisms.

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 levels suggests the possibility of a more sustained improvement in hearing levels 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 with conditions that include cleft palate, Down syndrome, or other neurobehavioral disabilities.

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 clearly supports topical treatment of TT otorrhea with a topical antibiotic or antibiotic-glucocorticoid drop. Both are more likely to result in clinical cure than watchful waiting. Antibiotic-glucocorticoid drops are superior to watchful waiting and are more effective than oral antibiotics with respect to treatment of otorrhea.

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