Washington State Health Care Authority

Health Technology Assessment

Tympanostomy Tubes in Children

Final Evidence Report: Appendices

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Tympanostomy Tubes

Provided by:

Spectrum Research, Inc.

Final Report
APPENDICES

October 16, 2015

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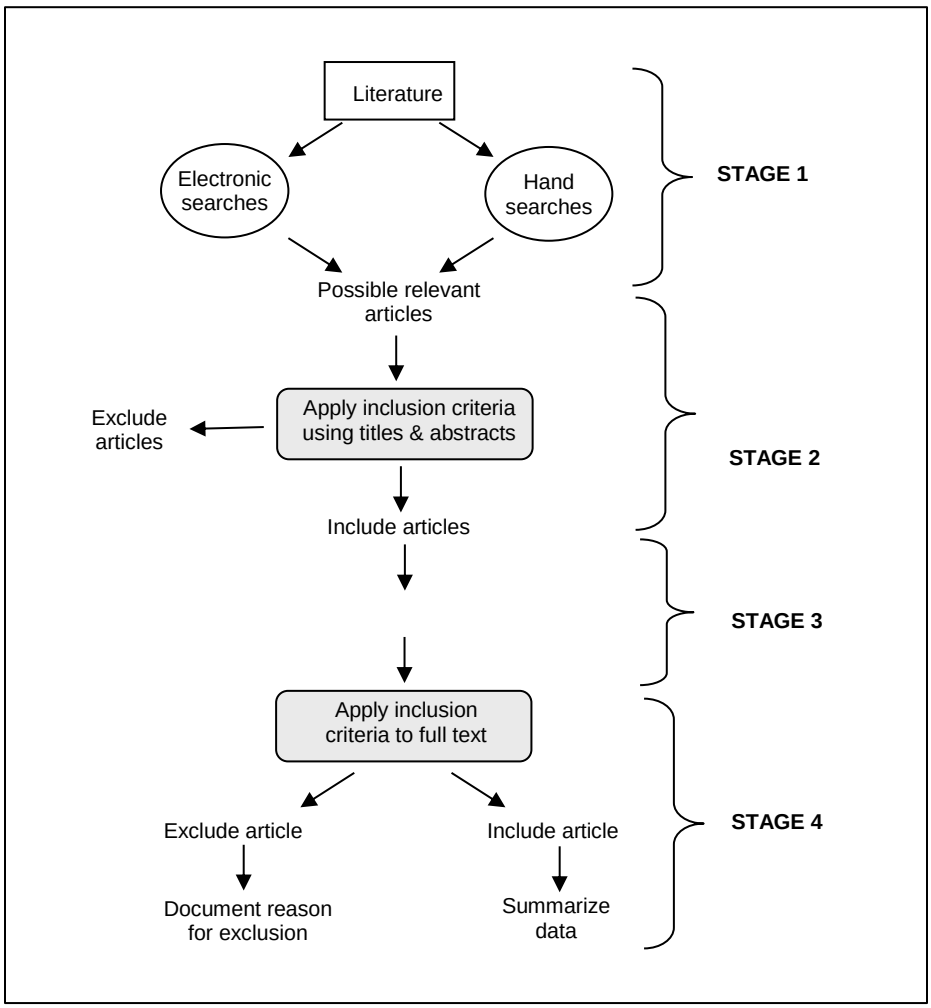
Tables

Abbreviations

Ad: adenoidectomy
Ad-Tons: adenotonsillectomy
AOM: acute otitis media
CI: confidence interval
CoE: class of evidence
dB: decibels
FDA: US Food and Drug Administration
f/u: follow-up
HTA: health technology assessment
HTE: heterogeneity of treatment effect
Hz: hertz
kHz: kilohertz
MD: mean difference
mos.: months
N: number of patients
NHS: National Health Services
NIH: National Institutes of Health
NA: not applicable
NC: not calculable
NR: not reported
NS: not statistically significant ($p \geq 0.05$)
OM: otitis media
OME: otitis media with effusion
RD: risk difference
RR: relative risk
SD: standard deviation
SoE: strength of evidence
SR: systematic review
Tons: tonsillectomy
TT: tympanostomy tubes
vs.: versus
WW: watchful waiting
yrs.: years

Appendix A. Algorithm for Article Selection



Appendix B. Search Strategies

Below is the search strategy for PubMed. Parallel strategies were used to search other electronic databases listed below. Keyword searches were conducted in the other listed resources.

Search strategy (PubMed)
Search date: 02/03/2015

Filters: Abstract available, English

	Search Code	Number of Articles
1	Tympanostomy OR "Middle Ear Ventilation"[MeSH] OR "ventilation tube" OR "ventilation tubes" OR "grommet" OR "grommets" OR "ear tube" OR "ear tubes"	2601
2	#1 AND (children OR child OR infant OR infants OR preschool OR adolescent OR adolescents OR infant[MeSH] OR child[MeSH] OR "child, preschool"[MeSH] OR adolescent[MeSH] OR pediatric OR pediatrics)	1865
3	#2 AND (otitis media OR "Otitis Media"[MeSH] OR OME OR AOM)	1471
4	#3 NOT ("Case Reports"[Publication Type] OR Letter[Publication Type] OR Comment[Publication Type])	1396
5	#4 NOT (Mastoid*[TI] OR "hearing aids"[TI] OR vaccin*[TI] OR tympanoplasty[TIAB] OR screening[TI] OR polymorphism*[TIAB] OR externa[TI] OR rat[TIAB] OR bacteri*[TI] OR receptor*[TI])	1233
	Additional references identified from hand searching	71
	Total	**1304**

Parallel strategies were used to search the Cochrane Library and others listed below. Keyword searches were conducted in the other listed resources.

Electronic Database Searches

The following databases have been searched for relevant information:

Agency for Healthcare Research and Quality (AHRQ)
Cumulative Index to Nursing and Allied Health (CINAHL)
Cochrane Database of Systematic Reviews
Cochrane Registry of Clinical Trials (CENTRAL)
Cochrane Review Methodology Database
Database of Reviews of Effectiveness (Cochrane Library)
EMBASE
PubMed
Informational Network of Agencies for Health Technology Assessment (INAHTA)
NHS Economic Evaluation Database
HSTAT (Health Services/Technology Assessment Text)
EconLIT

Additional Economics, Clinical Guideline and Gray Literature Databases

AHRQ - Healthcare Cost and Utilization Project
Canadian Agency for Drugs and Technologies in Health
Centers for Medicare and Medicaid Services (CMS)
Food and Drug Administration (FDA)
Google
Institute for Clinical Systems Improvement (ICSI)
National Guideline Clearinghouse

Appendix C. Excluded Articles

Note. As shown in Figure 1 of the Evidence Report, 64 studies were completely excluded from the report.

Articles excluded as primary studies after full text review, with reason for exclusion.

	Citation	Reason for exclusion after full-text review
	Studies Considered and Excluded	
1.	Al Anazy, F. H. (2006). "Iatrogenic cholesteatoma in children with OME in a training program." Int J Pediatr Otorhinolaryngol **70**(10): 1683-1686.	Case series; % follow-up is <80% for most time points and timing of complications was not reported (3 month follow-up is ~94% and decreases to ~64% at 6 months, ~37% at 1-2 years and ~21% at 3 years)
2.	Alexander, N. S., et al. (2011). "MRSA and non-MRSA otorrhea in children: a comparative study of clinical course." Arch Otolaryngol Head Neck Surg 137(12): 1223-1227.	Case series, number of patients not reported
3.	Augustsson, I. and I. Engstrand (2006). "Hearing loss as a sequel of secretory and acute otitis media as reflected by audiometric screening of Swedish conscripts." Int J Pediatr Otorhinolaryngol 70(4): 703-710.	Wrong outcomes, report data at baseline only
4.	Balkany, T. J., et al. (1986). "Ventilation tube surgery and middle ear irrigation." Laryngoscope 96(5): 529-532.	Is a study on irrigation, not tubes
5.	Baranano, C. F., et al. (2010). "The management of myringotomy tubes in pediatric cochlear implant recipients." Arch Otolaryngol Head Neck Surg 136(6): 557-560.	Wrong comparator (tubes placed before cochlear implant vs. tubes placed along with cochlear implant)
6.	Bidarian-Moniri, A., et al. (2013). "A new device for treatment of persistent otitis media with effusion." Int J Pediatr Otorhinolaryngol 77(12): 2063-2070.	Wrong intervention (tube insertion not performed)
7.	Birck, H. G. and J. J. Mravec (1976). "Myringostomy for middle ear effusions. Results of a two-year study." Ann Otol Rhinol Laryngol **85**(2 Suppl 25 Pt 2): 263-267.	Case series, % follow-up not reported
8.	Bozkurt, M. K. and M. Calguner (2004). "The efficacy of CO2 laser myringotomy in serous otitis media." Kulak Burun Bogaz Ihtis Derg **12**(3-4): 55-59.	Retrospective cohort study with N<100
9.	Brooks, D. N. and T. S. Dogra (1980). "Long term results of treatment of middle ear effusion." J Laryngol Otol **94**(10): 1107-1115.	Retrospective cohort study with N<100
10.	Carr, M. M., et al. (2001). "Incidence of reflux in young children undergoing adenoidectomy." Laryngoscope 111(12): 2170-2172.	Wrong population (current OME was not the surgical indication)
11.	Cassano, M. and P. Cassano (2010). "Retraction pockets of pars tensa in pediatric patients: clinical evolution and treatment." Int J Pediatr Otorhinolaryngol 74(2): 178-182.	Wrong population (only 12/37 patients had OME)

	Citation	Reason for exclusion after full-text review
12.	Costa, O. A. and R. O. Balieiro (1986). "Secretory otitis media in Brazilian children." Scand Audiol Suppl 26: 93-94.	Outcomes not reported for patients who did not receive tubes; not a case series focused on safety outcomes
13.	Cotter, C. S. and J. R. Kosko (2004). "Effectiveness of laser-assisted myringotomy for otitis media in children." Laryngoscope 114(3): 486-489.	Tube placement not performed
14.	Coyte, P. C., et al. (2001). "The role of adjuvant adenoidectomy and tonsillectomy in the outcome of the insertion of tympanostomy tubes." N Engl J Med 344(16): 1188-1195.	Outcomes not reported for patients who did not receive tubes; not a case series focused on safety outcomes
15.	Coyte, P. C., et al. (1998). "Comparative cost analysis of myringotomy with insertion of ventilation tubes in Ontario and British Columbia." J Otolaryngol 27(2): 69-75.	Wrong study type (cost study rather than a full economic evaluation)
16.	de Beer, B., et al. (2005). "The effect of otitis media in childhood on the development of middle ear admittance on reaching adulthood." Arch Otolaryngol Head Neck Surg 131(9): 777-781.	Retrospective cohort study, % follow-up not reported
17.	de Beer, B. A., et al. (2004). "Hearing loss in young adults who had ventilation tube insertion in childhood." Ann Otol Rhinol Laryngol **113**(6): 438-444.	Retrospective cohort study, % follow-up not reported
18.	Debruyne, F., et al. (1988). "Otorrhea during transtympanal ventilation." Am J Otol **9**(4): 316-317.	Case series, % follow-up not reported
19.	Diacova, S. and T. J. McDonald (2007). "A comparison of outcomes following tympanostomy tube placement or conservative measures for management of otitis media with effusion." Ear Nose Throat J **86**(9): 552-554.	Control group treated with “conservative care”, which was not defined
20.	Dragicevic, D., et al. (2010). "Transient evoked otoacoustic emissions in young children with otitis media with effusion before and after surgery." Auris Nasus Larynx 37(3): 281-285.	Outcomes not reported separately for tubes vs. no tubes groups
21.	Forquer, B. D. and F. H. Linthicum, Jr. (1982). "Middle ear effusion in children: a report of treatment in 500 cases." West J Med **137**(5): 370-374.	Wrong comparator (the control group was treated with antihistamines, decongestants, and/or antibiotics; the percent treated with each was not reported, and two of the three medications were excluded from this report)
22.	Gani, B., et al. (2012). "A review of hearing loss in cleft palate patients." Int J Otolaryngol 2012: 548698.	Wrong population (patients were not required to have AOM or OME for inclusion)
23.	Gates, G. A., et al. (1988). "Effect of adenoidectomy upon children with chronic otitis media with effusion." Laryngoscope **98**(1): 58-63.	Duplicate study, no additional outcomes of interest
24.	Gleinser, D. M., et al. (2011). "The relationship between repeat tympanostomy tube insertion and adenoidectomy." Int J Pediatr Otorhinolaryngol 75(10): 1247-1251.	Outcomes not reported for patients who did not receive tubes; not a case series focused on safety outcomes
25.	Gordon, A. S., et al. (1988). "Late ear sequelae in cleft palate patients." Int J Pediatr Otorhinolaryngol 15(2): 149-156.	Wrong population (no indication that patients had OME)

	Citation	Reason for exclusion after full-text review
26.	Gourin, C. G. and R. N. Hubbell (1999). "Otorrhea after insertion of silver oxide-impregnated silastic tympanostomy tubes." Arch Otolaryngol Head Neck Surg **125**(4): 446-450.	Case series, % follow-up not reported
27.	Hassmann, E., et al. (2004). "Laser myringotomy in otitis media with effusion: long-term follow-up." Eur Arch Otorhinolaryngol 261(6): 316-320.	Retrospective cohort study with <80% follow-up
28.	Higgins, T. S., et al. (2008). "Medical decision analysis: indications for tympanostomy tubes in RAOM by age at first episode." Otolaryngol Head Neck Surg 138(1): 50-56.	Wrong population- hypothetical population only with estimates for utility derived from literature review; no cost analysis)
29.	Hong, H. R., et al. (2014). "Long-term follow-up of otitis media with effusion in children: comparisons between a ventilation tube group and a non-ventilation tube group." Int J Pediatr Otorhinolaryngol **78**(6): 938-943.	Retrospective cohort study with N<100
30.	Hubbard, T. W., et al. (1985). "Consequences of unremitting middle-ear disease in early life. Otologic, audiologic, and developmental findings in children with cleft palate." N Engl J Med 312(24): 1529-1534.	Wrong population (patients not required to have AOM or OME for inclusion)
31.	Khan, F., et al. (2006). "Management outcome of secretory otitis media." J Ayub Med Coll Abbottabad 18(1): 55-58.	Outcomes not reported for patients who received tubes vs. those who did not receive tubes
32.	Klockars, T. and J. Rautio (2012). "Early placement of ventilation tubes in cleft lip and palate patients: does palatal closure affect tube occlusion and short-term outcome?" Int J Pediatr Otorhinolaryngol 76(10): 1481-1484.	All patients received tubes
33.	Kobayashi, H., et al. (2012). "Clinical outcomes of ventilation tube placement in children with cleft palate." Int J Pediatr Otorhinolaryngol **76**(5): 718-721.	Unable to determine number of patients included in the control group, so unable to determine results for outcomes of interest
34.	Kwan, W. M., et al. (2011). "Otitis media with effusion and hearing loss in Chinese children with cleft lip and palate." Cleft Palate Craniofac J **48**(6): 684-689.	Retrospective cohort study with N<100
35.	Lee, C. H., et al. (2014). "Flexible integration of laser myringotomy and ventilation tube for bilateral Otitis media with effusion: analysis of laser tympanostomy versus ventilation tube." PLoS One **9**(1): e84966.	Retrospective cohort study, % follow-up not reported
36.	Lildholdt, T. (1979). "Unilateral grommet insertion and adenoidectomy in bilateral secretory otitis media: preliminary report of the results in 91 children." Clin Otolaryngol Allied Sci **4**(2): 87-93.	Duplicate patients reported in Lildholdt 1983
37.	Luxford, W. M. and J. L. Sheehy (1982). "Myringotomy and ventilation tubes: a report of 1,568 ears." Laryngoscope **92**(11): 1293-1297.	Wrong population (both children and adolescents/adults were included and results not reported separately for these populations)
38.	Maheshwar, A. A., et al. (2002). "Use of hearing aids in the management of children with cleft palate." Int J Pediatr Otorhinolaryngol 66(1): 55-62.	Wrong population (OME or AOM not required for inclusion)

	Citation	Reason for exclusion after full-text review
39.	Mangat, K. S., et al. (1993). "T-tubes: a retrospective review of 1274 insertions over a 4-year period." Int J Pediatr Otorhinolaryngol **25**(1-3): 119-125.	Case series, % follow-up not reported
40.	Maw, A. R. (1983). "Chronic otitis media with effusion (glue ear) and adenotonsillectomy: prospective randomised controlled study." Br Med J (Clin Res Ed) **287**(6405): 1586-1588.	Results not reported for tubed ears
41.	Maw, A. R. and F. Herod (1986). "Otoscopic, impedance, and audiometric findings in glue ear treated by adenoidectomy and tonsillectomy. A prospective randomised study." Lancet **1**(8495): 1399-1402.	Incomplete patient set; results reported elsewhere in for this RCT (Maw & Bawden papers)
42.	Maw, A. R., et al. (1992). "The effect of parental smoking on outcome after treatment for glue ear in children." Clin Otolaryngol Allied Sci **17**(5): 411-414.	Results not reported for tubed ears
43.	Medical Research Council Multicentre Otitis Media Study Group (MRC) (2001). "Surgery for persistent otitis media with effusion: generalizability of results from the UK trial (TARGET). Trial of Alternative Regimens in Glue Ear Treatment." Clin Otolaryngol Allied Sci 26(5): 417-424.	Tubes not used
44.	Medical Research Council Multicentre Otitis Media Study Group (MRC) (2008). "An extension of the Jerger classification of tympanograms for ventilation tube patency--specification and evaluation of equivalent ear-canal volume criteria." Ear Hear 29(6): 894-906.	Study evaluates the cut off values to determine tympanometric patency
45.	Mohiuddin, S., et al. (2014). "Economic evaluation of surgical insertion of ventilation tubes for the management of persistent bilateral otitis media with effusion in children." BMC Health Serv Res **14**: 253.	Wrong comparator (hearing aids)
46.	Morton, R. P., et al. (1994). "Nasopharyngeal carcinoma and middle ear effusion: natural history and the effect of ventilation tubes." Clin Otolaryngol Allied Sci 19(6): 529-531.	Wrong population (adults)
47.	Mui, S., et al. (2005). "Tympanostomy tubes for otitis media: quality-of-life improvement for children and parents." Ear Nose Throat J **84**(7): 418, 420-412, 424.	No “no tubes” comparator
48.	Niemela, M., et al. (1999). "Costs arising from otitis media." Acta Paediatr **88**(5): 553-556.	Wrong study type (cost study rather than a full economic evaluation)
49.	Peters, S. A., et al. (1994). "The effects of early bilateral otitis media with effusion on educational attainment: a prospective cohort study." J Learn Disabil **27**(2): 111-121.	Retrospective cohort study, % follow-up not reported
50.	Phua, Y. S., et al. (2009). "Middle ear disease in children with cleft palate: protocols for management." Int J Pediatr Otorhinolaryngol 73(2): 307-313.	Wrong population (OME, AOM, or hearing loss not required for inclusion in all patients)
51.	Pichichero, M. E., et al. (1989). "Anatomic and audiologic sequelae after tympanostomy tube insertion or prolonged antibiotic therapy for otitis media." Pediatr Infect Dis J **8**(11): 780-787.	Retrospective cohort study with N<100
52.	Roydhouse, N. (1980). "Adenoidectomy for otitis media with mucoid effusion." Ann Otol Rhinol Laryngol Suppl **89**(3 Pt 2): 312-	Wrong comparator (all patients with chronic OME who did not respond to

	Citation	Reason for exclusion after full-text review
	315.	medical treatment received tubes)
53.	Ryborg, C. T., et al. (2014). "Quality of life in children with otitis media--a cohort study." Fam Pract 31(1): 30-37.	Wrong population (no tubes comparator group may not have had OME throughout entire follow-up period; tubes given or not during 13-month follow-up period and population characteristics may have changed between groups during that time)
54.	Schilder, A. G., et al. (1993). "Long-term effects of otitis media with effusion on language, reading and spelling." Clin Otolaryngol Allied Sci **18**(3): 234-241.	Retrospective cohort study, % follow-up not reported
55.	Schilder, A. G., et al. (1995). "Long-term effects of otitis media with effusion: otomicroscopic findings." Am J Otol **16**(3): 365-372.	Retrospective cohort study, % follow-up not reported
56.	Schilder, A. G., et al. (1997). "Long-term effects of ventilation tubes for persistent otitis media with effusion in children." Clin Otolaryngol Allied Sci **22**(5): 423-429.	Retrospective cohort study, % follow-up not reported
57.	Shaw, R., et al. (2003). "Conservative management of otitis media in cleft palate." J Craniomaxillofac Surg 31(5): 316-320.	Wrong population (no tubes comparator group did not have AOM or OME)
58.	Slack, R. W., et al. (1984). "Prospective study of tympanosclerosis developing after grommet insertion." J Laryngol Otol 98(8): 771-774.	Results reported for the TT ear only
59.	Spilsbury, K., et al. (2013). "Cholesteatoma in cleft lip and palate: a population-based follow-up study of children after ventilation tubes." Laryngoscope **123**(8): 2024-2029.	Case series, % follow-up not reported
60.	Szabo, C., et al. (2010). "Treatment of persistent middle ear effusion in cleft palate patients." Int J Pediatr Otorhinolaryngol 74(8): 874-877.	Case series not focused on safety
61.	van Dongen, T. M., et al. (2013). "Parent-reported otorrhea in children with tympanostomy tubes: incidence and predictors." PLoS One **8**(7): e69062.	Case series with 37% follow-up
62.	Wolter, N. E., et al. (2012). "Middle ear ventilation in children with primary ciliary dyskinesia." Int J Pediatr Otorhinolaryngol **76**(11): 1565-1568.	Retrospective cohort study with N<100
63.	Yagi, H. I. (1977). "The surgical treatment of secretory otitis media in children." J Laryngol Otol **91**(3): 267-270.	Retrospective cohort study, % follow-up not reported.
64.	Yousaf, M., et al. (2012). "Medical versus surgical management of otitis media with effusion in children." J Ayub Med Coll Abbottabad 24(1): 83-85.	Wrong population (no tubes comparator group already had resolution of OME)

Appendix D. Class of Evidence, Strength of Evidence, and QHES Determination

Each study is rated against pre-set criteria that resulted in an evidence rating (Class of Evidence I, II, III, or IV) and presented in a table. The criteria are listed in the Tables below.

Definition of the class of evidence and risk of bias for studies on therapy*

Class	Bias Risk	Studies of Therapy*	
		Study design	**Criteria***
I	**Low risk:** Study adheres to commonly held tenets of high quality design, execution and avoidance of bias	Good quality RCT	• Random sequence generation • Allocation concealment • Intent-to-treat analysis • Blind or independent assessment for important outcomes • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size
II	**Moderately low risk:** Study has potential for some bias; study does not meet all criteria for class I, but deficiencies not likely to invalidate results or introduce significant bias	Moderate quality RCT	• Violation of one or more of the criteria for good quality RCT (but not violation of both random sequence generation and allocation and one or more other criteria)
		Good quality cohort	• Blind or independent assessment in a prospective study, or use of reliable data† in a retrospective study • Co-interventions applied equally • F/U rate of 80%+ • Adequate sample size • Controlling for possible confounding‡
III	**Moderately High risk:** Study has significant flaws in design and/or execution that increase potential for bias that may invalidate study results	Poor quality RCT	• Violation of both random sequence generation and allocation concealment criteria, and • Violation of one other criteria for a good quality RCT
		Moderate or poor quality cohort	• Violation of any of the criteria for good quality cohort
		Case-control	• Any case-control design
IV	**High risk:** Study has significant potential for bias; lack of comparison group precludes direct assessment of important outcomes	Case series	• Any case series design

* Additional domains evaluated in studies performing a formal test of interaction for subgroup modification (i.e., HTE) based on recommendations from Oxman and Guyatt{Oxman, 1992 #1355}:

- Is the subgroup variable a characteristic specified at baseline or after randomization? (subgroup hypotheses should be developed a priori)
- Is the subgroup difference suggested by comparisons within rather than between studies?
- Does statistical analysis suggest that chance is an unlikely explanation for the subgroup difference?

- Did the hypothesis precede rather than follow the analysis and include a hypothesized direction that was subsequently confirmed?
- Was the subgroup hypothesis one of a smaller number tested?
- Is the subgroup difference consistent across studies and across important outcomes?
- Does external evidence (biological or sociological rationale) support the hypothesized subgroup difference?

† Outcome assessment is independent of healthcare personnel judgment. Reliable data are data such as mortality or re-operation.

‡ Authors must provide a description of robust baseline characteristics, and control for those that are unequally distributed between treatment groups.

Determination of Overall Strength of Evidence

Following the assessment of the quality of each individual study included in the report, an overall "strength of evidence" for the relevant question or topic is determined. Methods for determining the overall strength of evidence are variable across the literature and are most applicable to evaluation of therapeutic studies.

SRI's method incorporates the primary domains of quality (CoE), quantity of studies and consistency of results across studies as described by AHRQ.

The following four possible levels and their definition will be reported:

- **High** – High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** - Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low** - Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and likely to change the estimate.
- **Insufficient** – Evidence either is unavailable or does not permit a conclusion.

All AHRQ "required" and "additional" domains (risk of bias, consistency, directness, precision, publication bias) are assessed Bodies of evidence consisting of RCTs were initially considered as High strength of evidence, while those comprised of nonrandomized studies began as Low strength of evidence. The strength of evidence could be downgraded based on the limitations described above. There are also situations where the nonrandomized studies could be upgraded, including the presence of plausible unmeasured confounding and bias that would decrease an observed effect or increase an effect if none was observed, and large magnitude of effect (strength of association).

Table D3. Example methodology outline for determining overall strength of evidence (SoE):

All AHRQ "required" and "additional" domains* are assessed. Only those that influence the baseline grade are listed in table.

Baseline strength: Risk of bias (including control of confounding) is accounted for in the individual article evaluations. HIGH = majority of articles Level I/II. LOW = majority of articles Level III/IV.

DOWNGRADE: Inconsistency** of results (1 or 2); Indirectness of evidence (1 or 2); Imprecision of effect estimates (1 or 2); Sub-group analyses not stated *a priori* and no test for interaction (2)

UPGRADE: Large magnitude of effect (1 or 2); Dose response gradient (1)

Outcome	Strength of Evidence	Conclusions & Comments	Baseline	DOWNGRADE	UPGRADE
Outcome	**HIGH**	Summary of findings	**HIGH** Level I/II studies	**NO** consistent, direct, and precise estimates	**NO**
Outcome	**MODERATE**	Summary of findings	**LOW** Level III studies	**NO** consistent, direct, and precise estimates	**YES** Large effect
Outcome	**LOW**	Summary of findings	**HIGH** Level I/II studies	**YES (2)** Inconsistent Indirect	**NO**

* Required domains: risk of bias, consistency, directness, precision. Plausible confounding that would decrease observed effect is accounted for in our baseline risk of bias assessment through individual article evaluation.
Additional domains: dose-response, strength of association, publication bias.

** Single study = "consistency unknown"

Assessment of Economic Studies

Full formal economic analyses evaluate both costs and clinical outcomes of two or more alternative interventions. The four primary types are cost minimization analysis (CMA), cost-utility analysis (CUA), cost-effectiveness analysis (CEA), and cost-benefit analyses (CBA). Each employs different methodologies, potentially complicating critical appraisal, but some common criteria can be assessed across studies.

No standard, universally accepted method of critical appraisal of economic analyses is currently in use. A number of checklists [Canadian, BMJ, AMA] are available to facilitate critique of such studies. The Quality of Health Economic Studies (QHES) instrument developed by Ofman, et al[3]. QHES embodies the primary components relevant for critical appraisal of economic studies[2,3]. It also incorporates a weighted scoring process and which was used as one factor to assess included economic studies. This tool has not yet undergone extensive evaluation for broader use but provides a valuable starting point for critique.

In addition to assessment of criteria in the QHES, other factors are important in critical appraisal of studies from an epidemiologic perspective to assist in evaluation of generalizability and potential sources of study bias.

Such factors include:

- Are the interventions applied to similar populations (e.g., with respect to age, gender, medical conditions, etc.)? To what extent are the populations for each intervention comparable and are differences considered or accounted for? To what extent are population characteristics consistent with "real world" applications of the comparators?
- Are the sample sizes adequate so as to provide a reasonable representation of individuals to whom the technology would be applied?
- What types of studies form the basis for the data used in the analyses? Data (e.g., complication rates) from randomized controlled trials or well-conducted, methodologically rigorous cohort studies for data collection are generally of highest quality compared with case series or studies with historical cohorts.
- Were the interventions applied in a comparable manner (e.g., similar protocols, follow-up procedures, evaluation of outcomes, etc.)?
- How were the data and/or patients selected or sampled (e.g., a random selection of claims for the intervention from a given year/source or all claims)? What specific inclusion/exclusion criteria or processes were used?
- Were the outcomes and consequences of the interventions being compared comparable for each? (e.g., were all of the relevant consequences/complications for each intervention considered or do they primarily reflect those for one intervention?)

Assessment of the overall strength of evidence for formal economic analyses does not appear to be documented in the literature. For the purposes of this HTA, overall strength was determined by:

- Quality of the individual studies: Where the majority of quality indicators described in the QHES met and were the methods related to patient/claim selection, patient population considerations and other factors listed above consistent with a high quality design?
- Number of formal analyses (3 or more)
- Consistency of findings and conclusions from analyses across studies.

Appendix E. Study quality: CoE and QHES evaluation

CoE evaluation:

OME comparative studies

Methodological Principle	Austin	Bernard/ Stenstrom	Black 1990	Brown 1978	Casselbrant 2009	Caye-Thomasen	COMET§§
Study design							
Randomized controlled trial		■	■	■	■		■
Prospective cohort study	■						
Retrospective cohort study						■	
Case-control							
Case-series							
Random sequence generation*		?	+	?	?		+
Concealed allocation*		?	no**	?	?		+
Intention to treat*		no‡	?	?	Yes		+
Independent or blind assessment	?	varies§	+	?	?	?	+
Co-interventions applied equally	?	+	+	Yes	Yes	?	+
Complete follow-up of ≥80%	?	+	varies††	Yes	No	Yes (3 years: 87%) No (7 years: 68%; 25 years: 48%)	varies***
Controlling for possible confounding†	?	?	+	No	No	No‡‡	+
Class of evidence	**CoE III**		**CoE II**	**CoE III**	**CoE III**	**CoE III**	**CoE I**
Risk of bias	**Moderately high RoB**		**Moderately low RoB**	**Moderately high RoB**	**Moderately high RoB**	**Moderately high RoB**	**Low RoB**

Methodological Principle	D'Eredità 2006	Dempster 1993	Gates 1987, 1989	Kent 1989	Koopman 2004	Leek	Lildholdt 1983
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■	■	■	■	■	■	■
Random sequence generation*	?	no†††	+	no****	+		no****
Concealed allocation*	?	no†††	?	?	?		?
Intention to treat*	?	+	no§§§	?	no††††		+
Independent or blind assessment	no	? ‡‡‡	+	no	?	?	no
Co-interventions applied equally	+	+	+	+	+	?	+
Complete follow-up of ≥80%	?	+	no	?	no	?	+
Controlling for possible confounding†	?	?	+	?	+	?	+
Class of evidence	**CoE III**	**CoE III**	**CoE II**	**CoE III**	**CoE II**	**CoE III**	**CoE III**
Risk of bias	**Moderately high RoB**	**Moderately high RoB**	**Moderately low RoB**	**Moderately high RoB**	**Moderately low RoB**	**Moderately high RoB**	**Moderately high RoB**

Methodological Principle	Mandel 1989	Mandel 1992	Maw & Bawden 1993, 1994 (4 papers)	Maw 1991	Paradise§§	Popova
Study design						
Randomized controlled trial	■	■	■	■	■	■
Prospective cohort study						
Retrospective cohort study						
Case-control						
Case-series						
Random sequence generation*	?	?	+	?	+	?
Concealed allocation*	?	?	?	?	+	?
Intention to treat*	+	+	no‡‡‡‡	?	+	no*****
Independent or blind assessment	?	?	+	?	+	?
Co-interventions applied equally	+	+	+	+	+	Yes
Complete follow-up of ≥80%	+	+	varies§§§§	?	+	Yes
Controlling for possible confounding†	no	+	?	?	+	?*****
Class of evidence	**CoE III**	**CoE III**	**CoE II**	**CoE III**	**CoE I**	**CoE III**
Risk of bias	**Moderately high RoB**	**Moderately high RoB**	**Moderately low RoB**	**Moderately high RoB**	**Low RoB**	**Moderately high RoB**

Methodological Principle	Rach§§	Rovers§§	Ruckley	Shishegar	TARGET§§	To 1984	Tos 1983§§	Vlastos
Study design								
Randomized controlled trial	■	■	■	■	■	■		■
Prospective cohort study							■	
Retrospective cohort study								
Case-control								
Case-series								
Random sequence generation*	no††††††	?	Yes	?	no††††††	?		Yes
Concealed allocation*	?	?	Yes	?	+	?		?
Intention to treat*	no	+	?	?	+	?		?
Independent or blind assessment	?	?	?	?	+	Yes	?	?
Co-interventions applied equally	+	+	Yes	Yes	+	Yes	?	Yes
Complete follow-up of ≥80%	+	+	Yes	?	+	?	varies	No
Controlling for possible confounding†	?	+	?	?	+	No	yes	Yes
Class of evidence	**CoE III**	**CoE III**	**CoE II**	**CoE III**	**CoE II**	**CoE III**	**CoE III**	**CoE II**
Risk of bias	**Moderately high RoB**	**Moderately high RoB**	**Moderately low RoB**	**Moderately high RoB**	**Moderately low RoB**	**Moderately high RoB**	**Moderately high RoB**	**Moderately low RoB**

"+" indicates that the criteria were met

"?" indicates that the study had insufficient detail to determine whether criteria were met

"no" indicates that the criteria were not met

* Applies only to randomized controlled trials

† Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed

‡ Bernard/Stenstrom: 139 patients were randomized patients, but data (including baseline characteristics) only presented for 125.

§ Bernard/Stenstrom: Credit for tympanometry at 18 months and all outcomes at 6-10 years; otherwise, there was no indication that outcomes were assessed blindly or by an independent observer.

** Black: Treatment allocation was contained in sealed numbered envelopes but there was no indication that envelopes were opaque.

†† Black: Complete follow-up was not reported for 1.75 or 6 month outcomes, was ≥80% for outcomes at 12 months, and was ≤80% for outcomes reported at 24 months.

‡‡ Caye-Thomassen: Authors report primarily on those patients who underwent the original treatment only in order to control for confounding difference in disease severity and potential influence of repeated treatment; HOWEVER, no demographic table provided and baseline hearing levels were significantly difference and not controlled for.

§§ Associated studies:

- COMET: Maw 1999, Wilks 2000, Hall 2009
- Paradise: Paradise 2001/2003a,b/2005/2007, Johnston 2004
- Rach: Rach 1991, Zeilhuis 1989
  - Rovers: Rovers 2000/2001, Ingels 2005
  - TARGET: MRC 2003/2012

*** COMET: Less than 80% follow-up for hearing levels (9 months only), risk for behavioral outcomes (at 18 months only), academic achievement, and speech and language as measured by the Wechsler Objective Language Dimensions and Children's Nonword Repetitive Task outcome measures.

††† Dempster: Randomization by patient (adenoidectomy vs. no adenoidectomy) and ear (TT vs. no surgery) done by serially numbered envelopes; no indication envelopes were sealed or opaque.

‡‡‡ Dempster: Although evaluating physicians were blind to whether or not an adenoidectomy was performed, there was no indication that any outcomes evaluated were measured in a manner blinded to the presence or absence of tube placement.

§§§ Gates: After randomization, 15% of patients (87/578) withdrew prior to undergoing surgery due to parental refusal or resolution of effusion; these patients were excluded from all further analyses

**** Kent, Lilholdt: Ears randomized by birthdate

†††† Koopman: After enrollment and allocation, 9.6% of patients (22/230) were excluded (8 did not appear, 3 had spontaneous resolution of OME, 11 did not receive laser myringotomy at time of surgery); these patients were excluded from all further analyses.

‡‡‡‡ Maw & Bawden: After enrollment and allocation, six patients (2.6% (6/228)) were excluded from all analyses after moving or having poor attendance

§§§§ Maw & Bawden: Credit for no adenoidectomy patients outcomes reported at 6, 12, and 24 months (80-90% complete f/u); no credit for outcomes reported between 36-120 months (17-66% f/u); adenoidectomy or adenotonsillectomy patients outcomes reported at 12 and 36 months (84-97% completed f/u); no credit for outcomes reported at 6 months (79%), 24 months (75%), or 48 to 120 months (30% to 74%)

***** Popova: 12/90 patients did not complete follow-up and were completely excluded from the study

††††† Target, Rach: The first 5 patients were randomly allocated (details NR) and each subsequent child was allocated to the group that would create the most balance between groups in terms of age, sex, occupation of head of the household (manual vs. non-manual), and baseline hearing (TARGET); and age, gender, and language (Rach).

AOM comparative studies

Methodological Principle	Casselbrant 1992	El-Sayed 1996	Gebhart 1981	Gonzalez	Kujala 2012, 2014	Le
Study design Randomized controlled trial Prospective cohort study Retrospective cohort study Case-control Case-series	■	■	■	■	■	■
Random sequence generation*	?	?	?	+	+	?
Concealed allocation*	?	?	?	?	+	?
Intention to treat*	+	no‡	no‡	no‡	+	?
Independent or blind assessment	?	?	?	?	no	+
Co-interventions applied equally	+	+	+	?	+	+
Complete follow-up of ≥80%	no	+	+	?	varies§	+
Controlling for possible confounding†	+	no	+	no	+	+

"+" Indicates that the criteria were met

"?" Indicates that the study had insufficient detail to determine whether criteria were met

"no" Indicates that the criteria were not met

* Applies only to randomized controlled trials

† Groups must be comparable on a robust set of baseline characteristics or present evidence that controlling of confounding presented was performed

‡ All data (including baseline characteristics) reported for only patients with complete follow-up

§ 90% follow-up for all outcomes except QoL; % f/u for QoL subanalysis was unclear

Quality of Health Economic Studies (QHES) score of included articles

QHES Question (pts possible)		Hartman 2001
1.	Was the study objective presented in a clear, specific, and measurable manner? (7 pts)	4
2.	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated? (4 pts)	8
3.	Were variable estimates used in the analysis from the best available source (i.e. randomized controlled trial = best, expert opinion = worst)? (8 pts)	1
4.	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study? (1 pt)	9
5.	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions? (9 pts)	6
6.	Was incremental analysis performed between alternatives for resources and costs? (6 pts)	5
7.	Was the methodology for data abstraction (including the value of health states and other benefits) stated? (5 pts)	0
8.	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate? (7 pts)	8
9.	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described? (8 pts)	0
10.	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term and negative outcomes included? (6 pts)	7
11.	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used? (7 pts)	8
12.	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner? (8 pts)	0
13.	Were the choice of economic model, main assumptions, and limitations of the study stated and justified? (7 pts)	6
14.	Did the author(s) explicitly discuss direction and magnitude of potential biases? (6 pts)	8
15.	Were the conclusions/recommendations of the study justified and based on the study results? (8 pts)	3
16.	Was there a statement disclosing the source of funding for the study? (3 pts)	4
	Total score:	**80**

Appendix F. Study characteristics

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
Austin (1989 & 1994)	Prospective cohort (by ear) Selection for which ear to have tube inserted was based on chart number (even number = right ear, and vice versa)	US Single center	NR	Children for whom tonsillectomy and adenoidectomy had been scheduled and who were known to have bilateral catarrhal otitis with a minimum 1 month follow-up.	NR	NR
Bernard (1991) & Stenstrom (2005)	RCT	Canada Single center	National Health and Welfare Research and Development Program, Ottowa Canada, grant 6606-2944-42. Doctoral research fellowship from Health Canada, Ottowa, Ontario. Medication provided by Hoffmann-Laroche Canada Ltd.	(1) age 2.5 to 7 years; (2) longstanding (greater than 3 months) effusion as indicated by type "B" tympanogram (in at least one ear) and otoscopic evidence (fluid/air fluid levels) of effusion at least 3 months preceding entry into the trial; (3) at least two physician-documented trials of antibacterials for AOM or OME, of at least 10 days' duration in the 3 months preceding entry into the trial; (4) history of hearing loss (based on parental reports) of >3 months' duration; at the	(1) cervicofacial abnormality (cleft palate, Down syndrome); (2) documented immune insufficiency; (3) documented allergy to sulfonamide; (4) previous insertion	<u>For medical subjects:</u> AOM was diagnosed based on otomicroscopic findings (redness of the tympanic membrane, absence of landmarks) and acute-onset ear pair with or without fever or otorrhea. <u>For surgical subjects:</u> the diagnosis of AOM was contingent on discharge from the ear and presence of pathogens commonly associated with AOM. Using tympanocentesis

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
				time of entry into the trial: (5) hearing loss of at least 25 dB HL (hearing level based on the ANSI 53.6 1969 standard) air conduction at 2 or more frequencies 0.5, 1, 2, and 4 kHz (pure-tone audiometry) in at least one ear; (6) bone conduction thresholds within normal limits (0 to 10 dB HL) bilaterally; (7) otomicroscopic and tympanometric (type "B") evidence of MEE in at least one ear; and (8) air-bone gap of > 15 dB at frequencies with elevated air conduction thresholds.		as a gold standard, the study otolaryngologist's sensitivity in diagnosing OME was 96.9% (93/96 ears with effusion correctly identified) and specificity was 87.5% (21/24 ears with no effusion properly identified). Superinfection in surgical subjects was defined as tube otorrhea and presence of Gram-negative bacteria (excluding *Haemophilus influenzae*) and was treated with otic drops for 7 days. In absence of culture results, tube otorrhea was on several occasions classified as an AOM episode by the child's primary care physician, these were counted as AOM, not as side effects of surgical treatment.

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
Black (1990)	RCT (randomized both by ear and by patient)	UK Single-center	Financial support from Oxfordshire Health Authority, Oxford Regional Health Authority, and the Department of Health and Social Security	Children aged 4 to 9 years old who were admitted for surgery for bilateral glue ear.	Previous operations on their tonsils, their adenoids, or their ears and those in whom there was evidence of cleft palate or any sensorineural deafness; children who were to have surgery for conditions other than glue ear e.g., adenoidectomy for alleviating gross nasal obstruction.	NR
Bonding (1985), Tos (1983 & 1989), Khodaverdi (2013)	Prospective cohort	Denmark Single Center	NR	Children with bilateral OME	NR	NR
Brown (1978)	RCT (randomized by ear)	Wales Single center	NR	Children aged between 4 and 10 years with seromucinous otitis media in both ears were included.	NR	Diagnosis was made on a careful history, otoscopy and pure tone audiometry.
Casselbrant 2009	RCT (randomized by patient)	US Single center	Grant: NIH R01 DC003205	Patients with a documented history of bilateral middle ear effusion for at least 3 months, unilateral for 6 months or unilateral for 3 months after extrusion of one TT with the other still in place and have completed a course of 10 days of a broad spectrum antimicrobial agent within the last month	Previous tonsillectomy and/or adenoidectomy; previous ear surgery other than tympanocentesis or myringotomy with or without tube insertion; history of seizure disorder, diabetes mellitus, asthma requiring daily medication, or any health condition that could make entry potentially disadvantageous to the child; medical conditions	OME was defined as asymptomatic middle ear effusion or effusion without the symptoms of inflammation characteristic of AOM.

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
					with a predisposition for MEE, such as cleft palate, Down syndrome, congenital malformations of the ear; cholesteatoma or chronic mastoiditis; severe retraction pockets; acute or chronic diffuse external otitis; perforation of the tympanic membrane; intracranial or intratemporal complications of MEE; upper respiratory obstruction attributable to tonsil or adenoid enlargement or both with cor pulmonale, sleep apnea or severe dysphagia; conductive hearing loss attributable to destructive changes in the middle ear; sensorineural hearing loss; distance from CHP that would make follow-up difficult.	
Casselbrant 1992	RCT (randomized by patient)	United States 3 centers	Grant DC00158 from the National Institute on Deafness and Communication Disorders, NIH	Infants and children 7 to 35 months of age who had developed 3 or more episodes of acute otitis media during the preceding 6 months, or 4 or more episodes during the preceding 12 months with the most recent episode having occurred during the preceding 6 months.	At the time of entry children were required to be free of middle ear effusion. Children were excluded who had potentially complicating or confounding conditions, e.g. asthma, chronic sinusitis or previous tonsillectomy or adenoidectomy.	The presence of erythema or white opacification (other than that caused by scarring), fullness or bulging and decreased mobility of the tympanic membrane. Or fever, otalgia and irritability. Otitis media

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
						with effusion was defined as the presence of middle ear effusion in the absence of all of these symptoms and signs except decreased mobility.
Caye Thomasen (2008)	Retrospective cohort study	Demark Single center	NR	(1) Children (age range NR) (2) Chronic bilateral OME, duration ≥3 months; (3) Treated by myringtomy in one ear and TT in the other ear	NR	Type B tympanogram
COMET (Maw 1999, Wilks 2000, Hall 2009)	RCT (randomized by patient)	UK Single center	NHS Research and Development Directorate	Children with bilateral OME for at least 3 months; assessment of hearing loss; disruptions in speech, language or behavior; referred to hospital	Cleft palate & syndromes such as Down's, Hunter's, or Hurler's.	Bilateral type B or C2 tympanograms and hearing loss of 25-70 dB hearing level
Dempster (1993)	RCT (randomized by ear)	Scotland Single center	NR	Children aged 3.5 to 12 years old with a suspected hearing impairment with otoscopic evidence of bilateral otitis media with effusion that satisfied the following criteria: - Pure tone air conduction thresholds average over 0.5,1 and 2 kHz of ≥25 dB HL; - An air-bone gap of over 0.5, 1, and 2 kHz of ≥15 dB; - Type B tympanogram (as defined by Fiellau-Niklajsen, 1983).	- Previous adenoidectomy or aural surgery; - additional symptoms requiring surgical intervention, e.g., recurrent sore throat; - cleft palate.	Otoscopic evidence only by a previously validated otoscopist.

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
D'Eredita 2006	RCT (randomized by patient)	Italy Single-center	NR	Children aged 2 to 6 years with OME for at least 3 months' duration.	Children who had a history of prior middle ear surgery or PE tube insertion, Down or other syndrome involving the head and neck, cleft palate or previous pharyngeal surgery, mental retardation or other known cognitive or psychiatric disorder.	NR
El-Sayed (1996)	RCT (randomized by patient)	Saudi Arabia Single center	NR	Subjects were included if they had at least three attacks of AOM diagnosed, documented, and treated by their referring physician in the six-month period prior to referral. Only children who were under 3 years of age were included.	Children were excluded if they had a documented immune insufficiency or a cervicofacial abnormality) (e.g., cleft palate, Down's syndrome).	In the medical group, diagnosis of AOM was based on the inflammatory otoscopic findings and the acute onset of earache with or without otorrhea. For the surgical group, the diagnosis of AOM was contingent on ear discharge.
Gates (1987, 1989)	RCT Randomized, by patient, stratified according to age, sex, ethnic group, and previous placement of tubes	United States Multicenter (5 sites)	Grants from the National Institute of Neurological and Communicative Disorders and Stroke-National Institutes of Health contract (NS-NO-1-02328) and Ross Laboratories (grant-in-kind)	Children 4-8 years of age in whom chronic effusion was suspected Three pneumotoscopic assessments of the tympanum were permitted: normal mobility, intermediate, and abnormal (of fifteen possible assessments, with use of the criteria of Cantekin et al [17])	Children with a history of previous tonsil or adenoid surgery, placement of tympanostomy tubes (within 2 years) cleft palate, or any other otologic diagnoses; children with chronic illness; children with diagnoses other than chronic effusion, with advanced or irreversible structural changes of the tympanum [1987, 1988, 1989], or children who	Based on pneumotoscopic and tympanometric findings from an otoscopist whose diagnostic ability was ≥95% in terms of sensitivity and ≥80% in terms of specificity. Judgment that effusion was present was based on an algorithm derived from the pneumatoscopic (in

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
			[1987, 1988, 1989] Supported by the Xomed Corporation [1989]		required daily medication (with the exception of daily allergy therapy) [1989].	which normal, intermediate, and abnormal mobility were allowed) and tympanometric findings. Tympanometric findings were coded as one of 15 types (Cantekin et al. [25]), and grouped into probability of effusion as low, intermediate, or high. A positive fluid score was given to ears with abnormal pneumatoscopy, or the combination of intermediate otoscopy and either high-probability tympanogram (types 5, 8, 12, 13) or a type 14 tympanogram.

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
Gebhart (1981)	RCT (randomized by patient)	United States Single center	Supported In part by a grant from the Medical Research Foundation at Riverside Methodist Hospital and In part by NIH Grant NSO 8864.	Patients were included who had at least three episodes of acute purulent otitis media diagnosed and treated by their referring physician in the 6-month period prior to referral. It was necessary for the multiple episodes of otitis media to have occurred in spite of adequate medical therapy with antibiotics. For inclusion in the study, patients also had to be under 3 years of age.	Patients with cleft palate and Down's syndrome were not included, nor were the few patients with recurrent tonsillitis associated with otitis media.	A: drainage through the tympanostomy tube into the external canal B: entire tympanic membrane becoming erythematous and thickened with decreased mobility and the short process of the malleus no longer visible
Gonzalez (1986)	RCT (randomized by patient)	United States 2 centers	NR	Children between the ages of 6 months and 10 years were eligible for the study. Criteria for inclusion were three or more episodes of AOM during the previous 6 months or greater than four episodes in the previous 18 months.	Patients with cleft palate, Down's syndrome, previous tympanostomy tubes, or sulfonamide sensitivity were excluded.	AOM was defined as the rapid and short onset of signs and symptoms of inflammation in the middle ear. Diagnosis was also based on the following criteria: 1. otalgia (ear tugging in the infant); 2. fever; 3. tympanic membrane erythema or bulging; 4. decreased tympanic membrane mobility; 5. loss of tympanic membrane landmarks; 6. otorrhea.

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
Kent (1989)	RCT (randomized by ear)	UK Single center	NR	Children suffering from bilateral secretory otitis media of more than 3 months duration, all listed for insertion of grommets under general anesthetic.	NR	NR
Koopman (2004)	RCT (randomized by ear)	The Netherlands Multicenter (7 sites)	Funding by The Sophia Foundation For Medical Research and The Revolving Fund Sophia Children's Hospital, Erasmus Medica Centre, Rotterdam, Theia Foundation, and Silver Cross Company.	Children aged less than 11 years, impaired hearing noticed by parents during at least 3 successive months, and bilateral OME.	Unilateral OME, poorly cooperative children, clinically admitted patients, asymmetric perceptive HL, and previously operated ears with other than myringotomy or ventilation tubes.	OME was defined as otitis media with middle ear effusions of any color, but without fever, otalgia, or otorrhea. Diagnosis was made by an otolaryngologist with binocular otoscopy, in combination with a tube B tympanogram or pure tone audiometry. A bilateral tympanogram type C1 or C2, classified after Jerger, was considered to support the diagnosis of OME. If the child was too young or failed at audiometric testing, the diagnosis was based solely on otoscopic findings and history.

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
Kujala (2012 & 2014)	RCT (randomized by patient)	Finland Single center	Funding was received by Tiia Kujala from the Maud Kuistila Memorial Foundation, the Alma and K.A. Snellman Foundation, the Orion Pharmacy Foundation and the Päivikki and Sakari Sohlberg Foundation, Finland. The funding enabled T.K. to concentrate largely on this work between 2002 and 2005.	Between 10 months and 2 years of age, at least 3 AOM episodes during the past 6 months and residence within 25 miles of the hospital	Chronic otitis media with effusion, a prior adenoidectomy or tympanostomy tubes, cranial anomalies, documented immunological disorders or ongoing antimicrobial prophylaxis for a disease other than AOM	The criteria for AOM consisted of the presence of acute upper respiratory symptoms together with middle ear inflammation and effusion (bulging and/or decreased mobility of the ear drum, air-fluid level) detected in pneumatic otoscopy, tympanometry or otomicroscopy, or otorrhea
Le (1991)	RCT (randomized by ear)	United States Multicenter (# centers NR)	Research was supported by the Community Service Program of Kaiser Foundation Hospitals	Children with chart documentation of otitis events and all three of the following: 1. Recurrent acute otitis media, defined for children below 1 year of age as four or more documented episodes, and for children between 1 and 6 years as six or more, during the year preceding the referral; or persistent middle ear effusion documented by	Patients with Down's syndrome, cleft palate, known immunodeficiencies, prior tympanocentesis, myringotomy, ventilating tube, adenoidectomy or tonsillectomy were excluded.	For acute otitis media there must be documentation of acute otalgia (fussiness, pain) and the description of erythematous and distorted tympanic membranes with effusion. (Descriptive terms such as "red and bulging," "bullous," "hemorrhagic" or

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
				monthly pneumatic otoscopy and tympanometry for three consecutive months. 2. Bilateral disease of equal severity in each ear. The number of episodes of otitis media during the previous 12 months did not exceed the number in the other ear by more than one episode. When hearing can be adequately evaluated in each ear preoperatively, the difference in hearing levels in one ear did not exceed that in the other ear by 5 dB. 3. "Failure" of antimicrobial prophylaxis (usually with sulfisoxazole) defined as two or more "breakthrough" episodes of otitis while receiving prophylaxis for at least 3 months before study enrollment		"innamed" drums were accepted.) Otitis media with effusion was clinically diagnosed when there was no acute otalgia, but pneumatic otoscopy revealed decreased motility of the tympanic membrane from the presence of f1uids, and a type B tympanogram was documented.
Leek (1979)	Prospective cohort study	United States Centers NR	NR	All patients had bilaterally similar middle ear effusions and enlarged adenoids causing upper airway obstruction.	Children with allergic histories or allergic parents.	NR
Lildholdt (1983)	RCT (randomized by treating the right ear of	Denmark Single center	Grants from "Fonden for Laegevidenskabe	Previous treatment was accepted, such as various medications current	No concurrent disease, particularly cleft palate; previous use of tubes;	NR

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
	children born on even dates, and the insertion of a tube in the left ear of children born on odd-dates) Note: Stratified by ear		lig Forskning I Vejle Amt", "Aage Holm og Hustrus Mindefond", and The Danish Medical Research Council.	prescribed, and also a previous adenoidectomy and/or tonsillectomy with or without a paracentesis. Occurring earache for a day with slight fever was also accepted. All ears had to have a middle ear pressure below -150 mm H2O on both sides, and a maximum difference of 100 mm water. A maximum difference of 15 dB was permitted in the mean hearing level at 500, 1000, and 2000 Hz (pure tone average) in children where an audiogram could be obtained.	history of documented recurrent suppurative otitis media. If no aspirate was found during myringotomy + tube insertion procedure, the patient was excluded, irrespective of the content of the opposite ear (occurred in nine children).	
Mandel (1989)	RCT (randomized by patient)	United States Single-center	Grant MCJ-420434 from the Division of Maternal and Child Health, Bureau of Health Care Delivery and Assistance; grant NS16337 from the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of	Infants and children between 7 months and 12 years of age with documented MEE of at least 2 months' duration, persisting after at least one 14-day course of an antimicrobial drug (usually amoxicillin) and pseudoephedrine hydrochloride-chlorpheniramine maleate syrup, were eligible for the study.	Congenital craniofacial malformation; Down syndrome; systemic illness such as asthma, cystic fibrosis, or diabetes mellitus; seizure disorder; a history of tonsillectomy, adenoidectomy, or tympanostomy tube insertion structural middle-ear abnormality such at tympanic membrane perforation or adhesive OM; cholesteatoma; sensorineural hearing loss or conductive hearing loss not attributable to MEE; severe	Previously described in Cantekin 1983, which combines the findings obtained by a "validated otoscopist" with the results of tympanometry and middle-ear muscle-reflex testing.

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
			Health, Bethesda, MD		upper airway obstruction; AOM; or purulent rhinitis.	
Mandel (1992)	RCT (randomized by patient)	United States Single-center	Grant MCJ-420434 from the Division of Maternal and Child Health, Bureau of Health Care Delivery and Assistance; grant NS16337 from the National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, MD	Infants and children between 7 months and 12 years of age with documented MEE of at least 2 months' duration, persisting after at least one 14-day course of an antimicrobial drug (usually amoxicillin) and pseudoephedrine hydrochloride-chlorpheniramine maleate syrup, were eligible for the study.	Congenital craniofacial malformation; Down's syndrome; a chronic illness such as asthma, cystic fibrosis, diabetes mellitus or a seizure disorder; a history of tonsillectomy, adenoidectomy or tympanostomy tube insertion; severe upper airway obstruction; significant developmental or speech delay; a structural middle ear (ME) abnormality such as tympanic membrane perforation or adhesive otitis media; a sensorineural hearing loss or a conductive loss not attributable to MEE; cholesteatoma; and acute otitis media (AOM) or purulent rhinitis. Children whose pure tone average bilaterally or speech awareness threshold on audiometric testing was >35 dB hearing level (HL) also were excluded.	Previously described in Cantekin 1983, which combines the findings obtained by a "validated otoscopist" with the results of tympanometry and middle-ear muscle-reflex testing.
Maw (1991)	RCT	United Kingdom Single center	Funding NR	Established bilateral OME	NR	NR
Maw (1993,	RCT (random	United Kingdom	South West	(a) age between 2 and 11	Maw 1994: Any case with a	Type B tympanogram;

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
1994, 1994, 1994, and 1992)	number generator)	Single center	Regional Research Committee and Hearing Research Trust	years (but none were over 9); (b) pronounced subjective hearing loss; (c) pneumatic otoscopic confirmation of fluid in the middle ear of both ears; (d) tympanometry not showing a type A peaked curve (98% type B, 2% type Cl or C2); and (e) in excess of 25 dB pure audiometric or free field hearing loss in each ear at one or more frequencies. From Maw 1983: With bilateral OME.	type A tympanogram at any time was excluded.	pneumatic otoscopic confirmation of fluid in the middle ear of both ears
MRC (2004 subset of TARGET trial)	quasi-RCT (by patient) (see comments for details)	Ireland Single center	Medical Research Council	age 3.25–6.75 years on a first visit; no previous ear or adenoid surgery; bilateral OME with effusion and better ear hearing level (HL) ≥20 dB persistent for 3 months; underwent the Speech-in-noise (SiN) automated toy test (ATT)	NR	Had on two qualifying visits, 3 months apart: a bilateral B + B or B + C2 tympanogram combination (modified Jerger), and better ear HL ≥20 dB HL averaged across 0.5, 1, 2 and 4 kHz and air–bone gap >10 dB
Paradise (2001/ 2003otitis/ 2003early/ 2005/ 2007) & Johnston (2004)	RCT (randomized by patient)	United States Multicenter (8 sites)	Grant from the National Institute for Child Health and Human Development and the Agency for Healthcare Research and	Children were eligible for randomization if: beginning at the age of 2 months and within the first 3 years of life, children had middle-ear effusion that appeared substantial in degree and that persisted, despite treatment with antimicrobial drugs, for	Birth weight of less than 2270 g (5 lb.); small size for gestational age; history of neonatal asphyxia or other serious illness; major congenital malformation or chronic illness; product of a multiple birth; had a sibling enrolled in the study; in	Used pneumatic otoscopy, supplemented by tympanometry, to evaluate the middle-ear status at least monthly (no further details provided); the cumulative

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
			Quality and by gifts from SmithKline Beecham Laboratories and Pfizer	90 days in the case of bilateral effusion or 135 days in the case of unilateral effusion (children with intermittent bilateral or unilateral middle-ear effusion for specified proportions of longer periods were also eligible); written informed consent from parents or guardians	foster care or adopted; mother deceased, seriously ill, or a known drug or alcohol abuser, or (in the judgment of study personnel) too limited socially or intellectually to give informed consent or adhere to the study protocol; mother younger than 18 years of age; English not the only language spoken in the household.	proportions of days each child had unilateral and bilateral effusion, respectively, were estimated on the basis of diagnoses made at individual visits and interpolations for intervals between visits. The term “middle-ear effusion” was used to encompass all types of otitis media in which effusion is present: acute otitis media with or without otorrhea, otitis media with effusion, and otorrhea through a tympanostomy tube
Popova (2010)	RCT (randomized by patient)	Bulgaria Single center	No funding source for the research	Children with documented history of bilateral middle ear effusion for at least 3 months and conductive hearing loss greater than 20 dB were included in this study. Authors confirmed that they also fulfill the criteria of other studies in this field	Patients were excluded from the study group if one of the following conditions were present: previous myringotomy with or without insertion of ventilation tubes, previous adenoidectomy or tonsillectomy, history of ear surgery, cleft palate, Down’s syndrome, congenital malformations of the ear,	OME is defined as asymptomatic middle ear effusion without signs of inflammation characteristic of the acute otitis media (AOM). The presence of middle ear effusion was determined on the basis of certain criteria and tests that include tympanometry

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
					cholesteatoma or chronic mastoiditis, perforation of the tympanic membrane, conductive hearing loss attributed to destructive changes in the middle ear, sensorineural hearing loss.	(Interacoustics AT-235h) and pneumatic otoscopy by a validated otoscopist. Standard tympanometry (using a 226 Hz probe tone) was performed and tympanograms were categorized using the Jerger (1972) classification. Type B tympanograms and findings of fluid levels or bubbles on otoscopic examination validated the diagnosis. Diagnosis of AOM required the finding of middle ear effusion on otoscopy with at least one symptom, i.e., fever, earache or recent ear tugging, irritability and one sign of inflammation, i.e., erythema and/or white opacification of the tympanic membrane, otorrhea from a perforation of a previously intact tympanic membrane. For proper differentiation of

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
						otorrhea episodes from AOM episodes we defined otorrhea as mucous or mucopurulent discharge from the ear with no symptoms of acute inflammation.
Rach (1991) & Zielhuis (1989)	RCT (randomized by patient)	The Netherlands Single center	Grant from the Dutch Praevention-fund	Children aged 2-4 years with confirmed bilateral OME. Briefly, patients recruited from a birth cohort of 2 year old children who were screened for OME every 3 months. Those with bilateral flat tympanograms (Jerger type B) at two consecutive screens 3 months apart were referred for possible inclusion. Children with confirmed bilateral OME who did not have any exclusion criteria were eligible.	Congenital ear disorders (sensorineural loss) or defects in their speech-producing apparatus (e.g. cleft palate), neurological or serious visual disorders, emotional or mental troubles, chronic diseases with a history of 6+ weeks of hospitalization, chronic otorrhea, or a history of or treatment for OME. Children not raised in a Dutch-speaking environment were excluded.	Bilateral type B tympanograms; OME confirmed during routine ENT exam that included impedance measurements (details NR).
Rovers (2000/ 2001) & Ingels (2005)	RCT (randomized by patient)	Netherlands Multicenter (13 sites)	Dutch Investigative Medicine Fund of the National Health Insurance Board	Infants with persistent (4-6 months) bilateral OME and who failed 3 successive hearing screening tests, where in the last test there was a failure to respond to sound at 35 dB.	Down syndrome, schisis, asthma, cystic fibrosis, sensorineural hearing loss	Confirmed by tympanometry and otoscopy; classified according to the Maastrichts' Otitis Media With Effusion Study protocol
Ruckley (1988)	RCT (randomized by ear)	Scotland NR	NR	Children with bilateral secretory otitis media.	NR	NR

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
Shishegar (2007)	RCT (randomized by ear)	Iran Single center	NR	Children with bilateral chronic middle ears effusion unresponsive to medical therapy	Children with a history of prior adenotonsillectomy, tympanostomy tube placement, dry middle ear, cleft palate, and perforated tympanic membrane were excluded from the study.	The diagnosis of OME is established by the presence of persisting middle ear effusion behind an intact tympanic membrane without other signs of inflammation such as redness and bulging.
TARGET (MRC 2003/2012)	RCT (randomized by patient)	UK Multicenter (11 sites)	Medical Research Council	age 3.25–6.75 years on a first visit; no previous ear or adenoid surgery; bilateral OME with effusion and better ear hearing level (HL) ≥20 dB persistent for 3 months	NR	Had on two qualifying visits, 3 months apart: a bilateral B + B or B + C2 tympanogram combination (modified Jerger), and better ear HL ≥20 dB HL averaged across 0.5, 1, 2 and 4 kHz and air–bone gap >10 dB
To (1984)	RCT (randomized by ear)	UK Single center	NR	Children under the age of 14 who presented with secretory OM.	(1) Children with asymmetrical hearing losses, in whom the mean hearing levels on the 2 sides showed a difference of more than 6 dB. (This figure was chosen for the following reason: a good audiogram has an error of +10dB for each reading so that a significant difference can be taken as 12-14 dB and for the mean of 6 frequencies it can be taken as approximately 6 dB, that is, 14 dB divided by the	

Author, Year	Study Design	Country Number of Centers	Funding Source	Inclusion Criteria	Exclusion Criteria	Criteria for Diagnosis of OME and/or AOM
					square root of 6). (2) Where grommets were inserted for established complications of the disease, such as retraction pockets and obvious thinning of the drum.	
Vlastos (2011)	RCT (randomized by patient)	Greece Single center	NR	Children were eligible for inclusion in the study if they were scheduled for an adenoidectomy due to sleep-disordered breathing, were older than three years of age and had otitis media with effusion (OME) in both ears.	Children with no signs of effusion (purulent or otherwise) at the time of myringotomy were excluded from the study. We also excluded children with chronic otitis media, structural changes (e.g. tympanic membrane retraction pockets, ossicular chain erosion or cholesteatoma), previous ear surgery, language delays, behavioural problems and syndromes.	The diagnosis of OME was based on otoscopy, tympanography and pure tone audiometry. Specifically, the presence of an opaque or thickened tympanic membrane, air–fluid level, or bubbles, or the inability to visualize the incudostapedial joint, were considered signs of OME, in children with a type B tympanogram (compliance <0.2 ml) and an audiogram with an air–bone gap of 20 dB or a hearing loss of 30 dB but no more than 55 dB in at least one frequency in both ears.

Appendix G. Results Tables for Key Question 1 (Efficacy and Effectiveness)

Appendix Table G1. Hearing levels by child: TT vs. WW for OME

Hearing level* (mean ± SD) (dB)					
Time Point	**RCT**	**TT**	**WW**	**Mean Difference (95% CI)**	**P-Value**
Baseline	COMET	38.3 (n=92)	39.6 (n=90)	-1.3	NS
	TARGET	33.2 ± 4.6 (n=126)	33.8 ± 4.8 (n=122)	-0.60 (–1.78 to 0.58)	NS
	Rovers	46.4 ± 1.1 (SE) (n=93)	43.4 ± 1.2 (SE) (n=94)	3.0 (-0.21 to 6.21)	0.0671
	Paradise	NR	NR	NR	NR
3 mos.	TARGET	14.4 ± 6.9 (n = 109)	26.3 ± 9.9 (n = 106)	–11.90 (–14.19 to –9.61)	<0.0001
6 mos.	TARGET	17.5 ± 8.2 (n = 106)	23.1 ± 10.1 (n = 105)	–5.60 (–8.10 to –3.10)	<0.0001
	Rovers	35.9 ± 8.9† (n=86)	38.7 ± 8.9† (n=84)	-2.80 (-5.50 to -0.11)	0.0418
9 mos.	COMET	16.5 ± 13.0 (n=81)	21.6 ± 16.1 (n=60)	-5.10 (-9.95 to -0.25)	0.0394
12 mos.	TARGET	21.0 ± 9.4 (n=110)	20.5 ± 10.1 (n=100)	0.50 (–2.15 to 3.15)	NS
	Rovers	33.2 ± 7.2† (n=37)	34.7 ± 7.9† (n=81)	-1.50 (-4.52 to 1.52)	NS
18 mos.	COMET	12.7 ± 11.5 (n=75)	14.3 ± 10.5 (n=73)	-1.60 (-5.18 to 1.98)	NS
	TARGET	21.1 ± 10.2 (n=103)	19.7 ± 10.4 (n=98)	1.40 (–1.47 to 4.27)	NS
24 mos.	TARGET	18.7 ± 8.9 (n=108)	18.2 ± 8.1 (n = 102)	0.50 (–1.82 to 2.82)	NS
Age 6 years (~36-70 mos. f/u)	Paradise	6.2 ± 4.1 (L) 6.2 ± 4.1 (R) (n=147)	5.5 ± 3.4 (L) 6.0 ± 5.5 (R) (n=134)	0.70 (-0.12 to 1.59) (L) 0.20 (-0.93 to 1.33) (R)	NS (both)

NS: p-value ≥0.05

* Hearing measured by:

- COMET: pure tone audiometry in better ear (measured at 4000 Hz)
- TARGET: air conduction thresholds (average of thresholds measured at 500, 1000, 2000, and 4000 Hz)
- Rovers: pure tone audiometry in better ear (average of thresholds measured at 500, 1000, 2000, and 4000 Hz)
- Paradise: pure tone audiometry in each ear (average of thresholds measured at 500, 1000, 2000, and 4000 Hz)

† Data obtained from 2010 Cochrane report[1], which used patient-level data (the Rovers study reported mean ± SE)

Appendix Table G2. Otorrhea: TT vs. WW for OME

		Parent-Reported Otorrhea (% (N/N))			
RCT	Time Point	Tt	Ww	Risk Difference (95% Ci)	P-Value
Rovers	Baseline	9.8% (9/93)	11.9% (11/94)	-2.0% (-10.9% to 9.6%)	NS
	3 mos.	42.9% (40/93)	14.3% (13/94)	29.2% (16.9% to 41.4%)	<0.0001
	6 mos.	49.4% (46/93)	9.9% (9/94)	39.9% (28.1% to 51.7%)	<0.0001
	9 mos.	35.3% (33/93)	16.5% (16/94)	18.5% (6.1% to 30.8%)	<0.0001
	12 mos.	37.6% (35/93)	16.5% (16/94)	20.6% (8.2% to 33.1%)	<0.0001
	≤12 mos. (cumulative)	83% (77/93)	38% (36/94)	44.5% (32.0% to 57.0%)	<0.0001
TARGET	≤24 mos. (cumulative)	<2% of ears	0%	NC	NC
		Otorrhea Episodes/Year (Mean)			
RCT	Time Point	Tt	Ww	Mean Difference	P-Value
Mandel 1989	≤36 mos. (cumulative)	0.41 (n=30)	0.23 (n=29)	0.18	NR

NS: p-value ≥0.05

Appendix Table G3. AOM episodes: TT vs. WW for OME

		AOM Episodes/Year (Mean)		
Time Point	RCT	TT	WW	P-Value
≤12 mos. (cumulative)	Mandel 1992	0.23 (n=36)	0.95 (n=35)	<0.001
≤36 mos. (cumulative)	Mandel 1992	0.51 (n=36)	0.58 (n=35)	0.74
	Mandel 1989	0.18 (n=30)	0.38 (n=29)	NR

NS: p-value ≥0.05

Appendix Table G4. AOM or OME episodes: TT vs. WW for OME

		% Of Time Spent With AOM Or OME			
Time Point	**RCT**	**TT**	**WW**	**Mean Difference**	**P-Value**
0-6 mos.	Paradise	35% (n=183)	61% (n=183)	-26%	<0.001
0-12 mos.	Mandel 1989	16.4% (n=27)	56.3% (n=18)	-39.9%	<0.001
	Mandel 1992	17% (n=36)	64% (n=35)	-47%	<0.001
	Paradise	29% (n=159)	48% (n=157)	-19%	<0.001
12-24 mos.	Mandel 1989	20.4% (n=27)	28.2% (n=16)	-7.8%	NR
	Mandel 1992	49% (n=36)	38% (n=35)	11%	NR
0-18 mos.	Paradise	28% (n=121)	41% (n=118)	-13%	<0.001
0-24 mos.	Paradise	30% (n=57)	40% (n=62)	-10%	<0.001
24-36 mos.	Mandel 1989	25.0% (n=25)	19.2% (n=16)	5.8%	NR
	Mandel 1992	30% (n=36)	43% (n=35)	-13%	NR
0-36 mos.	Mandel 1989	21% (n=30)	38% (n=29)	-17%	NR
	Mandel 1992	31% (n=36)	49% (n=35)	-18%	NR
		AOM Or OME Present (% (N/N)			
Time Point	**RCT**	**TT**	**WW**	**Risk Difference (95% CI)**	**P-Value**
36-70 mos. (at age 6)	Paradise	10.9% (22/201)	11.9% (23/194)	-0.9% (-7.2% to 5.4%)	NS
~72-130 mos. (at age 9-11)	Paradise	6.2% (12/195)	5.1% (10/195)	1.1% (-3.6% to 5.6%)	NS

NS: p-value ≥0.05

Appendix Table G5. OME episodes: TT vs. WW for OME

		Bilateral OME present (% (n/N)			
RCT	**Time point**	**TT**	**WW**	**Risk difference (95% CI)**	**p-value**
Rovers	3 mos.	14.6% (14/93)	77.2% (73/94)	-62.6% (-73.7% to -51.5%)	<0.001
	6 mos.	29.3% (27/93)	65.9% (62/94)	-36.9% (-50.2% to -23.6%)	<0.001
	9 mos.	26.9% (25/93)	57.3% (54/94)	-30.6% (-44.0% to -17.1%)	<0.001
	12 mos.	26.6% (25/93)	53.2% (50/94)	-26.3% (-39.8% to -12.8%)	<0.001
	3, 6, 9, & 12 mos.	3% (3/93)	26.6% (25/94)	-23.3% (-33.0% to -13.7%)	<0.001

Appendix Table G6. Attention and behavioral outcomes: TT vs. WW for OME

				% Patients (n/N)		
RCT	Outcome Measure	Subscale	Time Point	TT	WW	P-Value
COMET	Richman Behavior Checklist score ≥10	-	Baseline	55% (41/75)	55% (33/60)	NS
		-	9 mos.	30% (25/84)	47% (31/66)	0.031
		-	18 mos.	24% (16/67)	20% (11/56)	NS

				Score (Mean ± SD)		
RCT	Outcome Measure*	Subscale	Time Point	TT	WW	P-Value
COMET	Richman Behavior Checklist score	-	9 mos.	8.2 ± 3.2 (n=84)	8.9 ± 4.1 (n=66)	NS
			18 mos.	7.9 ± 3.0 (n=84)	7.0 ± 3.5 (n=66)	NS
	Strengths and Difficulties Questionnaire (teacher-reported)	Total score	~28-82 mos. (age 7-8 yrs.)	9.1 (n=27)	10.4 (n=24)	NS
Paradise	Child Behavior Checklist (parent-reported)	Total Problems (z-scores)	~0-34 mos. (age 3)	50 ± 10 (n = 202)	49 ± 10 (n = 193)	NS
			~12-46 mos. (age 4)	50.1 ± 10.9 (n = 197)	49.2 ± 10.1 (n = 187)	NS
			~36-70 mos. (age 6)	49 ± 11 (n = 197)	48 ± 11 (n = 193)	NS
			~72-130 mos. (age 9-11)	51 ± 12 (n = 194)	48 ± 11 (n = 193)	0.0107
	" (teacher-reported)	Total Problems (z-scores)	~36-70 mos. (age 6)	49 ± 11 (n = 192)	48 ± 11 (n = 186)	NS
			~72-130 mos. (age 9-11)	52 ± 11 (n = 189)	50 ± 11 (n = 191)	0.0772
	Children's Disruptive Behavior Disorders Rating scale (parent-reported)	Inattention factor	~72-130 mos. (age 9-11)	0.70 ± 0.63 (n = 194)	0.65 ± 0.66 (n = 196)	NS
		Impulsivity and over activity factor		0.67 ± 0.57 (n = 194)	0.57 ± 0.54 (n = 196)	NS
		Oppositional defiant factor		0.57 ± 0.58 (n = 194)	0.52 ± 0.53 (n = 196)	NS
	" (teacher-reported)	Inattention factor	~72-130 mos. (age 9-11)	0.71 ± 0.74 (n = 190)	0.67 ± 0.75 (n = 192)	NS
		Impulsivity and over activity factor		0.48 ± 0.63 (n = 190)	0.40 ± 0.52 (n = 192)	NS

				Score (Mean ± SD)		
RCT	Outcome Measure*	Subscale	Time Point	TT	WW	P-Value
		Oppositional defiant factor		0.33 ± 0.56 (n = 190)	0.33 ± 0.58 (n = 192)	NS
	Impairment rating scales (parent-reported)	Overall functioning	~72-130 mos. (age 9-11)	0.82 ± 1.42 (n = 194)	0.68 ± 1.33 (n = 196)	NS
	" (teacher-reported)	Overall functioning		2.04 ± 2.24 (n = 190)	1.78 ± 2.19 (n = 192)	NS
	Social Skills rating system (parent-reported)	Social skills scale		96 ± 19 (n = 194)	98 ± 18 (n = 194)	NS
	" (teacher-reported)	Social skills scale		98 ± 13 (n = 184)	99 ± 13 (n = 186)	NS
	Visual Continuous Performance test	Inattention		9.7 ± 8.5 (n = 195)	9.5 ± 8.5 (n = 196)	NS
		Impulsivity		8.8 ± 16.5 (n = 195)	8.2 ± 15.6 (n = 196)	NS
	Auditory Continuous Performance test	Inattention		11.1 ± 7.2 (n = 155)	11.4 ± 8.0 (n = 153)	NS
		Impulsivity		3.3 ± 8.7 (n = 154)	4.2 ± 12.1 (n = 153)	NS

NS: p-value ≥0.05

Appendix Table G7. Academic achievement: TT vs. WW for OME

				Score (Mean ± SD)		
RCT	Outcome Measure	Subtest	Time Point	TT	WW	P-Value
COMET	UK local school entry tests	Language	~0-40 mos. (age 4.5 yrs.)	5.0 (n=76)	4.8 (n=60)	0.006†
		Reading		4.6 (n=76)	4.6 (n=60)	NS†
		Writing		4.7 (n=76)	4.5 (n=60)	0.004†
		Math		4.8 (n=76)	4.7 (n=60)	NS†
	SATS Key Stage 1	Reading	~28-82 mos. (age 7-8 yrs.)	2.6 (n=81)	2.5 (n=64)	NS†
		Writing		1.9 (n=81)	1.9 (n=64)	NS†
		Math		2.6 (n=81)	2.5 (n=64)	NS†
Paradise	Academic Achievement (Woodcock-Johnson III	Calculation	~72-130 mos. (age 9-11)	99 ± 13 (n=194)	99 ± 13 (n=195)	NS
	Tests of Achievement, Standard Battery)	Spelling		96 ± 13 (n=194)	97 ± 16 (n=196)	NS
		Writing		104 ± 14 (n=192)	105 ± 15 (n=195)	NS
	Literacy (Woodcock Reading Mastery Tests)	Word identification	~72-130 mos. (age 9-11)	98 ± 11 (n=195)	99 ± 12 (n=196)	NS
		Word attack		103 ± 13 (n=195)	104 ± 14 (n=196)	NS
		Page comprehension		98 ± 12 (n=195)	99 ± 12 (n=196)	NS
	Literacy (Oral reading fluency test)	- (grade 3)	~72-130 mos. (age 9-11)	78 ± 36 (n=37)	87 ± 41 (n=37)	NS
		- (grade 4)		89 ± 36 (n=87)	89 ± 38 (n=97)	NS
		- (grade 5)		97 ± 36 (n=54)	102 ± 37 (n=51)	NS
		- (grade 6)		102 ± 32 (n=12)	96 ± 43 (n=9)	NS

Appendix Table G8. Auditory processing: TT vs. WW for OME

		Speech-Recognition Threshold (Mean ± SD) (Db)			
Time Point	**RCT**	**TT**	**WW**	**Mean Difference (95% CI)**	**P-Value**
Baseline	Mandel 1989	19.2 (n=17)	16.2 (n=15)	3.0	NR
	Mandel 1992	19.1 (n=11)	18.5 (n=14)	0.6	NR
1 mos.	Mandel 1989	6.2 (n=17)	19.9 (n=15)	-13.7	NR
	Mandel 1992	12.5 (n=11)	18.4 (n=14)	-5.9	NR
2 mos.	Mandel 1989	7 (n=17)	17 (n=15)	-10	NR
	Mandel 1992	6.2 (n=11)	17.5 (n=14)	-11.3	NR
4 mos.	Mandel 1992	6.6 (n=11)	14.1 (n=14)	-7.5	NR
		Speech-In-Noise (Sin) Mccormick Automated Toy Test (Mean ± SD) Db SPL)			
Time Point	**RCT**	**TT**	**WW**	**Mean Difference (95% CI)**	**P-Value**
Baseline	MRC 2004 (subset of TARGET trial)	57.4 (n = 25)	55.8 (n = 31)	1.6	<0.044
3 mos.		51.3 ± 2.4 (n = 22)	52.8 ± 2.7 (n = 20)	-1.50 (-3.09 to 0.09)	0.06
3 mos.: change from baseline		-6.1	-3.0	-3.1	0.003
12 mos.		52.4 ± 3.4 (n = 27)	50.7 ± 2.0 (n = 16)	1.70 (-0.19 to 3.59)	0.08
12 mos.: change from baseline		-5.0	-5.1	0.1	NS
		SCAN Screening Test For Auditory Processing Disorders (Mean ± SD)			
Time point	**RCT**	**TT**	**WW**	**Mean Difference (95% CI)**	**P-Value**
~36-70 mos. (age 6)	Paradise	95 ± 15 (n = 178)	96 ± 14 (n = 177)	-1.0 (-4.0 to 2.0)	NS

		Hearing In Noise Test (Children's Version) (Mean ± SD) (Db)			
Time point	**RCT (subtest)**	**TT**	**WW**	**Mean Difference (95% CI)**	**P-Value**
~72-130 mos. (age 9-11)	Paradise (Competing noise from front)	–0.4 ± 1.7 (n = 195)	–0.6 ± 1.6 (n = 196)	0.2 (-0.1 to 0.5)	NS
	(Competing noise from right)	–7.0 ± 3.0 (n = 195)	–7.0 ± 2.4 (n = 196)	0.0 (-0.5 to 0.5)	NS
	(Competing noise from left)	–6.4 ± 2.5 (n = 195)	–6.8 ± 2.5 (n = 196)	0.4 (-0.1 to 0.9)	NS
		Speech-Recognition Threshold (Mean ± SD) (Db) In Right Ear At Any Time Point Through 36 Months			
Subgroup	**RCT**	**TT**	**WW**	**Mean Difference (95% CI)**	**P-Value**
Functioning tube	Mandel 1989	4.5 ± 2.5 (n=NR)	5.9 ± 3.1 (n=NR)	-1.4 (NC*)	NR
	Mandel 1992	6.9 ± 2.7 (n=33)	8.5 ± 4.5 (n=25)	-1.6 (-3.5 to 0.3)	0.0978
Intact eardrum, no effusion	Mandel 1989	6.2 ± 3.8 (n=NR)	7.1 ± 4.5 (n=NR)	-0.9 (NC*)	NR
	Mandel 1992	7.8 ± 3.8 (n=30)	8.3 ± 2.6 (n=27)	-0.5 (-2.2 to 1.2)	NS
Intact eardrum, with effusion	Mandel 1989	19 ± 8.7 (n=NR)	21.3 ± 5.7 (n=NR)	-2.3 (NC*)	NR†
	Mandel 1992	18.7 ± 6.0 (n=32)	21.4 ± 7.9 (n=34)	-2.7 (-6.2 to 0.8)	0.1246

NC: not calculable; NR: not reported; NS: p-value ≥0.05; SPL: sound pressure level

* Not calculable as patient numbers were not reported for each subgroup

† p<0.001 compared to threshold with functioning tube or intact eardrum without effusion

Appendix Table G9. Reynell or Schlichting test (Speech and Language): TT vs. WW for OME

Reynell Test Verbal Comprehension Standardized Scores (Mean ± SD)					
Time Point	**RCT**	**TT**	**WW**	**Mean Difference (95% CI)**	**P-Value**
6 mos.	Rovers	-0.06 ± 0.95 (n=93)	0.06 ± 1.05 (n=94)	-0.12 (-0.4 to 0.2)	NS
	Rach	0.17 ± 0.61† (n=22)	0.11 ± 0.55† (n=21)	0.06 (0.3 to 0.4)	NS
9 mos.	COMET	-0.04 ± 1.02† (n=87)	-0.35 ± 0.98† (n=77)	0.31 (0.0 to 0.62)	Adjusted‡: p=0.028
12 mos.	Rovers	0.87	0.59	0.28	NR
18 mos.	COMET	0.39 (n=81)	0.13 (n=71)	0.26	Adjusted‡: p=0.04
Expressive Language Standardized Scores (Mean ± SD)					
Time point	**RCT (test)**	**TT**	**WW**	**Mean Difference (95% CI)**	**P-Value**
6 mos.	Rovers (Schlichting)	-0.18 ± 1.19 (n=93)	0.17 ± 0.74 (n=94)	-0.35 (-0.64 to -0.06)	0.0166
	Rach (Reynell)	0.29 ± 0.75† (n=22)	0.18 ± 0.64† (n=21)	0.11 (-0.32 to 0.54)	NS
9 mos.	COMET (Reynell)	-0.62 ± 1.27† (n=87)	-1.00 ± 1.25† (n=76)	0.38 (-0.01 to 0.77)	Adjusted‡: p=NS
18 mos.	COMET (Reynell)	-0.07 (n=81)	-0.38 (n=71)	0.31	Adjusted‡: p=NS

NR: not reported; NS: p-value ≥0.05

† Data obtained from 2010 Cochrane report[1], which used patient-level data (all original studies missing some element of these data)

‡ Adjusted for baseline confounders

Appendix Table G10. Other Speech and Language outcome measures: TT vs. WW for OME

				Score (Mean ± SD)		
RCT	Outcome Measure	Subtest	Time Point	TT	WW	P-Value
COMET	Wechsler Objective Language Dimensions	Comprehension	~28-82 mos. (age 7-8 yrs.)	7.2 (n=35)	6.9 (n=33)	NS
		Oral expression		7.1 (n=34)	6.5 (n=32)	NS
	Children's Nonword Repetitive Task	Non-word total score		7.3 (n=35)	6.3 (n=32)	NS
Paradise	Receptive Language (Peabody Picture Vocabulary test-revised)	-	~0-34 mos. (age 3)	92 ± 13 (n = 203)	92 ± 15 (n = 192)	NS
			~12-46 mos. (age 4)	90.3 ± 14.5 (n = 202–204)	92.1 ± 15.7 (n = 193)	NS
			~36-70 mos. (age 6)	94 ± 14 (n = 200)	94 ± 20 (n = 193)	NS
	Expressive Language	Number of Different Words	~0-34 mos. (age 3)	124 ± 32 (n = 205)	126 ± 30 (n = 193)	NS
			~12-46 mos. (age 4)	149.9 ± 34.3 (n = 202–204)	149.6 ± 31.0 (n = 193)	NS
			~36-70 mos. (age 6)	183 ± 36 (n = 188)	175 ± 36 (n = 186)	NS
		Mean Length of Utterance (Morphemes)	~0-34 mos. (age 3)	2.7 ± 0.7 (n = 205)	2.8 ± 0.7 (n = 193)	NS
			~12-46 mos. (age 4)	3.4 ± 0.8 (n = 202–204)	3.4 ± 0.7 (n = 193)	NS
			~36-70 mos. (age 6)	3.9 ± 0.8 (n = 188)	3.8 ± 0.7 (n = 186)	NS
		Percentage of Consonants Correct-revised	~0-34 mos. (age 3)	85 ± 7 (n = 205)	86 ± 7 (n = 193)	NS
			~12-46 mos. (age 4)	92.0 ± 5.2 (n = 202–204)	92.7 ± 4.5 (n = 193)	NS
			~36-70 mos. (age 6)	96 ± 2 (n = 188)	96 ± 3 (n = 186)	NS
	Phonological memory (% total phonemes correct)	-	~12-46 mos. (age 4)	66.3 ± 11.9 (n = 153)	69.7 ± 12.3 (n = 151)	0.0149
			~36-70 mos. (age 6)	74 ± 10 (n = 182)	76 ± 10 (n = 176)	0.0593
	Phonological awareness (Comprehensive Test of Phonological	Elision	~72-130 mos. (age 9-11)	8.6 ± 4.9 (n = 195)	8.7 ± 3.0 (n = 196)	NS
		Rapid letter naming		9.3 ± 2.5 (n = 193)	9.6 ± 2.4 (n = 196)	NS

				Score (Mean ± SD)		
RCT	Outcome Measure	Subtest	Time Point	TT	WW	P-Value
	Processing)					

NR: not reported; NS: p-value ≥0.05

Appendix Table G11. Patient quality of life: TT vs. WW for OME

				Score (mean ± SEM)		
RCT	Outcome Measure*	Subtest	Time Point	TT	WW	P-Value
Rovers	TAIQOL (TNO-AZL Infant Quality of Life)	Vitality	Baseline	3.3 ± 0.8 (n=93)	3.3 ± 0.9 (n=91)	NS
			6 mos.	3.3 ± 0.9 (n=87)	3.3 ± 1.0 (n=89)	NS
			12 mos.	3.1 ± 0.5 (n=84)	3.2 ± 0.8 (n=81)	NS
		Appetite	Baseline	4.7 ± 1.5 (n=93)	4.4 ± 1.4 (n=91)	NS
			6 mos.	5.0 ± 1.4 (n=87)	4.7 ± 1.6 (n=89)	NS
			12 mos.	5.3 ± 1.6 (n=84)	4.9 ± 1.4 (n=81)	NS
		Communication	Baseline	6.8 ± 2.3 (n=93)	6.4 ± 2.0 (n=91)	NS
			6 mos.	6.7 ± 2.3 (n=87)	5.8 ± 2.1 (n=89)	NS
			12 mos.	5.9 ± 2.0 (n=84)	5.6 ± 1.9 (n=81)	NS
		Motoric	Baseline	5.8 ± 2.5 (n=93)	6.1 ± 2.8 (n=91)	NS
			6 mos.	4.4 ± 0.9 (n=87)	4.4 ± 1.1 (n=89)	NS
			12 mos.	4.2 ± 0.8 (n=84)	4.2 ± 1.0 (n=81)	NS
		Social	Baseline	3.6 ± 0.9 (n=93)	3.5 ± 0.8 (n=91)	NS
			6 mos.	4.4 ± 0.9 (n=87)	3.5 ± 0.9 (n=89)	NS
			12 mos.	3.5 ± 0.9 (n=84)	3.5 ± 0.9 (n=81)	NS
		Anxiety	Baseline	4.1 ± 1.2 (n=93)	4.0 ± 1.1 (n=91)	NS
			6 mos.	4.3 ± 1.1 (n=87)	4.1 ± 1.0 (n=89)	NS
			12 mos.	4.6 ± 1.3	4.3 ± 1.1	NS

				Score (mean ± SEM)		
RCT	Outcome Measure*	Subtest	Time Point	TT	WW	P-Value
				(n=84)	(n=81)	
		Aggression	Baseline	11.3 ± 2.2 (n=93)	10.9 ± 2.2 (n=91)	NS
			6 mos.	11.9 ± 2.4 (n=87)	11.1 ± 2.0 (n=89)	NS
			12 mos.	11.8 ± 2.4 (n=84)	11.5 ± 2.0 (n=81)	NS
		Eating	Baseline	3.4 ± 0.7 (n=93)	3.4 ± 0.6 (n=91)	NS
			6 mos.	3.3 ± 0.6 (n=87)	3.5 ± 0.8 (n=89)	NS
			12 mos.	3.3 ± 0.5 (n=84)	3.4 ± 0.6 (n=81)	NS
		Sleeping	Baseline	7.1 ± 2.2 (n=93)	6.8 ± 2.1 (n=91)	NS
			6 mos.	6.8 ± 2.1 (n=87)	6.6 ± 1.9 (n=89)	NS
			12 mos.	6.4 ± 2.2 (n=84)	6.4 ± 1.9 (n=81)	NS

Appendix Table G12. Patient and parent interaction: quality of life: TT vs. WW for OME

				Score (mean ± SEM)		
RCT	Outcome Measure*	Subtest	Time Point	TT	WW	P-Value
Rovers	Erikson Child-Parent Interaction	Parent hostility	Baseline	6.9 ± 0.7 (n=93)	6.9 ± 0.3 (n=91)	NS
			6 mos.	7.0 ± 0.2 (n=87)	6.9 ± 0.5 (n=89)	NS
			12 mos.	7.0 ± 0.2 (n=84)	7.0 ± 0.2 (n=81)	NS
		Parent structure	Baseline	4.6 ± 1.4 (n=93)	5.1 ± 1.2 (n=91)	NS
			6 mos.	4.8 ± 1.5 (n=87)	5.2 ± 1.2 (n=89)	NS
			12 mos.	4.8 ± 1.4 (n=84)	5.5 ± 1.0 (n=81)	NS
		Parent respect	Baseline	4.9 ± 1.4 (n=93)	5.3 ± 1.3 (n=91)	NS
			6 mos.	4.9 ± 1.3 (n=87)	5.4 ± 1.3 (n=89)	NS
			12 mos.	5.0 ± 1.3 (n=84)	5.3 ± 1.2 (n=81)	NS
		Parent	Baseline	4.9 ± 1.5	5.4 ± 1.3	NS

				Score (mean ± SEM)		
RCT	Outcome Measure*	Subtest	Time Point	TT	WW	P-Value
		supportive		(n=93)	(n=91)	
			6 mos.	4.9 ± 1.4 (n=87)	5.4 ± 1.4 (n=89)	NS
			12 mos.	5.0 ± 1.4 (n=84)	5.5 ± 1.2 (n=81)	NS
		Parent quality	Baseline	4.5 ± 1.6 (n=93)	5.0 ± 1.4 (n=91)	NS
			6 mos.	4.4 ± 1.5 (n=87)	5.2 ± 1.3 (n=89)	NS
			12 mos.	4.7 ± 1.4 (n=84)	5.3 ± 1.3 (n=81)	NS
		Child affection	Baseline	4.5 ± 1.4 (n=93)	4.7 ± 1.4 (n=91)	NS
			6 mos.	4.4 ± 1.3 (n=87)	4.6 ± 1.3 (n=89)	NS
			12 mos.	4.5 ± 1.4 (n=84)	4.9 ± 1.1 (n=81)	NS
		Child avoidance	Baseline	5.9 ± 1.5 (n=93)	6.2 ± 1.4 (n=91)	NS
			6 mos.	6.3 ± 1.1 (n=87)	6.5 ± 1.2 (n=89)	NS
			12 mos.	6.5 ± 0.9 (n=84)	6.9 ± 0.4 (n=81)	NS
		Child compliance	Baseline	4.6 ± 1.6 (n=93)	5.1 ± 1.4 (n=91)	NS
			6 mos.	5.1 ± 1.3 (n=87)	5.2 ± 1.3 (n=89)	NS
			12 mos.	5.2 ± 1.1 (n=84)	5.6 ± 1.0 (n=81)	NS
		Child negativism	Baseline	6.2 ± 1.5 (n=93)	6.5 ± 1.2 (n=91)	NS
			6 mos.	6.6 ± 1.0 (n=87)	6.7 ± 0.8 (n=89)	NS
			12 mos.	6.6 ± 1.1 (n=84)	6.9 ± 1.1 (n=81)	NS
		Child reliance	Baseline	6.5 ± 0.8 (n=93)	6.5 ± 1.0 (n=91)	NS
			6 mos.	6.5 ± 0.9 (n=87)	6.7 ± 0.7 (n=89)	NS
			12 mos.	6.6 ± 0.7 (n=84)	6.8 ± 0.4 (n=81)	NS

				Score (mean ± SD)		
RCT	Outcome measure*	Subtest	Time point	TT	WW	p-value
Paradise	Parent-Child Stress (Parenting Stress Index, Short-Form)	Parental Distress	~0-34 mos. (age 3)	23 ± 8 (n = 206)	24 ± 9 (n = 193)	NS
			~12-46 mos. (age 4)	23.4 ± 7.7 (n = 201)	22.3 ± 7.2 (n = 189)	NS
			~36-70 mos. (age 6)	22 ± 7 (n = 194)	23 ± 8 (n = 189)	NS
		Parent-Child Dysfunctional Interaction	~0-34 mos. (age 3)	18 ± 6 (n = 206)	18 ± 6 (n = 193)	NS
			~12-46 mos. (age 4)	18.4 ± 6.1 (n = 201)	18.2 ± 5.9 (n = 189)	NS
			~36-70 mos. (age 6)	19 ± 6 (n = 194)	19 ± 7 (n = 189)	NS
		Difficult Child	~0-34 mos. (age 3)	25 ± 8 (n = 206)	26 ± 9 (n = 193)	NS
			~12-46 mos. (age 4)	26.1 ± 7.8 (n = 201)	24.8 ± 7.8 (n = 189)	NS
			~36-70 mos. (age 6)	25 ± 8 (n = 194)	25 ± 9 (n = 189)	NS
		Total stress	~0-34 mos. (age 3)	66 ± 18 (n = 206)	68 ± 21 (n = 193)	NS
			~12-46 mos. (age 4)	68.0 ± 18.4 (n = 201)	65.3 ± 17.7 (n = 189)	NS
			~36-70 mos. (age 6)	66 ± 19 (n = 194)	66 ± 22 (n = 189)	NS

Appendix Table G13. Pain: TT vs. WW for OME

		Earache (parent-reported) (% (n/N)			
RCT	**Time point**	**TT**	**WW**	**Risk difference (95% CI)**	**p-value**
Rovers	Baseline	18.7% (17/93)	29.7% (28/94)	-11.5% (-23.6% to 0.6%)	0.0664
	3 mos.	22.0% (20/93)	18.7% (18/94)	2.4% (-9.2% to 13.9%)	0.6896
	6 mos.	27.9% (26/93)	17.6% (17/94)	9.9% (-2.1% to 21.9%)	0.1097
	9 mos.	23.5% (22/93)	19.8% (19/94)	3.4% (-8.4% to 15.3%)	0.5704
	12 mos.	21.1% (20/93)	17.7% (17/94)	3.4% (-8.0% to 14.8%)	0.5583
		Fever (parent-reported) (% (n/N)			
RCT	**Time point**	**TT**	**WW**	**Risk difference (95% CI)**	**p-value**
Rovers	Baseline	51.1% (48/93)	45.6% (43/94)	5.9% (-8.4% to 20.2%)	0.4234
	3 mos.	43.3% (40/93)	34.1% (32/94)	9.0% (-4.9% to 22.9%)	0.2088
	6 mos.	36.8% (34/93)	37.8% (36/94)	-1.7% (-15.6% to 12.1%)	0.8065
	9 mos.	38.1% (35/93)	48.8% (46/94)	-11.3% (-2.4% to 2.8%)	0.1199
	12 mos.	34.8% (32/93)	34.5% (32/94)	0.4% (-13.2% to 14.0%)	0.9580

Appendix Table G14. Surgery after initial treatment protocol: TT vs. WW for OME

			% (n/N)			
Surgery	RCT	Time point	TT	WW	Risk difference (95% CI)	p-value
Tubes*	Paradise	≤1 mos.	NR	2.0% (4/196)	NC	NC
		≤2 mos.	NR	4.6% (9/196)	NC	NC
		≤6 mos.	NR	11.2% (22/196)	NC	NC
		~0-34 mos. (age 3)	NR	33.2% (65/196)	NC	NC
		~12-46 mos. (age 4)	NR	38.3% (75/196)	NC	NC
		~36-70 mos. (age 6)	NR	40.3% (79/196)	NC	NC
		~72-130 mos. (age 9-11)	NR	45.0% (88/196)	NC	NC
	COMET	9 mos.	NR	48% (43/90)	NC	NC
	Rovers	0-6 mos.	9% (8/93)	NR		
	Rovers	0-12 mos.	NR	10.6% (10/94)	NC	NC
	COMET	0-18 mos.	19% (17/90)	88% (79/90)	-69% (-79% to -58%)	<0.001
	Mandel 1989	≤12 mos.	15% (4/27)	52% (13/25)	-37% (-61% to -13%)	0.0047
	Mandel 1992	≤12 mos.	2.9% (1/34)	56% (19/34)	-53% (-71% to -35%)	<0.001
	Mandel 1989	12-24 mos.	33% (9/27)	25% (4/16)	8% (-19% to 36%)	NS
	Mandel 1992	12-24 mos.	23% (7/30)	33% (11/33)	-10% (-32% to 12%)	NS
	Mandel 1989	24-36 mos.	8% (2/25)	6% (1/16)	2% (-14% to 18%)	NS
	Mandel 1992	24-36 mos.	22% (6/28)	28% (8/29)	-6% (-28% to 16%)	NS
	Mandel 1992	0-36 mos.	35% (13/37)	71% (25/35)	-36% (-58% to -15%)	0.0022
Tubes ± adenoidectomy ± tonsillectomy	TARGET	≤3 mos.	0.8% (1/126)	9.8% (12/122)	-9.0% (-14.6% to -3.5%)	0.0014
		3-12 mos.	2.4% (3/126)	33.6% (41/122)	-31.2% (-40.0% to -22.4%)	<0.001
		12-24 mos.	10.3% (13/126)	14.8% (18/122)	-4.4% (-12.7% to 3.8%)	0.2919
		0-24 mos.	12.7% (16/126)	56.6% (69/122)	-43.9% (-54.4% to -33.3%)	<0.001

* Data do not include initial placement of tubes in the TT group.

Appendix Table G15. Medication usage: TT vs. WW for OME

			% (n/N)			
RCT	Time Point	Medication Use	TT	WW	Risk Difference (95% CI)	P-Value
Rovers	≥12 mos.	≥1 course of antibiotics	34% (32/93)	22% (21/94)	12% (-1% to 25%)	0.0678
		≥2 courses of antibiotics	20% (19/93)	12% (11/94)	9% (-2% to 19%)	0.1049
		≥1 course of antibiotic ear drops	62%* (57/93)	10% (9/94)	52% (40% to 63%)	<0.0001
		≥2 courses of antibiotic ear drops	41% (38/93)	4% (4/94)	37% (26% to 47%)	<0.0001

* The study reported that 57 TT children (39%) were prescribed antibiotic ear drops and that 38 received more than one course. If 57 TT children received antibiotics, then this would correlate with 62% of TT patients, which is quite different than the 39% reported by the study.

Appendix Table G16. Hearing levels by ear: TT (one ear) vs. no treatment (opposite ear) for OME

		Hearing Level (Mean ± SD) (Db) (Air Conduction/Audiometry*)			
Time Point	RCT	TT (Unilateral)	No Treatment (Contralateral)	Mean Difference (95% CI)	P-Value
Baseline	Dempster	33.5 ± 6.3 (35 ears)	32.4 ± 7.1 (35 ears)	1.0 (-2.1 to 4.3)	NS
6 mos.	Black	NR (37 ears)	NR (37 ears)	-3.5 (-6.9 to -0.1)	<0.05
	Dempster	13.2 ± 9.0 (35 ears)	18.0 ± 13.0 (35 ears)	-4.8 (-10.1 to 0.5)	0.0769
	Lildholdt	~12 (72 ears†)	~14 (72 ears†)	~-2	NS
	Maw & Bawden	18.3 ± 9.1 (65 ears)	29.6 ± 10.9 (65 ears)	-11.3 (-14.8 to -7.8)	<0.001
12 mos.	Black	NR (37 ears)	NR (37 ears)	-1.0 (-4.2 to 2.1)	NS
	Dempster	15.9 ± 8.4 (35 ears)	15.6 ± 8.4 (35 ears)	0.3 (-3.7 to 4.3)	NS
	Lildholdt	~12 (70 ears†)	~12 (70 ears†)	~0	NS
	Maw & Bawden	19.8 ± 9.6 (78 ears)	28.6 ± 10.9 (76 ears)	-8.8 (-12.1 to -5.5)	<0.001
24 mos.	Black	NR (37 ears)	NR (37 ears)	2.4 (-3.9 to 8.7)	NS
	Lildholdt	~14 (65 ears†)	~14 (65 ears†)	~0	NS
	Maw &	20.9 ± 9.3	26.3 ± 11.4	-5.4 (-8.9 to -1.9)	0.0026

Time Point	RCT	Hearing Level (Mean ± SD) (Db) (Air Conduction/Audiometry*) TT (Unilateral)	No Treatment (Contralateral)	Mean Difference (95% CI)	P-Value
	Bawden	(69 ears)	(71 ears)		
36 mos.	Lildholdt	~13 (48 ears†)	~13 (48 ears†)	~0	NS
	Maw & Bawden	19.8 ± 9.4 (57 ears)	23.5 ± 10.5 (65 ears)	-3.7 (-7.3 to -0.1)	0.0437
48 mos.	Lildholdt	~10 (24 ears†)	~10 (24 ears†)	~0	NS
	Maw & Bawden	18.7 ± 7.3 (53 ears)	20.0 ± 8.8 (60 ears)	-1.3 (-4.3 to 1.7)	NS
60 mos.	Maw & Bawden	17.6 ± 7.0 (47 ears)	19.4 ± 8.6 (56 ears)	-1.8 (-4.9 to 1.3)	NS
84 mos.	Maw & Bawden	15.6 ± 6.2 (35 ears)	17.9 ± 9.0 (43 ears)	-2.3 (-5.9 to 1.3)	NS
120 mos.	Maw & Bawden	15.5 ± 7.1 (15 ears)	16.6 ± 8.8 (20 ears)	-1.1 (-6.7 to 4.5)	NS
Time Point	**RCT**	**Hearing Level (Mean ± SD) (Db) (Air Bone Gap‡) TT (Unilateral)**	**No Treatment (Contralateral)**	**Mean Difference (95% Ci)**	**P-Value**
Baseline	Dempster	33.0 ± 6.7 (35 ears)	32.2 ± 7.0 (35 ears)	0.8 (-2.5 to 4.1)	NS
6 mos.	Dempster	17.3 ± 11.3 (35 ears)	22.6 ± 11.0 (35 ears)	-5.3 (-10.6 to 0.02)	0.0508
12 mos.	Dempster	17.9 ± 9.9 (35 ears)	17.2 ± 10.0 (35 ears)	0.9 (-4.0 to 5.4)	NS

NS: p-value ≥0.05

* Hearing measured by:
- Black: pure tone audiogram (measured from 250 to 4000 Hz)
- Dempster: air conduction (measured at 500, 1000, and 2000 Hz).
- Lildholdt: audiography (no details reported)
- Maw & Bawden: pure tone audiography (measured from 250 to 8000 Hz)

† Lildholdt: hearing levels measured in the subset of patients aged 5-10 years (and not patients aged 1-4 years).

‡ Hearing measured by:
- Dempster: air bone gap (measured at 500, 1000, and 2000 Hz).

Appendix Table G17. OME recurrence by ear: TT (one ear) vs. no treatment (opposite ear) for OME

		OME Present (By Otoscopy) (% Ears)			
RCT	**Time Point**	**TT (Unilateral)**	**No Treatment (Contralateral)**	**Risk Difference (95% CI)**	**P-Value**
Dempster	6 mos.	14% (5/35)	74% (26/35)	-60% (-79% to -41%)	<0.0001
Maw & Bawden		17% (13/78)	80% (57/71)	-64% (-76% to -51%)	<0.0001
Dempster	12 mos.	31% (11/35)	63% (22/35)	-31% (-54% to -9%)	0.0089
Maw & Bawden		37% (29/78)	78% (62/79)	-41% (-55% to -27%)	<0.0001
	24 mos.	31% (22/70)	63% (45/72)	-31% (-47% to -15%)	0.0002
	36 mos.	35% (20/57)	41% (24/59)	-6% (-23% to 12%)	NS
	48 mos.	24% (12/51)	41% (24/59)	-17% (-34% to -0.04%)	0.0571
	60 mos.	7% (3/45)	31% (17/55)	-24% (-38% to -10%)	0.0027
	84 mos.	12% (4/33)	15% (6/40)	-3% (-19% to 13%)	NS
	120 mos.	7% (1/15)	10% (2/21)	-3% (-21% to 15%)	NS
		OME Present (By Tympanometry) (% Ears)			
Study	**Time Point**	**TT (Unilateral)**	**No Treatment (Contralateral)**	**Risk Difference (95% CI)**	**P-Value**
Dempster	6 mos.	34% (12/35)	79% (28/35)	-46% (-66% to -25%)	0.0001
	12 mos.	46% (16/35)	68% (24/35)	-23% (-45% to 0%)	0.0551
Lildholdt	38 mos. (mean)	41.3% (62/150)	48.7% (73/150)	-7.3% (-18.6% to 3.9%)	0.2025

Appendix Table G18. Hearing levels: TT vs. Myringotomy for OME

RCT	Time Point	Hearing Level (Mean ± SD) (Db) (Air Conduction/Audiometry*)		Mean Difference (95% Ci)	P-Value
		Tt (Unilateral)	Myringotomy (Contralateral)		
Black	**6 mos.**	NR (37 ears)	NR (37 ears)	-7.4 (-13.4 to -1.4)	<0.05
	12 mos.	NR (37 ears)	NR (37 ears)	-3.7 (-7.8 to 0.4)	NS
	24 mos.	NR (37 ears)	NR (37 ears)	-0.9 (-4.6 to 2.7)	NS
		Appointments With Hearing Levels ≥20 Db) (%)			
Time Point	**RCT**	**TT**	**Myringotomy**	**Mean Difference (95% CI)**	**P-Value**
≤24 mos. (cumulative)	Gates (better ear)	10.1 ± 14.1% (n=150)	18.6 ± 19.5% (n=127)	-8.5% (-12.5% to -4.5%)	<0.001
	Gates (worse ear)	30.4 ± 22.7% (n=150)	37.5 ± 25.3% (n=127)	-7.1% (-12.8% to -1.4%)	0.0145

NS: p-value ≥0.05

* Hearing measured by:

- Black: pure tone audiogram (measured from 250 to 4000 Hz)

Appendix Table G19. Otorrhea: TT vs. Myringotomy for OME

		Otorrhea (% (n/N))			
RCT	Time Point	TT	Myringotomy	Risk Difference (95% Ci)	P-Value
D'Eredita*	≤3 mos. (cumulative)	27% (4/15 patients)	13% (2/15 patients)	13% (-15% to 42%)	NS
Kent	3 mos.	0% (0/30 ears)	3% (1/30)	-3% (-10% to 3%)	NS
	6 mos.	0% (0/30 ears)	3% (1/30)	-3% (-10% to 3%)	NS
Gates†	≤24 mos. (cumulative)	29% (37/129 patients)	22% (24/107 patients)	6.3% (-4.5% to 17.4%)	NS
		Otorrhea Episodes/Year (Mean)			
RCT	Time Point	TT	Myringotomy	Mean Difference	P-Value
Mandel 1989 (no hearing loss subgroup)	≤36 mos. (cumulative)	0.41 (n=30)	0.15 (n=27)	0.26	NR
Mandel 1989 (hearing loss subgroup)	≤36 mos. (cumulative)	0.61 (n=11)	0.34 (n=12)	0.27	NR

NS: p-value ≥0.05

* Parent-reported otorrhea

† Gates: Distribution of episodes of patients with purulent otorrhea (%):

- 0 episodes: 71% (92/129) vs. 78% (83/107) (p=NS)
- 1 episode: 18% (23/129) vs. 13% (14/107) (p=NS)
- 2 episodes: 5% (6/129) vs. 6% (7/107) (p=NS)
- ≥3 episodes: 6% (8/129) vs. 3% (3/107) (p=NS)

Appendix Table G20. AOM episodes: TT vs. Myringotomy for OME

		AOM Episodes/Year (Mean)			
Time Point	RCT	TT	Myringotomy	Mean Difference (95% CI)	P-Value
≤12 mos. (cumulative)	Mandel 1992	0.23 (n=36)	0.81 (n=38)	-0.58	<0.001
≤36 mos. (cumulative)	Mandel 1992	0.51 (n=36)	0.57 (n=38)	-0.06	NS
	Mandel 1989* (no hearing loss subgroup)	0.18 (n=30)	0.58 (n=27)	-0.40	NR
	Mandel 1989* (hearing loss subgroup)	0.41 (n=11)	0.31 (n=12)	0.10	NR

		% Of Time Spent With AOM			
Time Point	**RCT**	**TT**	**Myringotomy**	**Mean Difference**	**P-Value**
0-24 mos.	Gates	4.1% ± 5.9% (n=129)	4.5% ± 5.2% (n=107)	-0.4% (-1.8% to 1.0%)	NS
		AOM Present (% (n/N)			
Time Point	**RCT**	**TT**	**Myringotomy**	**Risk Difference (95% CI)**	**P-Value**
0-24 mos.	Gates	35.7% (46/129)	44.9% (48/107)	-9.2% (-21.7% to 3.3%)	NS

NS: p-value ≥0.05

* Mandel 1989 weighted mean from both subgroups: TT: 0.24 (n=41); myringotomy: 0.50 (n=39); MD -0.26, p=NR.

Appendix Table G21. AOM or OME episodes: TT vs. Myringotomy for OME

		% Of Time Spent With AOM Or OME			
Time Point	**RCT**	**TT**	**Myringotomy**	**Mean Difference (95% CI)**	**P-Value**
0-12 mos.	Mandel 1989 (no hearing loss subgroup)	16.4% (n=27)	56.6% (n=24)	-40.2%	<0.001
	Mandel 1989 (hearing loss subgroup)	9.8% (n=11)	56.7% (n=12)	-46.9%	<0.001
	Mandel 1992	17% (n=36)	61% (n=38)	-44%	0.01
12-24 mos.	Mandel 1989 (no hearing loss subgroup)	20.4% (n=27)	35.2% (n=21)	-14.8%	NR
	Mandel 1989 (hearing loss subgroup)	28.3% (n=9)	39.9% (n=11)	-11.6%	NR
	Mandel 1992	49% (n=36)	29% (n=38)	20%	NR
24-36 mos.	Mandel 1989 (no hearing loss subgroup)	25.0% (n=25)	25.5% (n=17)	-0.5%	NR
	Mandel 1989 (hearing loss subgroup)	30.3% (n=9)	14.4% (n=11)	15.9%	NR
	Mandel 1992	30% (n=36)	31% (n=38)	-1%	NR
0-24 mos.	Gates	34.9 ± 23.5% (n=129)	49.1 ± 25.2% (n=107)	-14.2% (-20.5% to -7.9%)	<0.0001
0-36 mos.	Mandel 1989 (no hearing loss subgroup)	21.0% (n=30)	41.0% (n=27)	-20%	NR

		% Of Time Spent With AOM Or OME			
Time Point	RCT	TT	Myringotomy	Mean Difference (95% CI)	P-Value
	Mandel 1989 (hearing loss subgroup)	22% (n=11)	38% (n=12)	-16%	NR
	Mandel 1992	31% (n=36)	41% (n=38)	-10%	NR

NS: p-value ≥0.05

Appendix Table G22. OME episodes: TT vs. Myringotomy for OME

		OME Present (% (n/N)			
Time Point	RCT	TT	Myringotomy	Risk Difference (95% CI)	P-Value
3 mos.	Kent	0% (0/30)	7% (2/30)	-7% (-16% to 2%)	0.1538
	Koopman	18.5% (38/208)	62.9% (131/208)	-44.7% (-53.1% to -36.3%)	<0.0001
6 mos.	Kent	3% (1/30)	40% (12/30)	-37% (-55% to -18%)	0.0006
	Koopman	29.3% (61/208)	60.9% (127/208)	-31.7% (-40.8% to -22.7%)	<0.0001
0-24 mos.	Gates	85.3% (110/129)	89.7% (96/107)	-4.5% (-12.9% to 4.0%)	NS
		% Of Time Spent With OME			
Time Point	RCT	TT	Myringotomy	Mean Difference	P-Value
0-24 mos.	Gates	31.8% ± 23.2% (n=129)	46.6% ± 24.5% (n=107)	-14.8% (-20.9% to -8.7%)	<0.0001

Appendix Table G23. Auditory processing: TT vs. Myringotomy for OME

		Speech-Recognition Threshold (Mean ± SD) (Db)			
Time Point	**RCT**	**TT**	**Myringotomy**	**Mean Difference (95% CI)**	**P-Value**
Baseline	Mandel 1989 (no hearing loss subgroup)	19.2 (n=17)	17.2 (n=19)	2.0	NR
	Mandel 1989 (hearing loss subgroup)	33.6 (n=6)	30.2 (n=4)	3.4	NR
	Mandel 1992	19.1 (n=11)	16.8 (n=15)	2.3	NR
1 mos.	Mandel 1989 (no hearing loss subgroup)	6.2 (n=17)	15.3 (n=19)	-9.1	NR
	Mandel 1989 (hearing loss subgroup)	6.4 (n=6)	15.8 (n=4)	-9.4	NR
	Mandel 1992	12.5 (n=11)	15.5 (n=15)	-3.0	NR
2 mos.	Mandel 1989 (no hearing loss subgroup)	7 (n=17)	16.9 (n=19)	-9.9	NR
	Mandel 1989 (hearing loss subgroup)	5.5 (n=6)	26.7 (n=4)	-21.2	NR
	Mandel 1992	6.2 (n=11)	14.8 (n=15)	-8.6	NR
4 mos.	Mandel 1992	6.6 (n=11)	16.9 (n=15)	-10.3	NR

		Speech-Recognition Threshold (Mean ± SD) (Db) In Right Ear At Any Time Point Through 36 Months			
Subgroup	**RCT**	**TT**	**Myringotomy**	**Mean Difference (95% CI)**	**P-Value**
Functioning tube	Mandel 1989 (no hearing loss subgroup)	4.5 ± 2.5 (n=NR)	5.1 ± 2.9 (n=NR)	-0.6 (NC*)	NR
	Mandel 1989 (hearing loss subgroup)	6.8 ± 3.5 (n=NR)	5.8 ± 3.6 (n=NR)	1.0 (NC*)	NR
	Mandel 1992	6.9 ± 2.7 (n=33)	7.3 ± 3.6 (n=26)	-0.4 (-2.0 to 1.2)	NS
Intact eardrum, no effusion	Mandel 1989 (no hearing loss subgroup)	6.2 ± 3.8 (n=NR)	7.4 ± 3.8 (n=NR)	-1.2 (NC*)	NR
	Mandel 1989 (hearing loss subgroup)	5.6 ± 4.0 (n=NR)	7.9 ± 3.7 (n=NR)	-2.3 (NC*)	NR
	Mandel 1992	7.8 ± 3.8 (n=30)	8.3 ± 3.8 (n=29)	-0.5 (-2.5 to 1.5)	NS

		Speech-Recognition Threshold (Mean ± SD) (Db) In Right Ear At Any Time Point Through 36 Months			
Subgroup	**RCT**	**TT**	**Myringotomy**	**Mean Difference (95% CI)**	**P-Value**
Intact eardrum, with effusion	Mandel 1989 (no hearing loss subgroup)	19 ± 8.7 (n=NR)	17.5 ± 4.7 (n=NR)	1.5 (NC*)	NR†
	Mandel 1989 (hearing loss subgroup)	26.3 ± 7.7 (n=NR)	20.9 ± 8.7 (n=NR)	5.4 (NC*)	NR†
	Mandel 1992	18.7 ± 6.0 (n=32)	21.3 ± 6.0 (n=36)	-2.6 (-5.5 to 0.3)	0.0791

*not calculable as patient numbers were not reported for each subgroup

Appendix Table G24. Pain: TT vs. Myringotomy for OME

		Earache (Parent-Reported) (% (n/N))			
Rct	**Time Point**	**Tt**	**Myringotomy**	**Risk Difference (95% Ci)**	**P-Value**
Kent	1 mos.	3% (1/30)	3% (1/30)	0% (-9% to 9%)	NS
	2 mos.	7% (2/30)	10% (3/30)	-3% (-17% to 11%)	NS
	3 mos.	7% (2/30)	17% (5/30)	-10% (-26% to 6%)	NS
	6 mos.	10% (3/30)	23% (7/30)	-13% (-32% to 5%)	NS

Appendix Table G25. Surgery after initial treatment protocol: TT vs. Myringotomy for OME

			% (n/N)			
Surgery	**RCT**	**Time Point**	**TT**	**Myringotomy**	**Risk Difference (95% CI)**	**P-Value**
Tubes*	Mandel 1989† (no hearing loss subgroup)	≤12 mos.	15% (4/27)	58% (15/26)	-43% (-66% to -20%)	0.0013
	Mandel 1989† (hearing loss subgroup)	≤12 mos.	10% (1/10)	67% (8/12)	-57% (-89% to -24%)	0.0085
	Mandel 1992	≤12 mos.	3% (1/34)	64% (23/36)	-61% (-78% to -44%)	<0.001
	Mandel 1989† (no hearing loss subgroup)	12-24 mos.	33% (9/27)	33% (7/21)	0% (-27% to 27%)	NS
	Mandel 1989† (hearing loss subgroup)	12-24 mos.	44% (4/9)	73% (8/11)	-28% (-70% to 14%)	NS
	Mandel 1992	12-24 mos.	23% (7/30)	26% (9/34)	-3% (-24% to 18%)	NS
	Mandel 1989† (no hearing loss subgroup)	24-36 mos.	8% (2/25)	24% (4/17)	-16% (-38% to 7%)	NS
	Mandel 1989† (hearing loss subgroup)	24-36 mos.	44% (4/9)	27% (3/11)	17% (-25% to 59%)	NS
	Mandel 1992	24-36 mos.	22% (6/28)	16% (5/31)	5% (-15% to 25%)	NS
Surgical retreatment‡	Gates	0-24 mos.	24.0% (31/129)	45.8% (49/107)	-21.8% (-33.7% to -9.8%)	0.0005
Myringoplasty	D'Eredita	12 mos.	7% (1/15)	0% (0/15)	7% (NC)	NS

* Data do not include initial placement of tubes in the TT group.

† Mandel 1989 pooled data from no hearing loss and hearing loss subgroups (TT vs. myringotomy):

- 0-12 months: 14% (5/37) vs. 61% (23/38)
- 12-24 months: 36% (13/36) vs. 47% (15/32)
- 24-36 months: 18% (6/34) vs. 25% (7/28)

‡ Gates 1987, 1989: most surgical retreatments were done according to the protocol, however patients were able to select an alternative treatment (further details NR)

Appendix Table G26. Medication usage: TT vs. Myringotomy for OME

			% (n/N)			
RCT	Time Point	Medication Use	TT	Myringotomy	Risk Difference (95% CI)	P-Value
Gates	≥24 mos.	Medical retreatment for chronic otitis media	84.5% (109/129)	88.9% (95/107)	-4.3% (-12.9% to 4.4%)	NS
		Medical retreatment for AOM	48.1% (62/129)	56.1% (60/107)	-8.0% (-20.1% to 4.8%)	NS
			Mean Number Of Medical Retreatments Per Child			
RCT	Time Point	Medication Use	TT	Myringotomy	Mean Difference (95% Ci)	P-Value
Gates	≥24 mos.	Medical retreatment for OME	2.55 ± 1.75 (n=129)	3.30 ± 1.69 (n=107)	-0.75 (-1.19 to -0.31)	0.0010
Gates	≥24 mos.	Medical retreatment for AOM	1.23 ± 1.84 (n=129)	1.12 ± 1.27 (n=107)	0.11 (-0.30 to 0.52)	NS

Appendix Table G27. Office visits: TT vs. Myringotomy for OME

			% (n/N)			
RCT	Time Point	Office Visits	TT	Myringotomy	Risk Difference (95% CI)	P-Value
Gates	≥24 mos.	Unscheduled office visits for illness	44.2% (57/129)	41.1% (44/107)	3.1% (-9.6% to 15.7%)	NS
			Mean Number Of Office Visits For Illness Per Child			
RCT	Time Point	Office Visits	TT	Myringotomy	Mean Difference (95% CI)	P-Value
Gates	≥24 mos.	Unscheduled office visits for illness	0.8 ± 1.4 (n=129)	0.7 ± 1.2 (n=107)	0.10 (-0.24 to 0.44)	NS

Appendix Table G28. Hearing levels: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

RCT	Time Point	Hearing Level (Mean ± SD) (Db)* (By-Child Analysis)		Mean Difference (95% CI)	P-Value
		TT + Ad	Myringotomy + Ad		
Popova	Baseline	31.4 ± 6.4 (n=42)	32.3 ± 6.5 (n=36)	-0.9 (-3.8 to 2.0)	NS
Popova	6 mos.	8.0 ± 6.4 (n=42)	7.6 ± 5.5 (n=36)	0.4 (-2.3 to 3.1)	NS
Vlastos *(OME + sleep apnea)*	6 mos.	23.7 ± 9.6 (n=17)	28.9 ± 10.3 (n=17)	-5.2 (-12.2 to 1.8)	NS
Popova	12 mos.	6.3 ± 5.3 (n=42)	5.5 ± 3.3 (n=36)	0.8 (-1.2 to 2.8)	NS
Vlastos *(OME + sleep apnea)*	12 mos.	23.2 ± 9.7 (n=16)	25.5 ± 10.9 (n=15)	-2.3 (-9.9 to 5.3)	NS
		Appointments With Hearing Levels ≥20 Db (%) (By-Child Analysis)			
Time Point	RCT	TT + Ad	Myringotomy + Ad	Mean Difference (95% CI)	P-Value
≤24 mos. (cumulative)	Gates (better ear)	6.5% ± 11.6% (n=125)	7.8% ± 13.1% (n=130)	-1.3% (-4.4% to 1.8%)	NS
	Gates (worse ear)	22.4% ± 22.1% (n=125)	22.0% ± 23.9% (n=130)	0.4% (-5.3% to 6.1%)	NS

NS: p-value ≥0.05

* Hearing measured by:
- Popova: pure tone audiogram (measured from 500 to 4000 Hz)

Appendix Table G29. Hearing levels by ear: TT (unilateral) + adenoidectomy vs. Myringotomy (contralateral) + adenoidectomy for OME

Time Point	RCT	Hearing Level (Mean ± SD) (Db) (Air Conduction/Audiometry*) TT (Unilateral) + Ad	Myringotomy (Contralateral) + Ad	Mean Difference (95% CI)	P-Value
Baseline	To	33.7 (54 ears)	33.3 (54 ears)	0.4	NS
3 mos.	To	17.1 (54 ears)	21.4 (54 ears)	-4.3	<0.05
6 mos.	Black	NR (37 ears)	NR (37 ears)	-2.8 (-7.4 to 1.9)	NS
12 mos.	Black	NR (37 ears)	NR (37 ears)	1.0 (-4.0 to 6.1)	NS
	To	17.6 (54 ears)	19.0 (54 ears)	-1.4	NS
24 mos.	Black	NR (37 ears)	NR (37 ears)	-0.7 (-6.4 to 4.9)	NS
Time Point	**RCT**	**Hearing Level (Mean ± SD) (Db) (Air Bone Gap†) TT (Unilateral)**	**Myringotomy (Contralateral) + Ad**	**Mean Difference (95% CI)**	**P-Value**
Baseline	Ruckley	21.4 ± 6.5 (36 ears)	21.0 ± 6.6 (36 ears)	0.4 (-2.7 to 3.5)	NS
3 mos.		6.9 ± 4.6 (36 ears)	7.4 ± 3.2 (36 ears)	-0.5 (-2.4 to 1.4)	NS
6 mos.	Shishegar	17.62 (30 ears)	16.25 (30 ears)	1.37	NR
Time Point	**RCT**	**Hearing Level Improved By >6 Db TT (Unilateral) + Ad**	**Myringotomy (Contralateral) + Ad**	**Risk Difference (95% CI)**	**P-Value**
12 mos. (vs. baseline)	To	72% (39/54)	69% (37/54)	4% (-14% to 21%)	NS

Time Point	Cohort Study	Hearing Level (Mean ± SD) (Db) (Air Conduction/Audiometry*) TT (Unilateral) + Ad	Myringotomy (Contralateral) + Ad	Mean Difference (95% CI)	P-Value
Baseline	Tos, Bonding, Khodaverdi	29 ± 10 (148 ears)	27 ± 11 (148 ears)	2 (-0.4 to 4)	NS
"Grommet period" (i.e., TT functioning)		12 ± 5 (135 ears)	18 ± 12 (135 ears)	-6 (-8 to -4)	<0.0001
After TT extrusion		14 ± 9 (106 ears)	14 ± 9 (106 ears)	0 (NC)	NS
12-36 mos.		15 ± 9 (183 ears)	15 ± 9 (183 ears)	0 (NC)	NS
24-36 mos.		15.0 (143 ears)	14.7 (143 ears)	0.3	NR
72-84 mos.		11.7 (146 ears)	11.1 (146 ears)	0.6	NR
Time Point	**Cohort Study**	**Hearing Levels >20 Db TT (Unilateral) + Ad**	**Myringotomy (Contralateral) + Ad**	**Risk Difference (95% CI)**	**P-Value**
Baseline	Tos, Bonding, Khodaverdi	85.1% (126/148)	70.3% (104/148)	14.9% (5.5% to 24.2%)	0.0022
"Grommet period" (i.e., TT functioning)		4.4% (6/135)	31.1% (42/135)	-26.7% (-35.2% to -18.1%)	<0.0001
After TT extrusion		15.1% (16/106)	20.8% (22/106)	-5.7% (-16.0% to 4.6%)	NS
12-36 mos.		21.3% (39/183)	24.0% (44/183)	-2.7% (-11.3% to 5.8%)	NS

Time Point	Cohort Study	Hearing Levels >30 Db		Risk Difference (95% CI)	P-Value
		TT (Unilateral) + Ad	Myringotomy (Contralateral) + Ad		
Baseline	Tos, Bonding, Khodaverdi	45.3% (67/148)	43.9% (65/148)	1.4% (-10.0% to 12.7%)	NS
"Grommet period" (i.e., TT functioning)		1.5% (2/135)	19.3% (26/135)	-17.8% (-24.7% to -10.8%)	<0.0001
After TT extrusion		8.5% (9/106)	8.5% (9/106)	0%	NS
12-36 mos.		10.4% (19/183)	12.0% (22/183	-1.6% (-8.1% to 4.8%)	NS
Time Point	Cohort Study	Hearing Levels >40 Db		Risk Difference (95% CI)	P-Value
		TT (Unilateral) + Ad	Myringotomy (Contralateral) + Ad		
Baseline	Tos, Bonding, Khodaverdi	20.3% (30/148)	17.6% (26/148)	2.7% (-6.2% to 11.6%)	NS
"Grommet period" (i.e., TT functioning)		0% (0/135)	7.4% (10/135)	-7.4% (-11.8% to -3.0%)	0.0013
After TT extrusion		4.7% (5/106)	4.7% (5/106)	0%	NS
12-36 mos.		2.2% (4/183)	2.2% (4/183)	0%	NS

NC: not calculable; NS: p-value ≥0.05

* Hearing measured by:
  - Black: pure tone audiogram (measured from 250 to 4000 Hz)
  - To: audiogram (measured from 250 to 8000 Hz)
  - Tos, Bonding, Khodaverdi: pure tone audiogram (measured from 250 to 4000 Hz)

† Hearing measured by:
  - Ruckley: air bone gap (measured at 500, 1000, and 2000 Hz).
  - Shishegar: air bone gap (no details reported)

Appendix Table G30. Otorrhea: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		Otorrhea (% (n/N)) (By-Child Analysis)			
RCT	**Time Point**	**TT + Ad**	**Myringotomy + Ad**	**Risk Difference (95% CI)**	**P-Value**
Vlastos *(OME + sleep apnea)*	≤12 mos. (cumulative)	0% (0/25)	NR	NC	NC
Popova*	≤12 mos. (cumulative)	40% (17/42)	0% (0/36)	40%	<0.001
Casselbrant†	≤18 mos. (cumulative)	41% (9/22)	9% (2/22)	32% (8% to 56%)	0.0160
Gates‡	≤24 mos. (cumulative)	24% (30/125)	11% (14/130)	13.2% (4.0% to 22.4%)	0.0053
Casselbrant†	≤36 mos. (cumulative)	47% (9/19)	18% (3/17)	30% (1% to 59%)	0.0626

NC: not calculable; NS: p-value ≥0.05

* Popova: Distribution of episodes of patients with otorrhea through 12 months:
  - 1 episode: 24% (10/42) vs. 0% (0/36)
  - 2 episodes: 12% (5/42) vs. 0% (0/36)
  - ≥3 episodes: 5% (2/42) vs. 0% (0/36)

† Casselbrant: Distribution of episodes of patients with otorrhea through 18 months:
  - 1 episode: 27% (6/22) vs. 9% (2/22)
  - 2 episodes: 9% (2/22) vs. 0% (0/22)
  - 3-4 episodes: 5% (1/22) vs. 0% (0/22)

Distribution of episodes of patients with otorrhea through 36 months:
  - 1 episode: 21% (4/19) vs. 18% (3/17)
  - 2 episodes: 21% (4/19) vs. 0% (0/17)
  - 3-4 episodes: 5% (1/19) vs. 0% (0/17)

‡ Gates: Distribution of episodes of patients with purulent otorrhea through 36 months:
  - 0 episodes: 76% (95/125) vs. 89% (115/130) (RD -12.5%, 95% CI -21.8% to -3.2%), p=0.0092)
  - 1 episode: 20% (25/125) vs. 9% (11/130) (RD 11.5%, 95% CI, 3.1% to 20.0%, p=0.0083)
  - 2 episodes: 2% (3/125) vs. 1% (2/130) (p=0.6205)
  - ≥3 episodes: 2% (2/125) vs. 1% (2/130) (p=0.9685)

Appendix Table G31. Otorrhea by ear: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		Otorrhea (% (n/N)) (By-Ear Analysis)			
RCT	**Time Point**	**Tt + Ad**	**Myringotomy + Ad**	**Risk Difference (95% Ci)**	**P-Value**
Shishegar	≤6 mos. (cumulative)	27% (8/30)	7% (2/30)	20% (2% to 38%)	0.0393
		Otorrhea (% (n/N)) (By-Ear Analysis)			
Cohort Study	**Time Point**	**TT + Ad**	**Ad + Myringotomy**	**Risk Difference (95% CI)**	**P-Value**
Tos/Bonding	Grommet period	15% (34/224)	NR	NC	NC

Appendix Table G32. AOM: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		AOM (% (n/N)) (By-Child Analysis)			
RCT	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
Popova*	≤12 mos. (cumulative)	29% (12/42)	25% (9/36)	4%	NS
Casselbrant	≤18 mos. (cumulative)	27% (6/22)	27% (6/22)	0%	NS
Gates	≤24 mos. (cumulative)	38.4% (48/125)	34.6% (45/130)	3.8% (-8.0% to 15.6%)	NS
Casselbrant	≤36 mos. (cumulative)	53% (10/19)	53% (9/17)	0% (-33% to 33%)	NS
		% Time With AOM (n) (By-Child Analysis)			
RCT	Time Point	Tt + Ad	Myringotomy + Ad	Risk Difference (95% Ci)	P-Value
Gates	≤24 mos. (cumulative)	3.9% ± 5.7% (n=125)	3.6% ± 5.2% (n=130)	0.3% (-1.0% to 1.6%)	NS

NC: not calculable; NS: not statistically significant

*Popova: Distribution of episodes of patients with AOM:

- 1 episode: 17% (7/42) vs. 17% (6/36)
- 2 episodes: 7% (3/42) vs. 8% (3/36)
- 3 episodes: 2% (1/42) vs. 0% (0/36)
- ≥4 episodes: 2% (1/42) vs. 0% (0/36)

Appendix Table G33. AOM by ear: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		AOM (% (n/N)) (By-Ear Analysis)			
RCT	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
Ruckley	≤3 mos. (cumulative)	NR	3% (1/36)	NC	NC
		AOM (% (n/N)) (By-Ear Analysis)			
Cohort Study	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
Leek	≤19 mos. (mean) (cumulative)	5.5% (5/72)	NR	NC	NC
Tos, Bonding, Khodaverdi	After TT extrusion	5% (10/193)	6% (12/193)	-1% (-6% to 4%)	NS

NC: not calculable

Appendix Table G34. AOM or OME: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		% Time With AOM or OME (n) (By-Child Analysis)			
RCT	Time Point	Tt + Ad	Myringotomy + Ad	Risk Difference (95% Ci)	P-Value
Casselbrant	≤18 mos. (cumulative)	18.1% ± 20.2% (n=31)	35.7% ± 24.9% (n=33)	-17.6% (-29.0% to -6.2%)	0.0030
Gates	≤24 mos. (cumulative)	25.8% ± 21.2% (n=125)	30.2 ± 25.0% (n=130)	-4.4% (-10.1% to 1.3%)	0.1315
Casselbrant	≤36 mos. (cumulative)	20.6% ± 16.4% (n=31)	31.1% ± 20.8% (n=31)	-10.5% (-20.0% to -1.0%)	0.0311

Appendix Table G35. OME episodes: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		OME present (% (n/N) (By-Child Analysis)			
Time Point	RCT	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
0-12 mos.	Popova	10% (4/42)	14% (5/36)	-4% (-19% to 10%)	NS
0-24 mos.	Gates	81.6% (102/125)	81.5% (106/130)	0.1% (-9.5% to 9.6%)	NS
		% of time spent with OME (By-Child Analysis)			
Time Point	RCT	TT + Ad	Myringotomy + Ad	Mean Difference (95% CI)	P-Value
0-24 mos.	Gates	23.9% ± 20.7% (n=125)	29.1% ± 24.4% (n=130)	-5.2% (-10.8% to 0.4%)	0.0682

Appendix Table G36. OME episodes by ear: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		OME (% (n/N)) (By-Ear Analysis)			
RCT	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
Ruckley	≤3 mos. (cumulative)	NR	19% (7/36)	NC	NC
		OME (% (n/N)) (By-Child Analysis)			
Cohort Study	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
Leek	≤19 mos. (mean) (cumulative)	10% (7/72)	26% (19/72)	-17% (-29% to 4%)	0.0096

NC: not calculable

Appendix Table G37. Cholesteatoma by ear: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		Cholesteatoma (% (n/N)) (By-Ear Analysis)			
RCT	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
Gates	≤24 mos.	0% (0/150)	0% (0/151)	0%	NS
		Cholesteatoma (% (n/N)) (By-Ear Analysis)			
Cohort Study	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
Tos, Bonding, Khodaverdi	12-36 mos.	0% (0/193)	0% (0/193)	0%	NS
Leek	NR	0% ears (0/72 ears)	NR	NC	NC

NC: not calculable

Appendix Table G38. Auditory processing by ear: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		Speech-Recognition Threshold (Mean ± SD) (Db)			
RCT	Time Point	TT + Ad	Myringotomy + Ad	Mean Difference (95% CI)	P-Value
Shishegar	Baseline	25.6 (n=30)	24.8 (n=30)	0.8	NS
	6 mos.	19.3 (n=30)	17.2 (n=30)	2.1	NS

Appendix Table G39. Patient quality of life: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

			Score (mean ± SD) (By-Child Analysis)			
RCT	Outcome Measure	Time Point	TT + Ad	Myringotomy + Ad	Mean Difference (95% CI)	P-Value
Vlastos *(OME + sleep apnea)*	OM-6	Change, 0-6 mos.	-0.38 ± 0.45 (n=22)	0.00 ± 0.40 (n=22)	-0.38 (-0.64 to -0.12)	0.0050
		Change, 0-12 mos.	-0.32 ± 0.83 (n=20)	0.01 ± 0.47 (n=21)	-0.33 (-0.75 to 0.09)	0.1230
		Baseline	2.2 ± 0.6 (n=25)	2.0 ± 0.5 (n=27)	0.2 (-0.1 to 0.5)	NS
		6 mos.	1.88 ± 0.34 (n=22)	2.04 ± 0.53 (n=23)	-0.16 (-0.43 to 0.11)	NS
		12 mos.	1.84 ± 0.68 (n=20)	2.04 ± 0.49 (n=21)	-0.20 (-0.57 to 0.17)	NS

Appendix Table G40. Pain by ear: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		Earache (Child-Reported) (% (n/N)			
RCT	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
Ruckley	≤3 mos.	NR	3% (1/36)	NC	NC

NC: not calculable

Appendix Table G41. Surgery after initial treatment protocol: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

			% (n/N) (By-Child Analysis)			
Surgery	**RCT**	**Time Point**	**TT + Ad**	**Myringotomy + Ad**	**Risk Difference (95% CI)**	**P-Value**
TT	Popova	≤12 mos. (cumulative)	2% (1/42)	NR	NC	NC
	Vlastos	≤12 mos. (cumulative)	NR	15% (4/27)	NC	NC
	Casselbrant	≤18 mos. (cumulative)	10% (3/32)	24% (8/34)	-14% (-32% to 3%)	0.1259
	To	≤24 mos. (cumulative)	4% (2/54)	2% (1/54)	2% (-4% to 8%)	NS
	Casselbrant	≤36 mos. (cumulative)	29% (9/32)	24% (8/34)	5% (-17% to 26%)	NS
Tonsillectomy	Casselbrant	≤36 mos. (cumulative)	13% (4/32)	6% (2/34)	7% (-7% to 21%)	NS
Surgical retreatment*	Gates	≤24 mos. (cumulative)	11.2% (14/125)	11.5% (15/130)	-0.3% (-8.1% to 7.5%)	NS
			% (n/N) (By-Ear Analysis)			
Surgery	**Cohort Study**	**Time Point**	**TT + Ad-Tons**	**Myringotomy + Ad/Tons**	**Risk Difference (95% CI)**	**P-Value**
Bilateral TT	Leek	≤19 mos. (mean) (cumulative)	15% (11/72)	21% (15/72)	-6% (-18% to 7%)	NS
TT	Tos, Bonding, Khodaverdi	"Grommet period" (i.e., unilateral TT functioning)	0% (0/193)	14% (27/193)	-14% (-19% to -9%)	<0.001
		12-36 mos.	10% (19/193)	9% (17/193)	1% (-5% to 7%)	NS

NC: not calculable; NR: not reported; NS: not statistically significant

*Gates 1987, 1989: most surgical retreatments were done according to the protocol, however patients were able to select an alternative treatment (further details NR)

Appendix Table G42. Medication usage: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

			% (n/N) (By-Child Analysis)			
RCT	**Time Point**	**Medication Use**	**TT + Ad**	**Myringotomy + Ad**	**Risk Difference (95% CI)**	**P-Value**
Gates	≥24 mos.	Medical retreatment for chronic otitis media	77.6% (97/125)	79.2% (103/130)	-1.6% (-11.7% to 8.5%)	NS
		Medical retreatment for AOM	55.2% (69/125)	37.7% (49/130)	17.5% (5.5% to 29.6%)	0.0051
			Mean Number Of Medical Retreatments Per Child			
RCT	**Time Point**	**Medication Use**	**TT + Ad**	**Myringotomy + Ad**	**Mean Difference (95% CI)**	**P-Value**
Gates	≥24 mos.	Medical retreatment for OME	2.11 ± 1.74 (n=125)	2.37 ± 1.91 (n=130)	-0.26 (-0.71 to 0.19)	NS
Gates	≥24 mos.	Medical retreatment for AOM	1.03 ± 1.24 (n=125)	0.66 ± 1.00 (n=130)	0.37 (0.09 to 0.65)	0.0091

Appendix Table G43. Medication by ear: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

		Oral Antibiotics (% (n/N))			
RCT	**Time Point**	**TT + Ad**	**Myringotomy + Ad**	**Risk Difference (95% CI)**	**P-Value**
Ruckley	≤3 mos.	NR	3% (1/36)	NC	NC

NC: not calculable

Appendix Table G44. Office visits: TT + adenoidectomy vs. Myringotomy + adenoidectomy for OME

			% (n/N) (By-Child Analysis)			
RCT	**Time Point**	**Office Visits**	**TT + Ad**	**Myringotomy + Ad**	**Risk Difference (95% CI)**	**P-Value**
Gates	≥24 mos.	Unscheduled office visits for illness	44.0% (55/125)	27.7% (36/130)	16.3% (4.7% to 27.9%)	0.0067
			Mean Number Of Office Visits For Illness Per Child			
RCT	**Time Point**	**Office Visits**	**TT + Ad**	**Myringotomy + Ad**	**Mean Difference (95% CI)**	**P-Value**
Gates	≥24 mos.	Unscheduled office visits for illness	0.7 ± 1.0 (n=125)	0.4 ± 0.8 (n=130)	0.3 (0.1 to 0.5)	0.0085

Appendix Table G45. Hearing levels by ear: TT (unilateral) + adenoidectomy vs. Adenoidectomy for OME

Time Point		Hearing Level (Mean ± SD) (Db) (Air Conduction/Audiometry*)			
	RCT	TT (Unilateral) + Ad	Ad	Mean Difference (95% CI)	P-Value
Baseline	Brown	25 (60 ears)	23.1 (60 ears)	1.9	NR
	Dempster	31.4 ± 9.1 (37 ears)	32.5 ± 9.3 (37 ears)	-1.1 (-5.4 to 3.2)	NS
	Maw & Bawden	31.51 ± 8.58 (n=117)	31.54 ± 8.93 (n=118)	-0.03 (-2.28 to 2.22)	NS
3 mos.	Brown	11.4 (60 ears)	16.6 (60 ears)	-5.2	NR
6 mos.	Black	NR (38 ears)	NR (38 ears)	-2.8 (-7.8 to 2.2)	NS
	Brown	16.7 (55 ears)	~19 (55 ears)	~-2.3	NR
	Dempster	13.2 ± 9.0 (37 ears)	18.0 ± 13.0 (37 ears)	-4.8 (-10.0 to 0.4)	0.0689
	Maw & Bawden	17.6 ± 7.3 (n=98)	21.3 ± 10.0 (n=99)	-3.7 (-6.2 to -1.2)	0.0034
12 mos.	Black	NR (38 ears)	NR (38 ears)	-1.9 (-7.4 to 3.6)	NS
	Brown	13.9 (55 ears)	~14.9 (55 ears)	~-1.0	NR
	Dempster	15.9 ± 8.4 (37 ears)	15.6 ± 8.4 (37 ears)	0.3 (-3.6 to 4.2)	NS
	Maw & Bawden	19.1 ± 7.9 (n=122)	20.9 ± 9.5 (n=123)	-1.8 (-4.0 to 0.4)	0.1083
24 mos.	Black	NR (38 ears)	NR (38 ears)	-2.2 (-10.3 to 6.0)	NS
	Maw & Bawden	18.1 ± 8.8 (n=99)	20.0 ± 9.9 (n=100)	-1.9 (-4.5 to 0.7)	NS
36 mos.	Maw & Bawden	17.3 ± 8.2 (n=110)	17.0 ± 7.9 (n=112)	0.3 (-1.8 to 2.4)	NS
48 mos.	Maw & Bawden	17.5 ± 7.8 (n=100)	16.6 ± 7.8 (n=102)	0.9 (-1.3 to 3.1)	NS
60 mos.	Brown	17 (55 ears)	14 (55 ears)	3	NR
	Maw & Bawden	16.4 ± 7.6 (n=93)	17.0 ± 8.1 (n=94)	-0.6 (-2.9 to 1.7)	NS
84 mos.	Maw & Bawden	15.9 ± 11.2 (n=65)	14.8 ± 9.2 (n=67)	1.1 (-2.4 to 4.6)	NS
120 mos.	Maw & Bawden	14.7 ± 7.0 (n=42)	14.6 ± 5.7 (n=43)	0.1 (-2.7 to 2.9)	NS

Time Point		Hearing Level (Mean ± SD) (Db) (Air Bone Gap‡)			
	RCT	TT (Unilateral) + Ad	Ad	Mean Difference (95% CI)	P-Value
Baseline	Dempster	30.8 ± 8.9 (37 ears)	31.8 ± 8.5 (37 ears)	-1.0 (-5.1 to 3.1)	NS
6 mos.	Dempster	14.5 ± 8.3 (37 ears)	20.4 ± 11.5 (37 ears)	-5.9 (-10.5 to -1.3)	0.0136
12 mos.	Dempster	16.5 ± 8.1 (37 ears)	17.2 ± 10.6 (37 ears)	-0.7 (-5.1 to 3.7)	NS
Time Point		**Hearing Level (Mean ± SD) (Db) (Air Bone Gap)**			
	Cohort Study	**TT (Unilateral) + Ad/Tons**	**Ad/Tons**	**Mean Difference (95% CI)**	**P-Value**
Baseline	Austin	29.2 (31 ears)	26.6 (31 ears)	2.6	NS
1.6 mos.		13.2 (31 ears)	14.4 (31 ears)	-1.2	NS

NS: p-value ≥0.05

*Hearing measured by:

- Black: pure tone audiogram (measured from 250 to 4000 Hz)
- Brown: pure tone audiogram (measured from 500 to 4000 Hz)
- Dempster: air conduction (measured at 500, 1000, and 2000 Hz).
- Maw & Bawden: pure tone audiography (measured from 250 to 8000 Hz)

‡Hearing measured by:

- Dempster: air bone gap (measured at 500, 1000, and 2000 Hz).

Appendix Table G46. OME recurrence by ear: TT (unilateral) + adenoidectomy vs. Adenoidectomy (RCT data) for OME

		OME Present (By Otoscopy) (% Ears)			
RCT	Time Point	Tt (Unilateral) + Ad	Ad	Risk Difference (95% Ci)	P-Value
Dempster	6 mos.	11% (4/37)	51% (19/37)	-41% (-60% to -22%)	0.0002
Maw & Bawden		11.6% (13/112)	49.1% (56/114)	-37.5% (-48.4 to -26.6)	<0.0001
Dempster	12 mos.	24% (9/37)	46% (17/37)	-22% (-43% to -0.4%)	0.0530
Maw & Bawden		21.9% (30/137)	39.9% (55/138)	-18.0% (-28.7% to -7.3%)	0.0013
Maw & Bawden	24 mos.	21.7% (23/106)	33.3% (36/108)	-11.6% (-23.5% to 0.2%)	0.0574
	36 mos.	10.2% (12/118)	20.2% (24/119)	-10.0% (-19.0% to -1.0)	0.0324
	48 mos.	10.6% (11/104)	12.3% (13/106)	-1.7% (-10.3% to 6.9%)	NS
	60 mos.	8% (8/99)	18.0% (18/100)	-10% (-19% to -1%)	0.0384
	84 mos.	7% (5/68)	6% (4/70)	1% (-7% to 10%)	NS
	120 mos.	5% (2/43)	18% (9/49)	-14% (-26% to -1%)	0.0442
		OME Present (By Tympanometry) (% Ears)			
RCT	Time Point	TT (Unilateral) + Ad	Ad	Risk Difference (95% CI)	P-Value
Dempster	6 mos.	21% (8/37)	59% (22/37)	-38% (-58% to -17%)	0.0010
	12 mos.	51% (19/37)	49% (18/37)	3% (-20% to 35%)	NS
Brown	60 mos.	2% (1/55)	4% (2/55)	-2% (-8% to 4%)	NS

Appendix Table G47. OME episodes: TT + adenoidectomy vs. Adenoidectomy (RCT data) for OME

		OME Present (% (N/N) (By-Ear Analysis)			
Cohort Study	Time Point	TT + Ad	Ad	Risk Difference (95% CI)	P-Value
Austin	1.9 mos.	16% (5/31)	23% (7/31)	-7% (-26% to 13%)	NS

Appendix Table G48. Cholesteatoma: TT + adenoidectomy vs. Adenoidectomy (RCT data) for OME

		OME Present (% (n/N) (By-Ear Analysis)			
Time point	**RCT**	**TT + Ad**	**Ad**	**Risk difference (95% CI)**	**p-value**
60 mos.	Brown	0% (0/55)	0% (0/55)	0%	NS

Appendix Table G49. Hearing levels by patient: TT vs. Myringotomy + adenoidectomy for OME

		Appointments with hearing levels ≥20 dB) (%)			
Time point	**Study**	**TT**	**Myringotomy + Ad**	**Mean difference (95% CI)**	**p-value**
≤24 mos. (cumulative)	Gates (better ear)	10.1% ± 14.1% (n=150)	7.8% ± 13.1% (n = 130)	2.3% (-9.2% to 5.5%)	0.1606
	Gates (worse ear)	30.4% ± 22.7% (n=150)	22.0% ± 23.9% (n = 130)	8.4% (2.9% to 13.9%)	0.0028

Appendix Table G50. Otorrhea: TT vs. Myringotomy + adenoidectomy for OME

		Otorrhea (% (n/N))			
Study	**Time point**	**TT**	**Myringotomy + Ad**	**Risk difference (95% CI)**	**p-value**
Casselbrant*	≤18 mos. (cumulative)	36% (8/22)	9% (2/22)	27% (4% to 51%)	0.0329
Gates†	≤24 mos. (cumulative)	29% (37/129)	11% (14/130)	17.9% (8.5% to 27.4%)	0.0003
Casselbrant*	≤36 mos. (cumulative)	45% (9/20)	18% (3/17)	27% (-1% to 56%)	0.0806

NS: p-value ≥0.05

*Casselbrant: Distribution of episodes of patients with otorrhea through 18 months (%):

- 1 episode: 27% (6/22) vs. 9% (2/22)
- 2 episodes: 5% (1/22) vs. 0% (0/22)
- 3-4 episodes: 5% (1/22) vs. 0% (0/22)

Distribution of episodes of patients with otorrhea through 36 months (%):

- 1 episode: 25% (5/20) vs. 18% (3/17)
- 2 episodes: 15% (3/20) vs. 0% (0/17)
- 3-4 episodes: 5% (1/20) vs. 0% (0/17)

†Gates: Distribution of episodes of patients with purulent otorrhea (%) through 24 months:

- 0 episodes: 71% (92/129) vs. 89% (115/130) (RD -17.1%, 95% CI -26.7% to -7.6%, p=0.0006)
- 1 episode: 18% (23/129) vs. 9% (11/130) (RD 9.4%, 95% CI 1.2% to 17.5%, p=0.0259)
- 2 episodes: 5% (6/129) vs. 1% (2/130) (RD 3.1%, -1.1% to 7.3%, p=0.1485)
- ≥3 episodes: 6% (8/129) vs. 1% (2/130) (RD 4.7%, 95% CI -0.01% to 9.3%, p=0.0519)

Appendix Table G51. AOM: TT vs. Myringotomy + adenoidectomy for OME

		AOM (% (n/N))			
Study	**Time Point**	**TT**	**Myringotomy + Ad**	**Risk Difference (95% CI)**	**P-Value**
Casselbrant	≤18 mos. (cumulative)	23% (5/22)	27% (6/22)	-4.6% (-30.1% to 21.0%)	NS
Gates	≤24 mos. (cumulative)	35.7% (46/129)	34.6% (45/130)	10.4% (-10.6% to 12.7%)	NS
Casselbrant	≤36 mos. (cumulative)	55% (11/20)	53% (9/17)	2.2% (-30.2% to 34.3%)	NS
		% Time With AOM (n)			
Study	**Time Point**	**TT**	**Myringotomy + Ad**	**Mean Difference (95% CI)**	**P-Value**
Gates	≤24 mos. (cumulative)	4.1% ± 5.9% (n=129)	3.6% ± 5.2% (n=130)	0.5% (-0.9% to 1.9%)	NS

Appendix Table G52. AOM or OME: TT vs. Myringotomy + adenoidectomy for OME

		% Time With AOM Or OME (n)			
Study	**Time Point**	**TT**	**Myringotomy + Ad**	**Mean Difference (95% CI)**	**P-Value**
Casselbrant	≤18 mos. (cumulative)	11.9% ± 16.2% (n=31)	35.7% ± 24.9% (n=33)	-23.8% (-34.3% to -13.2%)	<0.0001
Gates	≤24 mos. (cumulative)	34.9 ± 23.5% (n=129)	30.2% ± 25.0% (n=130)	4.7% (-1.2% to 10.6%)	0.1203
Casselbrant	≤36 mos. (cumulative)	18.6% ± 14.2% (n=31)	31.1% ± 20.8% (n=31)	-12.5% (-21.5% to -3.5%)	0.0076

Appendix Table G53. OME episodes: TT vs. Myringotomy + adenoidectomy for OME

		OME Present (% (n/N)			
Time Point	**Study**	**TT**	**Myringotomy + Ad**	**Risk Difference (95% CI)**	**P-Value**
0-24 mos.	Gates	85.3% (110/129)	81.5% (106/130)	3.7% (-5.3% to 12.8%)	NS
		% of Time Spent With OME			
Time Point	**Study**	**TT**	**Myringotomy + Ad**	**Mean Difference**	**P-Value**
0-24 mos.	Gates	31.8% ± 23.2% (n=129)	29.1% ± 24.4% (n=130)	2.7% (-3.1% to 8.5%)	NS

Appendix Table G54. Surgery after initial treatment protocol: TT vs. Myringotomy + adenoidectomy for OME

			% (n/N)			
Surgery	**Study**	**Time Point**	**TT**	**Myringotomy + Ad**	**Risk Difference (95% CI)**	**P-Value**
TT + Ad	Casselbrant	≤18 mos. (cumulative)	10% (3/32)	24% (8/34)	-14% (-31% to 3%)	0.1259
		≤36 mos. (cumulative)	25% (8/32)	24% (8/34)	2% (-19% to 22%)	NS
Myringotomy	Casselbrant	≤36 mos. (cumulative)	3% (1/32)	0% (0/34)	3% (NC)	NS
Tonsillectomy	Casselbrant	≤36 mos. (cumulative)	0% (0/32)	6% (2/34)	-6% (-14% to 2%)	0.1668
Surgical retreatment*	Gates	≤24 mos. (cumulative)	24.0% (31/129)	11.5% (15/130)	12.5% (3.3% to 21.7%)	0.0087

NC: not calculable; NS: not statistically significant

* Gates 1987, 1989: most surgical retreatments were done according to the protocol, however patients were able to select an alternative treatment (further details NR)

Appendix Table G55. Medication usage: TT vs. Myringotomy + adenoidectomy for OME

			% (n/N)			
Study	**Time point**	**Medication use**	**TT**	**Myringotomy + Ad**	**Risk difference (95% CI)**	**p-value**
Gates	≥24 mos.	Medical retreatment for chronic otitis media	84.5% (109/129)	79.2% (103/130)	5.3% (-4.1% to 14.6%)	NS
		Medical retreatment for AOM	48.1% (62/129)	37.7% (49/130)	10.4% (-1.6% to 22.4%)	0.0924
			Mean number of medical retreatments per child			
Study	**Time point**	**Medication use**	**TT**	**Myringotomy + Ad**	**Mean difference (95% CI)**	**p-value**
Gates	≥24 mos.	Medical retreatment for OME	2.55 ± 1.75 (n=129)	2.37 ± 1.91 (n=130)	0.18 (-0.27 to 0.63)	NS
Gates	≥24 mos.	Medical retreatment for AOM	1.23 ± 1.84 (n=129)	0.66 ± 1.00 (n=130)	0.57 (0.21 to 0.93)	0.0021

Appendix Table G56. Office visits: TT vs. Myringotomy + adenoidectomy for OME

			% (n/N)			
Study	**Time point**	**Office visits**	**TT**	**Myringotomy + Ad**	**Risk difference (95% CI)**	**p-value**
Gates	≥24 mos.	Unscheduled office visits for illness	44.2% (57/129)	27.7% (36/130)	16.5% (5.0% to 28.0%)	0.0058
			Mean number of office visits for illness per child			
Study	**Time point**	**Office visits**	**TT**	**Myringotomy + Ad**	**Mean difference (95% CI)**	**p-value**
Gates	≥24 mos.	Unscheduled office visits for illness	0.8 ± 1.4 (n=129)	0.4 ± 0.8 (n=130)	0.40 (0.12 to 0.68)	0.005

Appendix Table G57. Hearing levels by ear: TT (unilateral) vs. No procedure (unilateral) + adenoidectomy for OME

Time point		Hearing level (mean ± SD) (dB) (Air conduction/audiometry*)			
	RCT	TT (unilateral)	Ad	Mean difference (95% CI)	p-value
Baseline	Dempster	33.5 ± 6.3 (35 ears)	32.5 ± 9.3 (37 ears)	1.00 (-2.76 to 4.76)	NS
	Maw & Bawden	30.90 ± 8.98 (73 ears)	31.54 ± 8.93 (118 ears)	-0.64 (-3.27 to 1.99)	NS
6 mos.	Dempster	13.2 ± 9.0 (35 ears)	18.0 ± 13.0 (37 ears)	-4.8 (-10.08 to 0.48)	0.0743
	Maw & Bawden	18.3 ± 9.1 (65 ears)	21.3 ± 10.0 (99 ears)	-3.00 (-6.04 to 0.04)	0.0533
12 mos.	Dempster	15.9 ± 8.4 (35 ears)	15.6 ± 8.4 (37 ears)	0.30 (-3.65 to 4.25)	NS
	Maw & Bawden	19.8 ± 9.6 (78 ears)	20.9 ± 9.5 (123 ears)	-1.10 (-3.82 to 1.62)	NS
24 mos.	Maw & Bawden	20.9 ± 9.3 (69 ears)	20.0 ± 9.9 (100 ears)	0.90 (-2.09 to 3.89	NS
36 mos.	Maw & Bawden	19.8 ± 9.4 (57 ears)	17.0 ± 7.9 (112 ears)	2.8 (0.09 to 5.51)	0.0428
48 mos.	Maw & Bawden	18.7 ± 7.3 (53 ears)	16.6 ± 7.8 (102 ears)	2.10 (0.60 to 3.61)	0.0066
60 mos.	Maw & Bawden	17.6 ± 7.0 (47 ears)	17.0 ± 8.1 (94 ears)	0.60 (-2.14 to 3.34)	NS
84 mos.	Maw & Bawden	15.6 ± 6.2 (35 ears)	14.8 ± 9.2 (67 ears)	0.80 (-2.64 to 4.24)	NS
120 mos.	Maw & Bawden	15.5 ± 7.1 (15 ears)	14.6 ± 5.7 (43 ears)	0.90 (-2.75 to 4.55)	NS
Time point		Hearing level (mean ± SD) (dB) (Air bone gap‡)			
	RCT	TT (unilateral)	Ad	Mean difference (95% CI)	p-value
Baseline	Dempster	33.0 ± 6.7 (35 ears)	31.8 ± 8.5 (37 ears)	1.20 (-2.41 to 4.81)	NS
6 mos.	Dempster	17.3 ± 11.3 (35 ears)	20.4 ± 11.5 (37 ears)	-3.10 (-8.46 to 2.26)	NS
12 mos.	Dempster	17.9 ± 9.9 (35 ears)	17.2 ± 10.6 (37 ears)	0.70 (-4.13 to 5.53)	NS

NS: p-value ≥0.05

*Hearing measured by:

- Dempster: air conduction (measured at 500, 1000, and 2000 Hz).
- Maw & Bawden: pure tone audiography (measured from 250 to 8000 Hz)

‡Hearing measured by:

- Dempster: air bone gap (measured at 500, 1000, and 2000 Hz).

Appendix Table G58. OME recurrence by ear: TT (unilateral) vs. No procedure (unilateral) + adenoidectomy for OME

		OME present (by otoscopy) (% ears)			
RCT	**Time point**	**TT (unilateral)**	**Ad**	**Risk difference (95% CI)**	**p-value**
Dempster	6 mos.	14% (5/35)	51% (19/37)	-37.1% (-56.9% to -17.2%)	0.0009
Maw & Bawden		17% (13/78)	49.1% (56/114)	-32.5% (-44.8% to -20.1%)	<0.001
Dempster	12 mos.	31% (11/35)	46% (17/37)	-14.5% (-36.8% to 7.7%)	NS
Maw & Bawden		37% (29/78)	39.9% (55/138)	-2.7% (-16.2% to 10.8%)	NS
Maw & Bawden	24 mos.	31% (22/70)	33.3% (36/108)	-1.9% (-16.0% to 12.1%)	NS
	36 mos.	35% (20/57)	20.2% (24/119)	14.9% (0.5% to 29.3%)	0.0329
	48 mos.	24% (12/51)	12.3% (13/106)	11.3% (-2.0% to 24.5%)	0.0717
	60 mos.	7% (3/45)	18.0% (18/100)	-11.3% (-21.8% to -0.9%)	0.0738
	84 mos.	12% (4/33)	6% (4/70)	6.4% (-6.0% to 18.8%)	NS
	120 mos.	7% (1/15)	18% (9/49)	-11.7% (-28.3% to 4.9%)	NS
		OME present (by tympanometry) (% ears)			
RCT	**Time point**	**TT (unilateral)**	**Ad**	**Risk difference (95% CI)**	**p-value**
Dempster	6 mos.	34% (12/35)	59% (22/37)	-25.2% (-47.5% to -2.9%)	0.0337
	12 mos.	46% (16/35)	49% (18/37)	-2.9% (-26.0% to 20.1%)	NS

Appendix Table G59. Hearing levels by child: TT vs. Antibiotics for OME

Hearing level* (mean ± SD) (dB)					
RCT	**Time point**	**TT**	**Antibiotics**	**Mean difference (95% CI)**	**p-value**
Bernard	Baseline	29.6 (n=65)	30.7 (n=60)	-1.1	NS
	2 mos.	~11 (n=65)	~20 (n=60)	~-9	<0.001
	4 mos.	~12 (n=65)	~17 (n=60)	~-5	0.0132
	6 mos.	~12 (n=65)	~13 (n=60)	~-1	NS
	12 mos.	~14 (n=65)	~15 (n=60)	~-1	NS
	18 mos.	~11 (n=65)	~11 (n=60)	~0	NS
	72-120 mos.	~10 (n=38 who received TT only once)	~5 (n=27 who never received TT)	~5	<0.05
		NR (n=56 as randomized)	NR (n=57 as randomized)	2.1-4.7 higher in TT patients across different frequencies	0.15
		NR (n=86 patients who received TT regardless treatment allocation)	NR (n=27 patients who never received TT)	5.1-10.8 higher in TT patients across different frequencies	<0.001
Hearing level > 25dB					
RCT	**Time point**	**TT**	**Antibiotics**	**Mean difference (95% CI)**	**p-value**
Bernard	Baseline	100% (65/65)	100% (60/60)	0%	NS
	2 mos.	NR	NR	NC	<0.001
	4 mos.	NR	NR	NC	0.001
	6 mos.	NR	NR	NC	NS
	12 mos.	NR	NR	NC	NS
	18 mos.	NR	NR	NC	NS
Hearing level > 15dB					
RCT	**Time point**	**TT**	**Antibiotics**	**Risk difference (95% CI)**	**p-value**
Bernard	72-120 mos.	37% (14/38 who received TT only once)	11% (3/27 who never received TT)	26% (6% to 45%)	0.0210
		NR (n=56 as randomized)	NR (n=57 as randomized)	RR 1.8 higher in TT group (95% CI 1.1, 3.1)	<0.05
		NR (n=86 patients who received TT regardless treatment allocation)	NR (n=27 patients who never received TT)	RR 3.8 higher in TT group (95% CI 1.3, 11.3)	<0.05

NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05)

* Hearing thresholds according to pure-tone audiometry (mean of thresholds at 500, 1000, 2000, and 4000 Hz)

Appendix Table G60. "Treatment failure*": TT vs. Antibiotics for OME

Treatment failure* (n/N)					
RCT	Time point	TT	Antibiotics	Risk difference (95% CI)	p-value
Bernard	6 mos.	20% (12/60)	34% (22/65)	-14% (-29% to 1%)	0.0834
	12 mos.	40% (24/60)	60% (39/65)	-20% (-37% to -3%)	0.0261
	18 mos.	48% (29/60)	68% (44/65)	-19% (-36% to -2%)	0.0289

NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05)

* Treatment failure was a composite outcome that was met when a patient met any of the following: (1) persistent/recurrent MEE and associated hearing loss (>25 dB HL at 2 or more frequencies 0.5, 1, 2, and 4 kHz, in at least one ear); (2) allergic reaction to sulfonamide (for medical group only); or (3) three or more AOM episodes over a 6-month period of the study

Appendix Table G61. Academic achievement: TT vs. Antibiotics for OME

School performance not adequate (parent-reported)* (n/N)					
RCT	Time point	TT	Antibiotics	Risk difference (95% CI)	p-value
Bernard	72-120 mos.	13% (5/38 who received TT only once)	7% (2/27 who never received TT)	6% (-9% to 20%)	NS

NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05)

* No definition reported

Appendix Table G62. Parent satisfaction: TT vs. Antibiotics for OME

Parental satisfaction with treatment* (n/N)					
RCT	Time point	TT	Antibiotics	Risk difference (95% CI)	p-value
Bernard	72-120 mos.	92% (35/38 who received TT only once)	81% (22/27 who never received TT)	11% (-6% to 28%)	NS

NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05)

* No definition reported

Appendix Table G63. Pain or decreased hearing (parent-reported): TT vs. Antibiotics for OME

Ear complaints* (n/N)					
RCT	Time point	TT	Antibiotics	Risk difference (95% CI)	p-value
Bernard	72-120 mos.	29% (11/38 who received TT only once)	11% (3/27 who never received TT)	18% (-1% to 37%)	NS

NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05)

* Pain or decreased hearing (parent-reported)

Appendix Table G64. Surgery: TT vs. Antibiotics for OME

TT (re)insertion (n/N)					
RCT	**Time point**	**TT**	**Antibiotics**	**Risk difference (95% CI)**	**p-value**
Bernard	≤18 mos.	38% (23/60)	48% (31/65)	-9% (-27% to 8%)	NS
	72-120 mos.	32% (18/56)	53% (30/57)	-20% (-38% to -3%)	0.0283

NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05)

Appendix Table G65. Medication: TT vs. Antibiotics for OME

Sulfonamide (re)treatment for 6 months) (n/N)					
RCT	**Time point**	**TT**	**Antibiotics**	**Risk difference (95% CI)**	**p-value**
Bernard	≤18 mos.	10% (6/60)	20% (13/65)	-10% (-22% to 2%)	0.1212

NC: not calculable; NR: not reported; NS: not statistically significant (p≥0.05)

Appendix Table G66. Hearing levels by child: TT vs. Prophylactic Antibiotics for Recurrent AOM

% of time with hearing level > 15dB*					
RCT	**Time point**	**TT**	**Antibiotics**	**Mean difference (95% CI)**	**p-value**
Casselbrant 1992	≤24 mos.	10% of time (n=77)	12% of time (n=86)	-2%	NR
Moderately severe sensorineural hearing loss					
RCT	**Time point**	**TT**	**Antibiotics**	**Risk difference (95% CI)**	**p-value**
Gebhart	42 mos.	2% (1/54)†	0% (0/41)	2%	NS

* Hearing in better ear

† Sensorineural hearing loss believed to be hereditary (patient had a family history of sensorineural hearing loss) and not related to TT or AOM history

Appendix Table G67. Otorrhea or AOM: TT vs. Prophylactic Antibiotics for Recurrent AOM

		New episodes of AOM or otorrhea per year (mean (95% CI))			
RCT	**Time point**	**TT**	**Antibiotics**	**Mean difference (95% CI)**	**p-value**
Casselbrant 1992	≤24 mos.	1.02 (0.86 to 1.21) (n=77)	0.60 (0.48 to 0.76) (n=86)	0.42	0.001

NS: p-value ≥0.05

Appendix Table G68. AOM episodes: TT vs. Prophylactic Antibiotics for Recurrent AOM

		AOM episodes (% (n/N))			
RCT	Time point	TT	Antibiotics	Risk difference (95% CI)	p-value
El Sayed*	≤6 mos.	35% (11/31)	55% (12/22)	-19% (-46% to 8%)	0.1718
Gebhart*	≤6 mos.	54% (29/54)	95% (39/41)	-41% (-56% to -27%)	<0.001
Gonzalez*	≤6 mos.	45% (10/22)	76% (16/21)	-31% (-58% to -3%)	0.0417
		AOM episodes per child (mean (95% CI))			
RCT	Time point	TT	Antibiotics	Mean difference (95% CI)	p-value
Gonzalez	≤6 mos.	0.9 (n=22)	1.4 (n=21)	-0.5	NR

NS: p-value ≥0.05

*Number of AOM episodes (TT vs. antibiotics):

- El Sayed: 1-2 AOM episodes: 31% (7/31) vs. 31% (7/22) (p=NS); ≥3 AOM episodes: 13% (4/31) vs. 23% (5/22) (p=NS)
- Gebhart: 1 AOM episode: ~45% vs. ~38%; ≥2 AOM episodes: ~9% vs. ~47% (p<0.001)
- Gonzalez: ≥2 AOM episodes within 3 months: 23% (5/22) vs. 38% (8/21) (p=NS)

Appendix Table G69. OME episodes: TT vs. Prophylactic Antibiotics for Recurrent AOM

		New episodes of OME per year (mean (95% CI))			
RCT	Time point	TT	Antibiotics	Risk difference 95% CI)	p-value
Casselbrant 1992	≤24 mos.	0.38 (n=77)	0.70 (n=86)	-0.32	NR

NS: p-value ≥0.05

Appendix Table G70. Cholesteatoma: TT vs. Prophylactic Antibiotics for Recurrent AOM

		AOM episodes (% (n/N))			
RCT	Time point	TT	Antibiotics	Risk difference (95% CI)	p-value
Casselbrant 1992	≤24 mos.	0% (0/77)	0% (0/86)	0%	NS
Gebhart	≤30 mos.	0% (0/54)	0% (0/41)	0%	NS

NS: p-value ≥0.05

Appendix Table G71. Surgery: TT vs. Prophylactic Antibiotics for Recurrent AOM

			Surgery (% (n/N))			
RCT	Surgery	Time point	TT	Antibiotics	Risk difference (95% CI)	p-value
Casselbrant 1992	TT (re)insertion	≤24 mos.	28%* (21/76)	NR	NC	NC
El Sayed		≤6 mos.	7%* (2/31)	NR	NC	NC
Gonzalez		≤6 mos.	NR	NR†	NC	NR
Gebhart		≤6 mos.	6% (3/54)	NR	NC	NC
		≤30 mos.	37% (20/54)	NR	NC	NC

NS: p-value ≥0.05

* Casselbrant: One TT reinsertion: 26% (20/76); two TT reinsertions: 1% (1/76)

† Gonzalez: For the antibiotics (n=21) and placebo (n=20) groups combined, 46% (19/41) underwent TT insertion

Appendix Table G72. Medication: TT vs. Prophylactic Antibiotics for Recurrent AOM

			Medication (% (n/N))			
RCT	Medication	Time point	TT	Antibiotics	Risk difference (95% CI)	p-value
Gonzalez	Chemoprophylaxis for treatment failure	≤6 mos.	18% (4/22)	NR	NC	NC

Appendix Table G73. Hearing levels by child: TT vs. Placebo or No treatment for Recurrent AOM

% of time with hearing level > 15dB*					
RCT	Time point	TT	Placebo	Mean difference (95% CI)	p-value
Casselbrant 1992	≤24 mos.	10% of time (n=77)	16% of time (n=80)	-6%	NR

*Hearing in better ear

Appendix Table G74. Otorrhea or AOM: TT vs. Placebo or No treatment for Recurrent AOM

		New episodes of AOM or otorrhea per year (mean (95% CI))			
RCT	Time point	TT	Placebo	Mean difference (95% CI)	p-value
Casselbrant 1992	≤24 mos.	1.02 (0.86 to 1.21) (n=77)	1.08 (0.89 to 1.30) (n=80)	-0.06	NS

NS: p-value ≥0.05

Appendix Table G75. AOM episodes: TT vs. Placebo or No treatment for Recurrent AOM

		AOM episodes (% (n/N))			
RCT	**Time point**	**TT**	**Placebo or No treatment**	**Risk difference (95% CI)**	**p-value**
Gonzalez*	≤6 mos.	45% (10/22)	85% (17/20)	-40% (-66% to -14%)	0.0083
Kujala†	≤12 mos.	52% (52/100)	66% (66/100)	-14% (-27% to -0.5%)	0.0447
		AOM episodes per child (mean (95% CI))			
RCT	**Time point**	**TT**	**Placebo or No treatment**	**Mean difference (95% CI)**	**p-value**
Gonzalez	≤6 mos.	0.9 (n=22)	2.0 (n=20)	-1.1	NR
Kujala	≤12 mos.	1.15 (n=100)	1.70 (n=100)	-0.55	NR

NS: p-value ≥0.05

* ≥2 AOM episodes within 3 months: 23% (5/22) vs. 60% (12/20) (RD -37%, 95% CI -65% to -10%, p=0.0152)

† ≥2 AOM episodes in 2 months, OR ≥3 episodes in 6 months OR middle ear effusion for ≥2 months: 21% (21/100) vs. 34 (34/100) (-13%, 95% CI -25% to -1%, p=0.0400); cumulative number of AOM episodes: 92 vs. 119 (p=NR)

Appendix Table G76. OME episodes: TT vs. Placebo or No treatment for Recurrent AOM

		New episodes of OME per year (mean (95% CI))			
RCT	**Time point**	**TT**	**Placebo or No treatment**	**Risk difference (95% CI)**	**p-value**
Casselbrant 1992	≤24 mos.	0.38 (n=77)	0.62 (n=80)	-0.24	NR

NS: p-value ≥0.05

Appendix Table G77. Cholesteatoma: TT vs. Placebo or No treatment for Recurrent AOM

		AOM episodes (% (n/N))			
RCT	**Time point**	**TT**	**Placebo or No treatment**	**Risk difference (95% CI)**	**p-value**
Casselbrant 1992	≤24 mos.	0% (0/77)	0% (0/86)	0%	NS

NS: p-value ≥0.05

Appendix Table G78. Patient quality of life: TT vs. Placebo or No treatment for Recurrent AOM

				Score (mean ± SD)		
RCT	Outcome measure*	Subtest	Time point	TT	Placebo or No treatment	p-value
Kujala subanalysis	Ear-related QoL (evaluated on 10-point VAS scale, higher scores = better QoL)	-	Baseline	~5.4 (n=47)	~5.2 (n=45)	NS
			4 mos.	~6.5 (n=42)	~6.7 (n=43)	NS
			12 mos.	~7.5 (n=43)	~7.4 (n=38)	NS
	OM-6 (1-7 scale, Lower scores = better QoL)	Caregiver concerns	Baseline	~3.7 (n=47)	~4.3 (n=45)	NS
			4 mos.	~2.2 (n=42)	~2.0 (n=43)	NS
			12 mos.	~1.7 (n=43)	~2.1 (n=38)	NS
		Emotional distress	Baseline	~3.2 (n=47)	~3.6 (n=45)	NS
			4 mos.	~3.0 (n=42)	~2.9 (n=43)	NS
			12 mos.	~2.2 (n=43)	~2.5 (n=38)	NS
		Physical suffering	Baseline	~3.4 (n=47)	~3.4 (n=45)	NS
			4 mos.	~3.4 (n=42)	~3.1 (n=43)	NS
			12 mos.	~2.2 (n=43)	~2.5 (n=38)	NS
		Activity limitations	Baseline	~2.4 (n=47)	~2.6 (n=45)	NS
			4 mos.	~2.3 (n=42)	~2.3 (n=43)	NS
			12 mos.	~1.9 (n=43)	~2.0 (n=38)	NS
		Hearing loss	Baseline	~1.5 (n=47)	~1.5 (n=45)	NS
			4 mos.	1.5 (n=42)	~1.5 (n=43)	NS
			12 mos.	~1.4 (n=43)	~1.4 (n=38)	NS
		Speech impairment	Baseline	~1.3 (n=47)	~1.5 (n=45)	NS
			4 mos.	1.6 (n=42)	~1.4 (n=43)	NS
			12 mos.	~1.4 (n=43)	~1.4 (n=38)	NS

Appendix Table G79. Surgery: TT vs. Placebo or No treatment for Recurrent AOM

			Surgery (% (n/N))			
RCT	Surgery	Time point	TT	Placebo or No treatment	Risk difference (95% CI)	p-value
Gonzalez	TT (re)insertion	≤6 mos.	NR	NR†	NC	NR
Casselbrant 1992		≤24 mos.	28%* (21/76)	NR	NC	NC

NS: p-value ≥0.05

* Casselbrant: One TT reinsertion: 26% (20/76); two TT reinsertions: 1% (1/76)

† Gonzalez: For the antibiotics (n=21) and placebo (n=20) groups combined, 46% (19/41) underwent TT insertion

Appendix Table G80. Hearing levels by ear: Hearing levels by ear: TT (one ear) vs. Myringotomy or No procedure (opposite ear) for OME or Recurrent AOM

		Hearing level (mean ± SD) (dB) (Pure tone audiogram*†)			
RCT	Time point	TT (unilateral)	Myringotomy or No procedure (opposite ear)	Mean difference (95% CI)	p-value
Le‡	Baseline	NR (37 ears)	NR (37 ears)	0.7 (-2, 3)	NS
	3 months	NR (37 ears)	NR (37 ears)	-3.4 (-6 to -1)	0.02
	6 months	NR (37 ears)	NR (37 ears)	-3.7 (-7 to 0)	0.05
	9 months	NR (37 ears)	NR (37 ears)	-3.5 (-6 to 0)	0.02
	12 months	NR (38 ears)	NR (38 ears)	-0.8 (-4 to 2)	NS
	15 months	NR (40 ears)	NR (40 ears)	0.2 (-2 to 1)	NS
	18 months	NR (40 ears)	NR (40 ears)	2.1 (0 to 4)	0.08
	24 months	NR (38 ears)	NR (38 ears)	0.2 (-4 to 4)	NS
	After 24 months	NR (49 ears)	NR (49 ears)	1.7 (0 to 4)	0.1

NS: not statistically significant

* Pure tone audiogram at 250-4000Hz

† Results reported only for those patients in whom audiograms can reliably distinguish hearing levels between ears

‡ Patients with ≥5 dB better hearing in ear with tube:

- 9 mos.: 31.9% (15/47), p = 0.04
- 17 mos.: 27.8% (15/54), p = 0.13
- 23 mos.: 13.0% (7/54), p = 0.36
- 24 mos.: 14.3% (7/49), p = 0.36

Appendix Table G81. Otorrhea by ear: Hearing levels by ear: TT (one ear) vs. Myringotomy or No procedure (opposite ear) for OME or Recurrent AOM

RCT		Otorrhea (% (n/N))			
	Time point	TT (unilateral)	Myringotomy or No procedure (opposite ear)	Risk difference (95% CI)	p-value
Le	≤0.5 months	4% (2/57)	2% (1*/57)	2% (-4% to 8%)	NS
	≤2 months	14% (8/57)	2% (1*/57)	12% (3% to 22%)	0.0155
	≤3 months	18% (10/57)	2% (1*/57)	16% (5% to 26%)	0.0045

NS: not statistically significant

*otorrhea occurred in myringotomy ear

Appendix Table G82. AOM by ear: Hearing levels by ear: TT (one ear) vs. Myringotomy or No procedure (opposite ear) for OME or Recurrent AOM

RCT		AOM (mean number episodes per 6 month interval)			
	Time point	TT (unilateral)	Myringotomy or No procedure (opposite ear)	Mean difference (95% CI)	p-value
Le	Before treatment	3.4 ± 1.3 (57 ears)	3.6 ± 1.6 (57 ears)	-0.2 (-0.7 to 0.3)	NS
	0-6 mos.	0.5 ± 0.8 (57 ears)	1.4 ± 1.4 (57 ears)	-0.9 (-1.3 to -0.5)	<0.0001
	7-12 mos.	0.6 ± 0.9 (55 ears)	1.0 ± 1.0 (55 ears)	-0.4 (-0.8 to -0.04)	0.0296
	13-18 mos.	0.9 ± 1.2 (55 ears)	0.8 ± 1.2 (55 ears)	0.1 (-0.4 to 0.6)	NS
	19-24 mos.	0.8 ± 0.8 (53 ears)	0.7 ± 0.8 (53 ears)	0.1 (-0.2 to 0.4)	NS

NS: not statistically significant

* Number of untreated ears with more AOM or OME episodes than contralateral ear with tube (paired sample analysis):

- 6 mos.: 58.0% (33/57), p = 0.001
- 12 mos.: 36.4% (20/55), p = 0.1
- 18 mos.: 12.7% (7/55), p = 0.17
- 24 mos.: 20.8% (11/53), p = 0.3
- 36 mos.: 18.6% (8/43), p = 0.29

Appendix Table G83. Surgery by ear: Hearing levels by ear: TT (one ear) vs. Myringotomy or No procedure (opposite ear) for OME or Recurrent AOM

RCT	Surgery	Time point	Surgery (% (n/N))		Mean difference (95% CI)	p-value
			TT (unilateral)	Myringotomy or No procedure (opposite ear)		
Le	TT (re)insertion	≤24 mos.	5% (3/57)	7% (4/57)	-2% (-11% to 7%)	NS

NS: not statistically significant

Appendix H. Results Tables for Key Question 2 (Safety)

Appendix Table H1. Adverse events by child: TT vs. WW for OME

			% (n/N)			
Adverse Event	Study	Time Point	TT	WW	Risk Difference (95% CI)	P-Value
Perforation	TARGET	≤24 mos. (as treated analysis)	1.3% ears that received tubes (8/635 ears)	NR	NC	NC
	Mandel 1989	≤36 mos.	13.7% (11/80)†‡		NC	NC
	Mandel 1992	≤36 mos.	11.2% (10/89)†§		NC	NC
Perforation with other abnormality	Paradise	Age 5	4.1% (6/147)	1.5% (2/134)	2.6% (-1.2% to 6.4%)	NS
Chronic otorrhea (≥3 episodes/year) (parent-reported)	Rovers	≤12 mos.	25% (23/93)	5% (5/94)	19% (10% to 29%)	<0.01
Otorrhea (persistent, requiring hospitalization for	Mandel 1989	≤36 mos.	2.4%** (1/41)	3.4%** (1/29)	-1% (-9% to 7%)	NS
IV antibiotics and daily suctioning through tube	Mandel 1992	≤36 mos.	2.2% (2/89)†,†† of patients in all three groups who received TT		NC	NC
Tympanosclerosis	TARGET	≤24 mos. (as treated analysis)	20.2% ears that received tubes (128/635 ears)	0% ears that did not undergo surgery (0/117 ears)	20.2%	<0.01
	Paradise	Age 5 (as treated analysis)	4.1% patients that received tubes* (7/172)	1.0% patients that did not receive tubes* (1/109)	3.2% (0.3% to 6.6%)	0.122
	Paradise	Age 5	2.7% (4/147)	3.0% (4/134)	-0.3% (-4.2% to 3.6%)	NS
Tympanosclerosis + segmented atrophy	Paradise	Age 5	21.1% (31/147)	14.2% (19/134)	6.9% (-1.9% to 15.8%)	0.131
Infection (procedure-related)	TARGET	≤24 mos. (as treated analysis)	6.8% ears that received tubes (43/635 ears)	NA	NC	NC
Premature tube extrusion	Rovers & Ingels	≤6 months	8.6% (8/93)	NR	NC	NC
Fibrosis	Paradise	Age 5	0.7% (1/147)	7.5% (10/134)	-6.8% (-11.4% to -2.1%)	0.004

			% (n/N)			
Adverse Event	Study	Time Point	TT	WW	Risk Difference (95% CI)	P-Value
Segmental atrophy	Paradise	Age 5	32.7% (48/147)	11.9% (16/134)	20.7% (11.4% to 30.1%)	<0.01
	Paradise	Age 5 (as treated analysis)	33.7% patients that received tubes* (58/172)	5.5% patients that did not receive tubes* (6/109)	28.2% (20.2% to 36.5%)	<0.01
Retraction pocket with other abnormality	Paradise	Age 5	0.7% (1/147)	0.7% (1/134)	-0.1% (-2.0% to 1.9%)	NS
Any abnormality	Paradise	Age 5	70.7% (104/147)	42.5% (57/134)	28.2% (17.1% to 39.4%)	<0.01
Problems with anesthesia	Mandel 1989	Peri-operative	0% (0/41)	NR	NC	NC

NA: not applicable; NC: not calculable; NR: not reported; NS: not statistically significant

* There was a discrepancy between what was reported in the results section and the corresponding table of this paper for the following; after consultation with one of our clinical experts it was decided that the results from the table would be used:
  - **Segmental atrophy**:
    - The results (page e60) indicate this occurred in 74.7% of patients who received tubes (including crossovers) and 3.0% of patients who did not receive tubes (including crossovers).
    - According to Table 2 RCT data, segmental atrophy occurred in 33.7% (58/172) of tubed patients and 5.5% (6/109) of patients who did not receive tubes.
  - **Tympanosclerosis**:
    - The results (see highlighted area, page e60) indicate this occurred in 40.4% of patients who received tubes (including crossovers) and 0.6% of patients who did not receive tubes (including crossovers).
    - According to Table 2 RCT data, I come up with 4.1% (7/172) of tubed patients and 1.0% (1/109) of patients who did not receive tubes

† Also includes patients in the myringotomy only group

‡ 6 (54.5%) healed within 3 months; 2 (18.2%) healed within 13 months; 1 (9.1%) was persistent requiring bilateral tympanoplasties; and 2 (18.2%) were lost to follow-up.

§ 5 (50%) healed within 3 months; 2 (20%) healed within 5 months; 2 (20%) persisted past 2 years requiring tympanoplasty; and 1 (10%) persisted past 4 years.

** Persistent, requiring hospitalization for IV antibiotics and daily suctioning through tube

†† One patient tested positive for Candida, responded with ketoconazole, and was treated as an outpatient; the other patient requiring hospitalization, antibiotics and aura toilet.

Appendix Table H2. Adverse events by ear: TT (unilateral) vs. No treatment (contralateral) for OME

			% (n/N)			
Adverse Event	Study	Time Point	TT	No Treatment	Risk Difference (95% CI)	P-Value
Perforation following spontaneous extrusion	Lildholdt	60 months	0% (0/134)	NA	NC	NC
Perforation following tube removal after 3 years *in situ*	Lildholdt	60 months	0.75% (1/134) (requiring myringo-plasty)	NA	NC	NC
Perforation/ retraction	Dempster	6 months	5.7% (2/35)	2.9% (1/35)	2.8% (-6.6% to 12.3%	NS
		12 months	5.7% (2/35)	8.6% (3/35)	-2.9% (-14.9% to 9.2%)	NS
Attic retraction	Maw & Bawden†	12 months	0.92%† (2/218)	2.3%† (5/218)	-1.4% (-3.7% to 1.0%)	NS
		24 months	7.4%† (13/175)	7.9%† (15/189)	-0.5% (-6.0% to 5.0%)	NS
		36 months	16.2%† (32/198)	17.3% † (34/197)	-1.1% (-8.5% to 6.3%)	NS
		48 months	26.1%† (47/180)	29.2%† (52/178)	-3.1% (-12.4% to 6.2%)	NS
		60 months	34.1%† (58/170)	38.7%† (65/168)	-4.6% (-14.8% to 5.7%)	NS
		84 months	36.2%† (47/130)	39.7%† (50/126)	-3.5% (-15.4% to 8.4%)	NS
		120 months	36.2%† (25/69)	40.3%† (27/67)	-4.1% (-20.4% to 12.3%)	NS
Tympanosclerosis	Maw 1991†	6 weeks	4.5%‡ (9/184)**	0.5%‡ (1/184)	4.4% (1.1% to 7.6%)	0.01
		3 months	19%‡ (16/84)	NR (NR)	NC	NC
	Dempster	6 months	20.0% (7/35)	0% (0/35)	20%	<0.01
	Maw 1991†	6 months	31.3%‡ (58/185)**	NR	NC	NC
		9 months	34.5%‡ (56/162)	0.6%‡ (1/162)	34.0% (26.5% to 41.4%)	<0.01
	Dempster	12 months	31.4% (11/35)	2.8% (1/35)	28.6% (12.2% to 44.9%)	0.002
	Maw 1991†	12 months	36.1%‡ (60/166)**	NR	NC	NC
		15 months	38.2%‡ (62/162)	0.6% ‡ (1/162)	37.7% (30.1% to 45.2%)	<0.01
		18 months	38.6%‡	1.1%‡	37.5% (30.1% to 44.9%)	<0.01

			% (n/N)			
Adverse Event	Study	Time Point	TT	No Treatment	Risk Difference (95% CI)	P-Value
			(68/176)	(2/176)		
		24 months	40.0%‡ (72/180)**	1.1%‡ (2/180)	38.9% (31.6% to 46.2%)	<0.01
		36 months	47.4%‡ (85/179)**	NR	NC	NC
		48 months	44.6%‡ (62/139)**	0.7%‡ (1/139)	43.9% (35.5% to 52.3%)	<0.01
	Lildholdt	60 months	33.3%§ (44/132)	6.8%§ (9/132)	26.5% (17.4% to 35.6%)	<0.01
	Maw 1991†	60 months	48.6%‡ (53/109)**	2.8%‡ (3/109)	45.9% (36.0% to 55.7%)	<0.01
Segmental atrophy	Maw & Bawden†	12 months	5.6%† (12/216)	0.5%† (1/216)	5.1% (1.9% to 8.3%)	0.002
		24 months	8.7%† (16/184)	0.0% † (0/184)	8.7%	<0.01
		36 months	19.4%† (38/196)	1.5% † (3/196)	17.9% (12.1% to 23.7%)	<0.01
		48 months	24.4%† (43/176)	1.1%† (2/176)	23.3% (16.8% to 29.8%)	<0.01
	Lildholdt	60 months	34.8%§ (46/132)	7.6%§ (10/132)	27.3% (17.8% to 36.6%)	<0.01
	Maw & Bawden†	60 months	15.5%† (26/168)	3.0%† (5/168)	12.5% (6.5% to 18.5%)	<0.01
		84 months	20.8%† (26/125)	1.6%† (2/135)	19.3% (11.9% to 26.7%)	<0.01
		120 months	22.4%† (15/67)	4.5%† (3/67)	17.9% (6.8% to 29.1%)	<0.01
Minor scarring or thickening of the pars tensa (distinct from Tympanosclerosis, related to the middle ear condition)	Maw & Bawden†	12 months	14%† (28/200)	7.5%† (15/200)	6.5% (0.5% to 12.5%)	0.036
		24 months	11%† (18/164)	10.4%† (17/164)	0.6% (-6.1% to 7.3%)	NS
		36 months	18.2%† (27/148)	13.5%† (20/148)	4.7% (-3.6% to 13.0%)	NS
		48 months	15.1%† (19/126)	18.3%† (23/126)	-3.2% (-12.4% to 6.0%)	NS
		60 months	12.6%† (16/127)	14.2%† (18/127)	-1.6% (-10.0% to 6.8%)	NS
		84 months	12.5%† (11/88)	19.3%† (17/88)	-6.8% (-17.6% to 3.9%)	NS
		120 months	8.9%† (4/45)	20.0%† (9/45)	-11.1% (-25.5% to 3.2%)	0.14
Granulation tissue in ear canal	Maw & Bawden†	60 months	4.5%† (6/134) (5 remained abnormal at	NR	NC	NC

			% (n/N)			
Adverse Event	Study	Time Point	TT	No Treatment	Risk Difference (95% CI)	P-Value
			final check-up)			
Atelectasis	Maw & Bawden†	12 months	3.7%† (8/214)	4.2%† (9/214)	-0.5% (-4.2% to 3.2%)	NS
		24 months	7.7%† (14/181)	6.0%† (11/183)	1.7% (-3.5% to 6.9%)	NS
		36 months	3.1%† (6/191)	6.3%† (12/191)	-3.1% (-7.4% to 1.1%)	0.15
		48 months	5.6%† (10/177)	8.2%† (14/171)	-2.5% (-7.9% to 2.8%)	NS
		60 months	7.2%† (12/166)	6.5%† (10/155)	0.8% (-4.7% to 6.3%)	NS
		84 months	13.0%† (16/123)	16.5%† (19/115)	-3.5% (-12.5% to 5.5%)	NS
		120 months	14.7%† (10/68)	11.1%† (7/63)	3.6% (-7.9% to 15%)	NS

CI: confidence interval; NA: not applicable; NR: not reported; NS: not statistically significant

† Also includes those who received adenoidectomy/adenotonsillectomy

‡ Reported as cumulative incidence; unable to determine n/N.

§ Reported by pathology score of pars tensa. Scores 0 and 1 are considered "Normal" and scores 2 or 3 are considered "Pathological"; these percentages represent scores 2 and 3 only.

** Maw 1991: the following percentage of patients had moderate, major, or severe tympanosclerosis:

- 1.5 mos.: 0.5% (moderate: 1/184)
- 6 mos.: 10.8% (moderate: 16/185, major: 4/185)
- 12 mos. 11.4% (moderate: 15/166, major: 6/166)
- 24 mos. 18.9% (moderate: 22/180, major: 10/180, severe: 2/180)
- 36 mos.: 22.9% (moderate: 29/179, major: 7/179, severe: 5/179)
- 48 mos.: 24.5% (moderate: 23/139, major: 10/139, severe: 1/139)
- 60 mos.: 30.3% (moderate: 28/109, major: 3/109, severe: 2/109)

Appendix Table H3. Adverse events: TT vs. Myringotomy for OME

			% (n/N)*			
Adverse Event	**Study**	**Time Point**	**TT**	**Myringotomy**	**Risk Difference (95% CI)**	**P-Value**
Perforation	Gates	≤24 months	1.2%§ (3/254)	1.3%§ (3/237)	-0.1% (-2.0% to 1.9%)	NS
	Mandel 1989	36 months	13.7%‡** (11/80)		NC	NC
	Mandel 1992	NR	11.2%‡†† (10/89)		NC	NC
Tube extrusion into middle ear	Gates	≤24 months	0.5%‡‡ (3/578)		NC	NC
Necrosis of the long process of the incus requiring ossiculoplastic repair	Gates	≤24 months	0.8% (1/129)	0% (0/107)	0.8%	NS
Surgical complications (not specified)	D'Eredita	Peri-operative	0% (0/15)	0% (0/15)	0%	NS
	Kent	Post-operative	0% ears (0/30 ears)	0% ears (0/30 ears)	0%	NS
Problems with anesthesia	Mandel 1989	Peri-operative	0% (0/41)	0% (0/39)	0%	NS
Death	Gates	24 months	0% (0/129)	0% (0/107)	0%	NS
Severe otalgia	Koopman	2 days post-operative	NR	0.4% ears (1/208 ears)	NC	NC
Epidermal pearl on tympanic membrane (removed via suction as an outpatient)	Koopman	NR	NR	0.4% ears (1/208 ears)	NC	NC
Nystagmus	Kent	Post-operative	0% ears (0/30 ears)	0% ears (0/30 ears)	0%	NS
Otorrhea (persistent, requiring hospitalization for IV antibiotics and daily suctioning through tube)	Mandel 1989	NR	2.4% (1/41)	0% (0/39)	2.4%	NS
	Mandel 1992	NR	2.2% (2/89)		NC	NC

CI: confidence interval; NA: not applicable; NR: not reported; NS: not statistically significant

* Outcomes reported by patient unless otherwise indicated.

† Requiring repeat myringotomy and insertion of new TT.

‡ Reported out of all patients who received tubes, regardless of original assignment; includes patients in the "no surgery" group.

§ Of the 6 total, 4 underwent tympanoplastic repair and 2 were lost to follow-up. Authors do not indicate to which groups the patients belonged.

** 6 (54.5%) healed within 3 months, 2 (18.2%) within 13 months; 1 (9.1%) required bilateral tympanoplasty at >36 months and 2 (18.2%) were lost-to-follow-up.

†† 5 (50%) healed within 3 months, 2 (20%) within 5 months; 2 (20%) required tympanoplasty for perforations persisting > 2 years, and 1 (10%) persisted > 4 years.

‡‡ Reported out of all patients who underwent tube placement regardless of group assignment (including +/- adenoidectomy); these patients required a repeat myringotomy for removal and insertion of a new tube.

Appendix Table H4. Adverse events: TT plus adenoidectomy vs. Myringotomy plus adenoidectomy for OME

			% (n/N)*			
Adverse Event	Study†	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
Chronic otorrhea (≥3 episodes per year)	Popova	≤12 mos.	5% (2/42)	0% (0/36)	2%	NS
Perforation‡‡‡	Caye-Thomasen	36 months	3% ears (4/146 ears)	1% ears (2/146 ears)	1.4% (-1.9% to 4.6%)	NS
		84 months	1% ears (1/115 ears)	1% ears (1/115 ears)	0.0% (-2.4 % to 2.4%)	NS
		300 months	1% ears (1/80 ears)	1% ears (1/80 ears)	0.0% (-3.4% to 3.4%)	NS
Perforation (persistent)	Casselbrant 2009	NR	3.2%‡ (1/31)	0% (0/33)	3.2%	NS
	Gates	≤24 months	1.2%§ (3/254)	1.3%§ (3/237)	-0.1% (-2.0% to 1.9%)	NS
	Leek	NR	0% ears (0/72 ears)	NR	NC	NC
	Bonding	12-36 months	1% ears (2/193 ears)	0% ears (0/193 ears)	1.0%	0.1568
Perforation (permanent)	Ruckley	3 months	NR	0% ears (0/36 ears)	NC	NC
Subtotal perforation	To	9-21 months	2% ears (1/56 ears)	NR	NC	NC
Tube extrusion into middle ear	Gates	≤24 months	0.5% (3/578)§**		NC	NC
Premature extrusion	Popova	NR	2.4% (1/42)	NR	NC	NC
Displacement of tube	Leek	NR	4.1% ears (3/72 ears)	NR	NC	NC
Blockage of tube	Ruckley	3 months	5.5% ears (2/36 ears)	NR	NC	NC
	Popova	NR	7.1% (3/42)	NR	NC	NC
Tube occlusion	Popova	NR	16.7% (7/42)	NR	NC	NC
	Shishegar	6 months	17% ears (5/30 ears)	NR	NC	NC
Tympanosclerosis	Ruckley	3 months	0% ears (0/36 ears)	0% ears (0/36 ears)	0.0%	NC
	To	Mean 24 months	16% ears†† (9/56 ears)	2% ears (1/56 ears)	14.3% (4.1% to 24.5%)	0.0083
	Tos & Bonding	12-36 months	48% ears (92/193 ears)	19% ears (37/193 ears)	28.5% (19.5% to 37.5%)	<0.001
	Tos/	12-36	Including	Including	37.8% (29.8% to	<0.001

			% (n/N)*			
Adverse Event	Study†	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
	Bonding/ Khodaverdi	months	crossover: 48% ears (114/238 ears)	crossover: 10% ears (15/148 ears)	45.8%)	
	Tos/ Bonding/ Khodaverdi	72-84 months	Including crossover: 59% ears (106/181 ears)	Including crossover: 13% ears (14/111 ears)	46.0% (36.5 to 55.4%)	<0.001
Myringosclerosis	Caye-Thomasen	36 months	46% ears††† (67/146 ears)	10% ears††† (15/146 ears)	35.6% (26.2% to 45.1%)	<0.0001
		84 months	50% ears††† (58/115 ears)	15% ears††† (17/115 ears)	35.7% (24.5% to 46.9%)	<0.0001
		300 months	54% ears††† (43/80 ears)	20% ears††† (16/80 ears)	33.8% (19.7% to 47.8%)	<0.0001
	Tos/ Bonding/ Khodaverdi	300 months	57% ears (59/104 ears)	29% ears (30/104 ears)	27.9% (15.0% to 40.8%)	<0.001
Pars tens atrophy	Bonding 1985	12-36 months	9% ears (17/193 ears)	10% ears (19/193 ears)	-1.0% (-6.8% to 4.8%)	NS
	Tos/ Bonding/ Khodaverdi	300 months	30% ears (31/104 ears)	18% ears (19/104 ears)	11.5% (0.0% to 23.1%)	0.0521
Pars tens atrophy with secondary TT insertion	Tos/ Bonding/ Khodaverdi	12-36 months	NR	42% ears (11/26 ears)	NC	NC
Pars tens atrophy and tympanosclerosis	Tos/ Bonding/ Khodaverdi	12-36 months	5% ears (10/193 ears)	4% ears (8/193 ears)	1.0% (-3.2% to 5.2%)	NS
Atrophy†††	Caye-Thomasen	36 months	13% ears (19/146 ears)	8% ears (12/146 ears)	4.8% (-2.3% to 11.8%)	NS
		84 months	15% ears (17/115 ears)	13% ears (15/115 ears)	1.7% (-7.2% to 10.7%)	NS
		300 months	27% ears (22/80 ears)	12% ears (10/80 ears)	15.0% (2.8% to 27.2%)	0.009
Retraction segments requiring TT (re)insertion	To	9-24 months	4% ears (2/56 ears)	2% ears (1/56 ears)	1.8% (-4.2% to 7.8%)	NS
Flaccida retraction	Tos/ Bonding/ Khodaverdi	300 months	19% ears (20/104 ears)	17% ears (18/104 ears)	1.9% (-8.6% to 12.4%)	NS
Attic retraction‡‡	Tos/ Bonding/ Khodaverdi	12-36 months	29.7% (52/175 ears)	34.9% (61/175 ears)	-5.1% (-14.9% to 4.6%)	NS
Attic retraction‡‡	Tos/ Bonding/ Khodaverdi	12-36 months	Stage I: 20% ears (35/175 ears) Stage II: 7.4% ears	Stage 1: 14% ears (25/175 ears) Stage II: 17% ears	Stage I: 5.7% (-2.2% to 13.6%) Stage II: -9.7% (-16.5 to -2.9%)	Stage I: 0.1567 Stage II: 0.0057

			% (n/N)*			
Adverse Event	Study†	Time Point	TT + Ad	Myringotomy + Ad	Risk Difference (95% CI)	P-Value
			(13/175 ears) Stage III: 2% ears (4/175 ears) Stage IV: 0% ears (0/175 ears)	(30/175 ears) Stage III: 3% ears (6/175 ears) Stage IV: 0% ears (0/175 ears)	Stage III: -1.1 (-4.6% to 2.4%) Stage IV: 0%	Stage III: NS Stage IV: NC
Retraction-flaccida†††	Caye-Thomasen	36 months	30% ears (44/146 ears)	30% ears (44/146 ears)	0.0% (-10.5 % to 10.5%)	NS
		84 months	20% ears (23/115 ears)	20% ears (25/115 ears)	0.0% (-10.3 % to 10.3%)	NS
		300 months	15% ears (12/80 ears)	18% ears (14/80 ears)	-2.5% (-13.9% to 8.9%)	NS
Retraction-tensa†††	Caye-Thomasen	36 months	12% ears (18/146 ears)	12% ears (18/146 ears)	0.0% (-7.5 % to 7.5%)	NS
		84 months	5% ears (6/115 ears)	5% ears (6/115 ears)	0.0% (-5.8 % to 5.8%)	NS
		300 months	3% ears (2/80 ears)	1% ears (1/80 ears)	1.3% (-3.0% to 5.5%)	NS
Difficulty during anesthesia	Casselbrant 2009	Peri-operative	3.2%§§ (1/31)	0% (0/33)	3.2%	NS
	Gates	Peri-operative	0% (0/125)	0% (0/130)	0.0%	NC
Bleeding after adenoidectomy requiring subsequent operation	Gates	Peri-operative	0.4% (1/254)***		NC	NC
Tube-related complications (not specified)	Vlastos	NR	0% (0/25)	NA	NC	NC
Death	Gates	≤24 months	0% (0/129)	0% (0/130)	0%	NS

CI = confidence interval; N/A = not applicable; NR = not reported; TT = tympanostomy tubes.

* Outcomes reported by patient unless otherwise indicated.

† Tos 1983, Bonding 1985, and Khodaverdi 2013 report data for the same study at different follow-up times.

‡ Lead to bilateral tympanoplasties

§ Reported out of all patients who underwent tube placement regardless of group assignment (including +/- adenoidectomy);

** Required a repeat myringotomy for removal and insertion of a new tube.

†† Same patients with extrusion; tympanosclerosis was only noted after extrusion.

‡‡ Stage 0 = normal (not included in table); Stage I = slight, insignificant retraction; Stage II = moderate retraction with adhesion to the neck of the malleus; Stage III = slight erosion of the scutum; Stage IV = deep retraction pocket.

§§ Underwent treatment with myringotomy and tubes only.

*** Unclear to which group this ear was allocated.

††† Percentages were estimated from figure 2 of the article using the range of percentages provided in the text as a guide; numerators were back-calculated and the number of patients lost-to-follow-up was used as the denominator for each time-point.

‡‡‡numerators were back-calculated using percentages provided in the text and the number of patients lost-to-follow-up as the denominator for each time-point.

Appendix Table H5. Adverse events: TT + adenoidectomy vs. Adenoidectomy only for OME‡

			% (n/N)*			
Adverse Event	**Study†**	**Time Point**	**TT + Ad**	**Ad Only**	**Risk Difference (95% CI)**	**P-Value**
Perforation	Brown 1978	60 months	0% ears (0/55 ears)	0% ears (0/55 ears)	0%	NC
Perforation/ retraction	Dempster 1993	6 months	5% ears (2/37 ears)	3% ears (1/37 ears)	2.7% (-6.3% to 11.7%)	NS
	Dempster 1993	12 months	11% ears (4/37 ears)	11% ears (4/37 ears)	0.0% (-14.2% to 14.2%)	NS
Scar at site of former grommet	Brown 1978	NR	13% ears (7/55 ears)	0% ears (0/55 ears)	12.7%	0.007
Tympanosclerosis	Dempster 1993	6 months	40% ears (15/37 ears)	0% ears (0/37 ears)	40.5%	<0.001
	Dempster 1993	12 months	46% ears (17/37 ears)	0% ears (0/37 ears)	46.0%	<0.001
	Brown 1978	60 months	42% ears† (23/55 ears)	0% ears (0/55 ears)	41.8%	<0.001
Retracted tympanic membrane	Brown 1978	60 months	18% ears (10/55 ears)	16% ears (9/55 ears)	1.8% (-12.3% to 15.9%)	NS
Attic retraction‡	Brown 1978	60 months	5% ears (3/55 ears)	0% ears (0/55 ears)	5.5%	0.08
	Maw & Bawden‡	*12 months*	*0.92%† (2/218)*	*2.3%† (5/218)*	*-1.4% (-3.7% to 1.0%)*	*NS*
		24 months	*7.4%† (13/175)*	*7.9%† (15/189)*	*-0.5% (-6.0% to 5.0%)*	*NS*
		36 months	*16.2%† (32/198)*	*17.3% † (34/197)*	*-1.1% (-8.5% to 6.3%)*	*NS*
		48 months	*26.1%† (47/180)*	*29.2%† (52/178)*	*-3.1% (-12.4% to 6.2%)*	*NS*
		60 months	*34.1%† (58/170)*	*38.7%† (65/168)*	*-4.6% (-14.8% to 5.7%)*	*NS*
		84 months	*36.2%† (47/130)*	*39.7%† (50/126)*	*-3.5% (-15.4% to 8.4%)*	*NS*
		120 months	*36.2%† (25/69)*	*40.3%† (27/67)*	*-4.1% (-20.4% to 12.3%)*	*NS*
Immediate postoperative complications (not specified)	Dempster 1993	Post-operative	0% ears (0/37 ears)	0% ears (0/37 ears)	0.0%	NC
Segmental atrophy‡	*Maw & Bawden‡*	*12 months*	*5.6%† (12/216)*	*0.5%† (1/216)*	*5.1% (1.9% to 8.3%)*	*0.002*
		24 months	*8.7%† (16/184)*	*0.0% † (0/184)*	*8.7%*	*<0.01*
		36 months	*19.4%† (38/196)*	*1.5% † (3/196)*	*17.9% (12.1% to 23.7%)*	*<0.01*
		48 months	*24.4%† (43/176)*	*1.1%† (2/176)*	*23.3% (16.8% to 29.8%)*	*<0.01*

			% (n/N)*			
Adverse Event	Study†	Time Point	TT + Ad	Ad Only	Risk Difference (95% CI)	P-Value
		60 months	15.5%† (26/168)	3.0%† (5/168)	12.5% (6.5% to 18.5%)	<0.01
		84 months	20.8%† (26/125)	1.6%† (2/135)	19.3% (11.9% to 26.7%)	<0.01
		120 months	22.4%† (15/67)	4.5%† (3/67)	17.9% (6.8% to 29.1%)	<0.01
Minor scarring or thickening of the pars tensa‡ (distinct from Tympanosclerosis, related to the middle ear condition)	Maw & Bawden‡	12 months	14%† (28/200)	7.5%† (15/200)	6.5% (0.5% to 12.5%)	0.036
		24 months	11%† (18/164)	10.4%† (17/164)	0.6% (-6.1% to 7.3%)	NS
		36 months	18.2%† (27/148)	13.5%† (20/148)	4.7% (-3.6% to 13.0%)	NS
		48 months	15.1%† (19/126)	18.3%† (23/126)	-3.2% (-12.4% to 6.0%)	NS
		60 months	12.6%† (16/127)	14.2%† (18/127)	-1.6% (-10.0% to 6.8%)	NS
		84 months	12.5%† (11/88)	19.3%† (17/88)	-6.8% (-17.6% to 3.9%)	NS
		120 months	8.9%† (4/45)	20.0%† (9/45)	-11.1% (-25.5% to 3.2%)	0.14
Granulation tissue in ear canal‡	Maw & Bawden‡	60 months	4.5%† (6/134) (5 remained abnormal at final check-up)	NR	NC	NC
Atelectasis	Maw & Bawden‡	12 months	3.7%† (8/214)	4.2%† (9/214)	-0.5% (-4.2% to 3.2%)	NS
		24 months	7.7%† (14/181)	6.0%† (11/183)	1.7% (-3.5% to 6.9%)	NS
		36 months	3.1%† (6/191)	6.3%† (12/191)	-3.1% (-7.4% to 1.1%)	0.15
		48 months	5.6%† (10/177)	8.2%† (14/171)	-2.5% (-7.9% to 2.8%)	NS
		60 months	7.2%† (12/166)	6.5%† (10/155)	0.8% (-4.7% to 6.3%)	NS
		84 months	13.0%† (16/123)	16.5%† (19/115)	-3.5% (-12.5% to 5.5%)	NS
		120 months	14.7%† (10/68)	11.1%† (7/63)	3.6% (-7.9% to 15%)	NS

CI = confidence interval; N/A = not applicable; NR = not reported; TT = tympanostomy tubes.

* Outcomes reported by ears.

† Includes diffuse and anteroinferior types.

‡ Duplicate data: Data for all patients (with or without adenoidectomy) in Maw & Bawden trial were also reported in Appendix Table H2 for the following adverse events: attic retraction, segmental atrophy, minor scarring or thickening of the pars tensa, granulation tissue in ear canal, atelectasis

Appendix Table H6. Adverse events: TT vs. Myringotomy + Adenoidectomy for OME

			% (n/N)*			
Adverse Event	**Study**	**Time Point**	**TT**	**Myringotomy + Ad**	**Risk Difference (95% CI)**	**P-Value**
Perforation	Gates	≤24 months	1.2%* (3/254)	1.3%* (3/237)	-0.1% (-2.0% to 1.9%)	NS
Perforation (persistent)	Casselbrant 2009	≤36 months	0% (0/33)	0% (0/33)	0%	NS
Tube extrusion into middle ear	Gates	≤24 months	0.5%† (3/578)		NC	NC
Necrosis of the long process of the incus requiring ossiculoplastic repair	Gates	≤24 months	0.8% (1/129)	0% (0/107)	0.8%	NS
Death	Gates	≤24 months	0% (0/129)	0% (0/125)	0%	NS
Difficulty during anesthesia	Casselbrant 2009	Peri-operative	0% (0/33)	0% (0/33)	0%	NS

CI: confidence interval; NA: not applicable; NR: not reported; NS: not statistically significant

* Of the 6 total, 4 underwent tympanoplastic repair and 2 were lost to follow-up. Authors do not indicate to which groups the patients belonged.

† Reported out of all patients who underwent tube placement regardless of group assignment (including +/- adenoidectomy); these patients required a repeat myringotomy for removal and insertion of a new tube.

Appendix Table H7. Adverse events: TT (unilateral) vs. No procedure (unilateral) + adenoidectomy for OME

			% (n/N)			
Adverse Event	Study	Time Point	TT	No Treatment + Ad	Risk Difference (95% CI)	P-Value
Immediate postoperative complications (not specified)	Dempster 1993	Post-operative	0% ears (0/35 ears)	0% ears (0/37 ears)	0.0%	NC
Tympanosclerosis	Dempster	6 months	20% (7/35)	0% ears (0/37 ears)	20%	0.0045
		12 months	31% (11/35)	0% ears (0/37 ears)	31%	0.0002
Perforation/ retraction	Dempster	6 months	6% (2/35)	3% ears (1/37 ears)	3% (-6% to 12%)	NS
		12 months	6% (2/35)	11% ears (4/37 ears)	-5% (-18% to 8%)	NS
Attic retraction‡	*Maw & Bawden‡*	*12 months*	*0.92%† (2/218)*	*2.3%† (5/218)*	*-1.4% (-3.7% to 1.0%)*	*NS*
		24 months	*7.4%† (13/175)*	*7.9%† (15/189)*	*-0.5% (-6.0% to 5.0%)*	*NS*
		36 months	*16.2%† (32/198)*	*17.3% † (34/197)*	*-1.1% (-8.5% to 6.3%)*	*NS*
		48 months	*26.1%† (47/180)*	*29.2%† (52/178)*	*-3.1% (-12.4% to 6.2%)*	*NS*
		60 months	*34.1%† (58/170)*	*38.7%† (65/168)*	*-4.6% (-14.8% to 5.7%)*	*NS*
		84 months	*36.2%† (47/130)*	*39.7%† (50/126)*	*-3.5% (-15.4% to 8.4%)*	*NS*
		120 months	*36.2%† (25/69)*	*40.3%† (27/67)*	*-4.1% (-20.4% to 12.3%)*	*NS*
Segmental atrophy‡	*Maw & Bawden‡*	*12 months*	*5.6%† (12/216)*	*0.5%† (1/216)*	*5.1% (1.9% to 8.3%)*	*0.002*
		24 months	*8.7%† (16/184)*	*0.0% † (0/184)*	*8.7%*	*<0.01*
		36 months	*19.4%† (38/196)*	*1.5% † (3/196)*	*17.9% (12.1% to 23.7%)*	*<0.01*
		48 months	*24.4%† (43/176)*	*1.1%† (2/176)*	*23.3% (16.8% to 29.8%)*	*<0.01*
		60 months	*15.5%† (26/168)*	*3.0%† (5/168)*	*12.5% (6.5% to 18.5%)*	*<0.01*
		84 months	*20.8%† (26/125)*	*1.6%† (2/135)*	*19.3% (11.9% to 26.7%)*	*<0.01*
		120 months	*22.4%† (15/67)*	*4.5%† (3/67)*	*17.9% (6.8% to 29.1%)*	*<0.01*
Minor scarring or thickening of the	*Maw & Bawden‡*	*12 months*	*14%† (28/200)*	*7.5%† (15/200)*	*6.5% (0.5% to 12.5%)*	*0.036*

			% (n/N)			
Adverse Event	Study	Time Point	TT	No Treatment + Ad	Risk Difference (95% CI)	P-Value
pars tensa‡ (distinct from Tympanosclerosis, related to the middle ear condition)		*24 months*	*11%† (18/164)*	*10.4%† (17/164)*	*0.6% (-6.1% to 7.3%)*	*NS*
		36 months	*18.2%† (27/148)*	*13.5%† (20/148)*	*4.7% (-3.6% to 13.0%)*	*NS*
		48 months	*15.1%† (19/126)*	*18.3%† (23/126)*	*-3.2% (-12.4% to 6.0%)*	*NS*
		60 months	*12.6%† (16/127)*	*14.2%† (18/127)*	*-1.6% (-10.0% to 6.8%)*	*NS*
		84 months	*12.5%† (11/88)*	*19.3%† (17/88)*	*-6.8% (-17.6% to 3.9%)*	*NS*
		120 months	*8.9%† (4/45)*	*20.0%† (9/45)*	*-11.1% (-25.5% to 3.2%)*	*0.14*
Granulation tissue in ear canal‡	*Maw & Bawden‡*	*60 months*	*4.5%† (6/134) (5 remained abnormal at final check-up)*	*NR*	*NC*	*NC*
Atelectasis‡	*Maw & Bawden‡*	*12 months*	*3.7%† (8/214)*	*4.2%† (9/214)*	*-0.5% (-4.2% to 3.2%)*	*NS*
		24 months	*7.7%† (14/181)*	*6.0%† (11/183)*	*1.7% (-3.5% to 6.9%)*	*NS*
		36 months	*3.1%† (6/191)*	*6.3%† (12/191)*	*-3.1% (-7.4% to 1.1%)*	*0.15*
		48 months	*5.6%† (10/177)*	*8.2%† (14/171)*	*-2.5% (-7.9% to 2.8%)*	*NS*
		60 months	*7.2%† (12/166)*	*6.5%† (10/155)*	*0.8% (-4.7% to 6.3%)*	*NS*
		84 months	*13.0%† (16/123)*	*16.5%† (19/115)*	*-3.5% (-12.5% to 5.5%)*	*NS*
		120 months	*14.7%† (10/68)*	*11.1%† (7/63)*	*3.6% (-7.9% to 15%)*	*NS*

CI: confidence interval; NA: not applicable; NR: not reported; NS: not statistically significant

† Also includes those who received adenoidectomy/adenotonsillectomy

‡ Reported as cumulative incidence; unable to determine n/N.

§ Reported by pathology score of pars tensa. Scores 0 and 1 are considered "Normal" and scores 2 or 3 are considered "Pathological"; these percentages represent scores 2 and 3 only.

** Maw 1991: the following percentage of patients had moderate, major, or severe tympanosclerosis:

- 1.5 mos.: 0.5% (moderate: 1/184)
- 6 mos.: 10.8% (moderate: 16/185, major: 4/185)
- 12 mos. 11.4% (moderate: 15/166, major: 6/166)
- 24 mos. 18.9% (moderate: 22/180, major: 10/180, severe: 2/180)
- 36 mos.: 22.9% (moderate: 29/179, major: 7/179, severe: 5/179)
- 48 mos.: 24.5% (moderate: 23/139, major: 10/139, severe: 1/139)
- 60 mos.: 30.3% (moderate: 28/109, major: 3/109, severe: 2/109)

Appendix Table H8. Adverse events: TT vs. Antibiotics for OME

			% (n/N)			
Study	Adverse Event	Time Point	TT	Antibiotics	Risk Difference (95% CI)	P-Value
Bernard, Stenstrom	Myringosclerosis	≤18 mos.	13% (17/60)	NR	NC	NC
		72-120 mos.	66% (25/38 who received TT only once)	15% (4/27 who never received TT)	51% (31% to 71%)	0.0001
	Superinfection	≤18 mos.	30% (18/60)	NR	NC	NC
	Foreign body reaction*	≤18 mos.	13% (17/60)	NR	NC	NC
	Chronic perforation	≤18 mos.	0% (0/60)	NR	NC	NC
	Perforation, retraction, or atelectasis	72-120 mos.	NR (n=57 as allocated)	NR (n=56 as allocated)	RR 1.5 (1.2-1.9)	<0.05
		72-120 mos.	37% (14/38 who received TT only once)	4% (1/27 who never received TT)	33% (16% to 50%)	0.0019
		72-120 mos.	NR (n=86 who received TT)	NR (n=27 who never received TT)	RR 4.8 (2.2 to 10.6)	<0.05
	Allergic reaction to medication	≤18 mos.	NR	6.2% (4/65)	NC	NC
	Nausea due to medication	≤18 mos.	NR	3.1% (2/65)	NC	NC
	Vomiting due to medication	≤18 mos.	NR	0% (0/65)	NC	NC
	Serious side effects of medication	≤18 mos.	NR	0% (0/65)	NC	NC

* Purulent discharge and formation of pyogenic granuloma

Appendix Table H9. Adverse events: TT vs. Prophylactic Antibiotics for Recurrent AOM

			% (n/N)*			
Adverse Event	Study	Time Point	TT	Antibiotics	Risk Difference (95% CI)	P-Value
Perforation	Casselbrant 1992	Various up to 21 months	13.2%† (10/76)	NR	NC	NC
	Gebhart	NR (healed by 9 months)	3.7% (2/54)	NR	NC	NC
Premature extrusion (requiring reinsertion)	El-Sayed		6.5% (2/31)	NR	NC	NC
Tube pushed into middle ear space	Gebhart	NR	0% (0/54)	NR	NC	NC
Persistent otorrhea	El-Sayed	6 months	0% (0/31)	NR	NC	NC
3+ episodes of otorrhea or AOM††	Casselbrant 1992	Various up to 21 months	25%†† (10/76)	NR	NC	NC
Infection (persistent)	Gebhart	NR	0% (0/54)	NR	NC	NC
Adverse events related to general anesthesia	Gebhart	NR	0%‡ (0/54)	NR	NC	NC
Adverse reaction to medication	Casselbrant	NR	NR	7.0%§ (6/90)	NC	NC
	El-Sayed	6 months	NR	9.1%** (2/22)	NC	NC
Any adverse event (i.e. to surgery, anesthesia) medication)	Gonzalez	6 months	0% (0/22)	0% (0/21)	0%	NS
Suppurative complication	Casselbrant	24 months	0% (0/64)	0% (0/42)	0%	NS

CI = confidence interval; N/A = not applicable; NR = not reported; TT = tympanostomy tubes.

* Outcomes reported by patient unless otherwise indicated.

† 7 perforations healed spontaneously within a few months; 3 (3.9%) persisted for 5, 9, and 21 months but were all were later noted to have healed spontaneously.

‡ To include cardiac arrhythmia, aspiration, cardiac arrest, and respiratory arrest.

§ Amoxicillin. Suspected urticaria in 4 children and vaginitis in 2 children; these patients were withdrawn from the study.

** Sulfamethoxazole and trimethoprim (SMZ-T) syrup. Two children developed a skin rash.

†† The study indicated that "most of these episodes consisted of otorrhea" but results were not stratified by AOM vs. otorrhea

Appendix Table H10. Adverse events: TT vs. Placebo or No treatment for Recurrent AOM

			% (n/N)*			
Adverse Event	**Study**	**Time Point**	**TT**	**Placebo Or No Treatment**	**Risk Difference (95% CI)**	**P-Value**
Perforation‡‡	*Casselbrant 1992*	*Various up to 21 months*	*13.2%†, ‡‡ (10/76)*	NR	NA	NA
3+ episodes of otorrhea or AOM††, ‡‡	*Casselbrant 1992*	*Various up to 21 months*	*25%††, ‡‡ (10/76)*	NR	NC	NC
Any serious adverse event‡	Gonzalez 1986	6 months	0% (0/22)	0% (0/20)	NA	NA
	Kujala 2012, 2014	12 months	0% (0/100)	0% (0/100)	NA	NA
Suppurative complication	Casselbrant 1992	24 months	0% (0/64)	0% (0/41)	NA	NA

CI = confidence interval; N/A = not applicable; NR = not reported; TT = tympanostomy tubes.

* Outcomes reported by patient unless otherwise indicated.

† 7 perforations healed spontaneously within a few months; 3 (3.9%) persisted for 5, 9, and 21 months but were all were later noted to have healed spontaneously.

‡ Including events related to the surgical procedure (e.g., hemorrhage), anesthesia, medication, or other.

†† The study indicated that "most of these episodes consisted of otorrhea" but results were not stratified by AOM vs. otorrhea

‡‡ Outcomes duplicated in Adverse Events table comparing TT to antibiotics

Appendix Table H11. Adverse events: TT (one ear) vs. Myringotomy or No procedure (opposite ear) for OME or Recurrent AOM

			% (n/N)*			
Study	**Adverse Event**	**Time Point**	**TT (Unilateral)**	**Myringotomy Or No Treatment (Contralateral)**	**Risk Difference (95% CI)**	**P-Value**
Le	Permanent perforation	24 months	3% (2/61 ears treated with TT)	0% (0/26 ears that never received TT)	3%	0.353
	Tympanosclerosis	24 months	57% (35/61 ears treated with TT)	19% (5/26 ears that never received TT)	38% (19% to 58%)	0.001
	Retraction or atrophy	24 months	25% (15/61 ears treated with TT)	31% (8/26 ears that never received TT)	-6% (-27% to 15%)	NS
			% (n/N)*			
Study	**Adverse Event**	**Time Point**	**TT (Unilateral)**	**Myringotomy Or No Treatment (Contralateral)**	**Risk Difference (95% CI)**	**P-Value**
Le	Permanent perforation	24 months	3% (2/61 ears treated with TT)	0% (0/27 ears that never received TT)	3%	0.344
	Tympanosclerosis	24 months	57% (35/61 ears treated with TT)	7% (2/27 ears that never received TT)	50% (34% to 66%)	<0.01
	Retraction or atrophy	24 months	25% (15/61 ears treated with TT)	4% (1/27 ears that never received TT)*	21% (8% to 34%)	0.020

Appendix Table H12. Adverse events from case series: TT for OME or Recurrent AOM

Complication	Follow-Up	% (N/N)	Case Series
Cholesteatoma	≥1 year	1.1% (62/5575)	Golz
	NR (mean 2.8 yrs. in study)	0.8% (4/507)	Lindstrom
Adverse effects of anesthesia (total)*	Intraoperative and Perioperative	3.9% (126/3198)	Hoffmann
Death	Perioperative	0% (0/3198)	Hoffmann
Upper airway obstruction	Perioperative	0.9% (9/1000)	Hoffmann
Agitation†	Perioperative	5.7% (57/1000)	Hoffmann
Prolonged recovery‡	Perioperative	2.7% (27/1000)	Hoffmann
Emesis	Perioperative	1.6% (16/1000)	Hoffmann
Laryngospasm	Perioperative	0.9% (9/1000)	Hoffmann
Desaturation	Perioperative	0.4% (4/1000)	Hoffmann
Bradycardia	Perioperative	0.1% (1/1000)	Hoffmann
Dysrhythmia	Perioperative	0.1% (1/1000)	Hoffmann
Stridor	Perioperative	0.2% (2/1000)	Hoffmann
Persistent perforation after extrusion	NR (mean 2.8 yrs. in study)	1.3% (10/756 ears)	Lindstrom
Retained tube§	NR (mean 2.8 yrs. in study)	12.1% (92/756 ears)	Lindstrom
Removal of retained tube**	NR (mean 2.8 yrs. in study)	1.3% (10/756 ears)	Lindstrom
Chronic otorrhea	NR (mean 2.8 yrs. in study)	1.7% (13/756 ears)	Lindstrom

*Sum of all adverse events, intraoperative and perioperative, minor and major. Major events were laryngospasm, desaturation, bradycardia, dysrhythmia, sridor; minor events were upper airway obstruction, agitation, prolonged recovery, emesis.

†Also "persistent agitation," described as "a subjective measure that was determined by recovery room nursing staff in the care and recovery of pediatric surgical patients." (Hoffman 2002).

‡"Recovery longer than 30 minutes" (Hoffman 2002).

§Patients who had tubes in place for longer than 2 years, 4 (4.3%) of the 92 resulted in tympanic membrane perforations. (Lindstrom 2004)

**Patients whose tubes were surgically removed after two years. (Lindstrom 2004)

Appendix I. Clinical Experts

The following have served as clinical experts:

Carol J. MacArthur, M.D
Pediatric Otolaryngologist
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References

1. Browning GG, Rovers MM, Williamson I, Lous J, Burton MJ. Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. Cochrane Database Syst Rev 2010:CD001801.
2. Chiou CF, Hay JW, Wallace JF, et al. Development and validation of a grading system for the quality of cost-effectiveness studies. Med Care 2003;41:32-44.
3. Ofman JJ, Sullivan SD, Neumann PJ, et al. Examining the value and quality of health economic analyses: implications of utilizing the QHES. J Manag Care Pharm 2003;9:53-61.