National Institute for Health and Care Excellence

Final

Otitis media with effusion in under 12s

[E] Evidence reviews for ventilation tubes

NICE guideline NG233

Evidence reviews underpinning recommendations 1.6.1 to 1.6.2 and recommendations for research in the NICE guideline

August 2023

Final

This evidence review was developed by NICE

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Ventilation tubes

Review question

What is the effectiveness of ventilation tubes for managing otitis media with effusion (OME) with associated hearing loss in children under 12 years?

Introduction

The aim of this review is to assess the effectiveness of ventilation tubes in managing otitis media with effusion (OME) with associated hearing loss in children under 12 years.

At the start of development, the term ventilation tube (VT) was used to refer to tubes inserted during surgery for OME. However, the committee later agreed that the term grommet should be used as this is likely to be the term that is more familiar to readers of the guideline and would avoid confusion with tubes used to assist with breathing. In order to maintain transparency and accuracy (for example, in reference to the terms used in the original protocol and the Cochrane review), both terms appear in this evidence review as appropriate.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	**Inclusion:** Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME) • If a study includes children aged younger than 6 months and older than 12 years, we will only include the study if the majority of children fit our inclusion criteria or only if the trialists present outcome data by age group • Include all children regardless of any comorbidity such as Down syndrome or cleft palate • Include studies where children have had OME for at least three months • Include children who have previously had ventilation tubes inserted • Clinical diagnosis of OME will be confirmed by oto(micro)scopy or tympanometry or both
Intervention	Insertion of ventilation tube performed either unilaterally or bilaterally. We will not assess different types of ventilation tubes or surgical approaches to insertion
Comparison	• Bilateral ventilation tubes versus no treatment/watchful waiting; • Bilateral ventilation tubes versus hearing aids • Bilateral ventilation tubes versus non-surgical treatment;

	• Bilateral ventilation tubes versus myringotomy alone; • Unilateral ventilation tubes versus no treatment/watchful waiting; • Unilateral ventilation tubes versus myringotomy alone in the other ear/other children If study participants have received other treatments in addition to the main intervention, for example, adenoidectomy, intranasal steroids, oral steroids, antibiotics, mucolytics or decongestants, we will include these studies if both arms of the study received similar treatment

Outcomes	We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies. We will assess all outcomes in the very short term (< 6 weeks for postoperative adverse events), short term (</= 3 months), medium term (> 3 months to </= 1 year) and long term (> 1 year).
	
	Critical
	• Hearing:
	  ○ proportion of children whose hearing has returned to normal;
	  ○ mean final hearing threshold (determined for the child or ear, depending on the unit of analysis);
	  ○ change in hearing threshold from baseline (determined for the child or ear, depending on the unit of analysis)
	• Disease-specific quality of life measured using a validated instrument, for example:
	  ○ OM8-30;
	  ○ Otitis Media-6
	• Adverse events: Persistent perforation
	
	Important
	• Presence/persistence of OME
	• Adverse events - measured by the number of participants affected
	  ○ Tympanic membrane changes, such as:
	  - atrophy;
	  - atelectasis or retraction;
	  - myringosclerosis;
	  - tympanosclerosis
	  ○ Tube-related, such as:
	  - blockage;
	  - extrusion;
	  - granulation tissue formation;
	  - otorrhoea/perforation;
	  - displacement of the ventilation tube into the middle ear space

	○ Patient-related, such as: - vomiting; - diarrhoea; - dry throat; - nasal stinging; - cough; - long-term hearing loss; - postsurgical haemorrhage; - pain • Receptive language skills, measured using a validated scale, for example: ○ Peabody Picture Vocabulary Test – Revised; ○ relevant domains of the Reynell Developmental Language Scales; ○ relevant domains of the Preschool Language Scale (PLS); ○ relevant domains of the Sequenced Inventory of Communication (SCID) • Speech development, or expressive language skills, measured using a validated scale, for example: ○ Schlichting test; ○ Lexi list; ○ relevant domains of the Reynell Developmental Language Scales; ○ relevant domains of the PLS; ○ relevant domains of the SCID • Cognitive development, measured using a validated scale, for example: ○ Griffiths Mental Development Scales; ○ McCarthy General Cognitive Index; ○ Bayley Scales of Infant and Toddler Development • Psychosocial outcomes, measured using a validated scale, for example: ○ the Social Skills Scale of the Social Skills Rating System; ○ Child behaviour Checklist; ○ Strengths and Difficulties Questionnaire; ○ Pediatric Symptom Checklist • Listening skills, for example, listening to stories and instructions effectively. Given that there are few validated scales to assess listening skills in children with OME, we will include any methods used by trialists. • Generic health-related quality of life assessed using a validated instrument, for example: ○ EQ-5D; ○ TNO AZL Children's QoL (TACQOL); ○ TNO AZL Pre-school children QoL (TAPQOL); ○ TNO AZL Infant Quality of Life (TAIQOL); ○ Infant Toddler Quality of Life Questionnaire (ITQOL); ○ Child Heath Questionnaire (CHQ)

	• Parental stress, measured using a validated scale, for example: ○ Parenting Stress Index • Vestibular function: ○ balance; ○ coordination • Number of doctor-diagnosed AOM episodes within a specified time frame

AOM: acute otitis media; EQ: EuroQol; OM: otitis media; OME: otitis media with effusion; PLS: Preschool Language Scale; QoL: quality of life; SCID: Sequenced Inventory of Communication; TNO AZL: The Netherlands Organisation for Applied Scientific Research Academic Medical Centre

For further details see the review protocol in appendix A.

Methods and process

During the development of this guideline, a registered Cochrane protocol was identified which matched the committee's intended PICOs. The Cochrane protocol differed from the committee's intended population in that the Cochrane protocols excluded studies that did not meet their inclusion criteria for trustworthiness (that is, those identified as being potentially 'high-risk' using a screening tool developed by Cochrane Pregnancy and Childbirth which included specified criteria to identify studies that are considered sufficiently trustworthy), however no studies were identified that were excluded from the review on these grounds alone.

The Cochrane review team completed a review investigating the effectiveness of ventilation tubes for OME in children (MacKeith 2023a) during guideline development and presented their results to the committee, who used them to make recommendations. Cochrane's methods are closely aligned to standard NICE methods, minor deviations (summary of findings tables instead of full GRADE tables, defining primary and secondary outcomes as opposed to critical and important, assessing the risk of bias in primary studies using version 1 (as opposed to version 2) of the Cochrane Risk of Bias tool, how clinically important differences are determined, and including countries from a broader range of income categories than the majority of the other reviews in the guideline) relevant to the topic area were highlighted to the committee and taken into account in discussions of the evidence. Where results were reported per ear instead of per child, Cochrane used an assumed intra-cluster correlation coefficient of 0.5 to adjust the sample size. Full details of the Cochrane review, including methods, are available in the review of ventilation tubes for children with OME, see MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

We thank the Cochrane ENT Group for their assistance in providing the literature searches and data for review questions relating to Otitis media with effusion in under 12s.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

A Cochrane review (MacKeith 2023a) including 16 randomised controlled trials (Bernard 1991, Dempster 1993, D'Eredita 2006, Gates 1989, Haggard 2012, Koopman 2004, Maw 1988, Maw 1999, Paradise 2007, Popova 2010, Rach 1991, Rovers 2000, Ruckley 1988, To 1984, Velepic 1987, Yousaf 2016) is considered in this report. This review was used for making recommendations by the committee, as it was considered sufficiently relevant, high quality and up to date.

Two studies included children aged up to 4 years (Rach 1991; Rovers 2000), and 14 studies included children aged over 4 years (Bernard 1991; Dempster 1993; D'Eredita 2006; Gates 1989; Haggard 2012; Koopman 2004; Maw 1988; Maw 1999; Paradise 2007; Popova 2010; Ruckley 1988; To 1984; Velepic 2011; Yousaf 2016). None of the studies reported data on participants' hearing levels at baseline, or whether participants had allergy, previous ventilation tubes, cleft palate, or Down's syndrome.

The Cochrane review is summarised in Table 2, however full details of the Cochrane review including methods are available in the review of Ventilation tubes for children with OME, see MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

See the Cochrane review for the literature search strategies, study selection flow charts, forest plots and summary of findings tables, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

Excluded studies

See the lists of excluded studies in the Cochrane review with reasons for their exclusions, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Comparison	Outcomes
MacKeith 2023a Systematic review	Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion for a duration of at least three months. Number of studies: 16 Number of participants: 2736	**VT insertion vs no treatment** 3 trials, N=266 children with OME (Dempster 1993, Maw 1988, Rach 1991) **VT insertion vs watchful waiting (later VT if required)** 5 trials, N=1261 children with OME (Haggard 2012, Maw 1999, Paradise 2007, Rovers 2000, Velepic 1987) **VT insertion vs non-surgical treatment** 1 trial, N=139 children with OME (Bernard 1991) **VT insertion vs myringotomy** 7 trials, overall N=1070 children with OME: • 3 cold-steel (conventional) myringotomy, N=710 children with OME (Gates 1989, Popova 2010, To 1984) • 3 laser myringotomy, N=320 children with OME	Primary: • Hearing as (i) return to normal; (ii) mean threshold; and (iii) change from baseline • Disease-specific quality of life • Persistent perforation Secondary: • Persistence of OME • Other adverse events: (i) ear drum; (ii) VT; and (iii) patient-related • Receptive and expressive language • Cognitive development • Psychosocial development • Listening skills • Generic health-related QoL • Parental stress • Vestibular function

Study	Population	Comparison	Outcomes
		(D'Eredita 2006, Koopman 2004, Yousaf 2016) • 1 thermal myringotomy, N=40 children with OME (Ruckley 1988)	• Number of episodes of acute otitis media

N: number; OME: otitis media with effusion; VT: ventilation tubes

See the Cochrane review for characteristics of studies tables, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

Summary of the evidence

The Cochrane review of ventilation tubes for children with OME investigated 5 comparisons, with the following findings:

- Comparison 1: Unilateral or bilateral VT insertion versus no treatment. VT insertion had an important benefit for persistence of OME (when randomised by child) in the medium-term (low quality evidence according to GRADE criteria), but had an important harm for tympanosclerosis (when randomised by ear) in the medium-term (low quality evidence according to GRADE criteria). There was no important difference or no evidence of an important difference between VT insertion and no treatment for the other outcomes: return to normal hearing in the medium-term; final hearing threshold in the medium-term; change in hearing threshold in the medium-term; persistence of OME (when randomised by ear) in the medium-term; improvement in comprehensive language; improvement in expressive language; perforation/ retraction (when randomised by ear) (low to very low quality evidence according to GRADE criteria). There was no evidence available for this comparison for any of the other outcomes specified in the protocol
- Comparison 2: Unilateral or bilateral VT insertion versus watchful waiting. VT insertion had an important benefit for final hearing threshold in the short-term (very low quality evidence according to GRADE criteria), presence/ persistence of OME in the medium-term (as measured by tympanometry or in mean percentage of days), behaviour in the medium-term (as measured by using a dichotomised Richman score), receptive language development in the medium-term (as measured by the Reynell test using adjusted mean difference), and expressive language development in the medium-term (as measured by the Reynell test using adjusted mean difference) (all low to very low quality evidence according to GRADE criteria). There was a possible important benefit of VT insertion for receptive language development in the medium-term (as measured by the Reynell test; 90% CI: 0.02 to 0.59), expressive language development in the medium-term (as measured by the Reynell test; 90% CI: 0.06 to 0.70), and cognitive development in the medium-term (using total IQ as measured by the WISC-III test; 90% CI: 1.00 to 5.71) (all very low quality evidence according to GRADE criteria). VT insertion had an important harm for segmental atrophy in the long term, and parent-child interaction in the medium-term (as measured by the Erickson child or the Erickson parent scale (all very low quality evidence according to GRADE criteria). There was no important difference or no evidence of an important difference between VT insertion and watchful waiting for the other outcomes: hearing returned to normal in the long-term; final hearing threshold in the medium-term (as assessed using air conduction or air-bone gap) or the long-term; hearing in noise test with competing noise from the front, right, or left; change in hearing threshold in the medium-term; mean difference in hearing improvement in the medium-term; persistent perforation in the medium or long-term; presence/ persistence of OME in the medium-term (as measured by otoscopy) or in the long-term (when using adjusted odds ratios or risk ratios); tympanosclerosis in the long-term; fibrosis in the long-term; retraction pocket with other abnormality in the long-

term; receptive language development in the long-term (as measured by the Reynell test, including when using adjusted mean difference, or the WOLD test); expressive language development in the medium-term (as measured by the Schlichting test, including when using adjusted mean difference) or long-term (as measured by the Reynell test, including when using adjusted mean difference, or the WOLD test); non-word repetition in the long-term; reading in the long-term (as measured by the WORD test); spelling in the long-term (as measured by the ALSPAC test); phoneme deletion in the long-term; cognitive development in the medium-term (as measured by the Griffiths practical reasoning test or using total IQ as measured by the WISC-III test); behaviour in the medium-term (as measured by the Richman score and when using adjusted odds ratios) or long-term (as measured by the Richman score, including when using a dichotomised Richman score, or the SDQ teacher report); parental stress in the long-term (as measured by the Parental Stress Index); generic health-related quality of life in the medium-term (as measured by the TAIQOL questionnaire (in the domains vitality, appetite, communication, motoric, social, anxiety, aggression, eating, and sleeping)); literacy in the long-term (as measured by the Woodcock Reading Mastery Tests (in the subtests word identification, word attack, and passage comprehension), the Oral reading fluency tests for children in grades 3-6, or the Woodcock–Johnson III Tests of Achievement (in the subtests spelling and writing)); phonological awareness in the long-term (as measured by the Comprehensive Test of Phonological Processing (in the subtests elision and rapid letter naming)); attention, impulsivity, and psychosocial function in the long-term (as measured by the parent's and teacher's ratings of the Disruptive Behavior Disorders Rating Scale (for the factors inattention, impulsivity and overactivity, and oppositional defiant), the parent's and teacher's ratings of the Child Behavour Checklist (for the total problems score), the parent's and teacher's ratings of the Impairment Rating Scales (for overall functioning), the parent and teacher versions of the Social Skills Rating System, the Visual Continuous Performance Test (in the domains inattention and impulsivity), or the Auditory Continuous Performance Test (in the domains inattention and impulsivity)); intelligence and academic achievement in the long-term (as measured by the Wechsler Abbreviated Scale of Intelligence or the Calculation subtest of the Woodcock–Johnson III Tests of Achievement) (all low to very low quality evidence according to GRADE criteria)

- Comparison 3: Unilateral or bilateral VT insertion versus non-surgical treatment
    - Comparison 3.1: Unilateral or bilateral VT insertion versus 6 months sulfisoxazole. VT insertion had an important harm of myringosclerosis in the long-term (very low quality evidence according to GRADE criteria). There was no important difference between VT insertion and 6 months sulfisoxazole for the other outcomes: final hearing threshold in the short- or medium-term; number of doctor-diagnosed AOM episodes in the medium- or long-term (all very low quality evidence according to GRADE criteria). There was no evidence available for this comparison for any of the other outcomes specified in the protocol
- Comparison 4: Unilateral or bilateral VT insertion versus myringotomy
    - Comparison 4.1: Unilateral or bilateral VT insertion versus cold-steel (conventional) myringotomy. VT insertion had an important benefit for number of days to first recurrence of OME, but it also had the important harm of persistent perforation in the medium-term, and the possible important harm of otorrhoea in the long-term (90% CI: 1.10 to 2.22) (all very low quality evidence according to GRADE criteria). There was no important difference or no evidence of an important difference between VT insertion and cold-steel myringotomy for the other outcomes: final hearing threshold in the short-term (as randomised by ear or by child) or the medium-term (as assessed using pure tone audiometry or air bone gap); persistence of OME in the medium- or the long-term (in terms of number of children with OME); number of episodes of AOM in 12 months (when comparing number of children with 0, 1, 2, 3, or

≥4 episodes) (all low to very low quality evidence according to GRADE criteria). There was no evidence available for this comparison for any of the other outcomes specified in the protocol

- Comparison 4.2: Unilateral or bilateral VT insertion versus laser myringotomy. VT insertion had an important benefit for persistence of OME (as randomised by child or by ear) in the medium-term (very low quality evidence according to GRADE criteria). There was no important difference or no evidence of an important difference between VT insertion and laser myringotomy for the other outcomes: hearing returned to normal in the medium-term; persistent perforation in the medium-term; persistence of OME in the short-term; hypertrophic scarring of the tympanic membrane in the medium-term; otorrhoea in the medium term; retraction of tympanic membrane in the medium-term (all very low quality evidence according to GRADE criteria). There was no evidence available for this comparison for any of the other outcomes specified in the protocol
- Comparison 4.3: Unilateral or bilateral VT insertion versus thermal myringotomy. VT insertion had an important benefit for persistence of OME in the short-term (as randomised by ear) (very low quality evidence according to GRADE criteria). There was no evidence available for this comparison for any of the other outcomes specified in the protocol

Unilateral or bilateral VT insertion versus hearing aids was another comparison included in the Cochrane review protocol, but no evidence was found.

See the Cochrane review for summary of findings tables and full results, including all primary and secondary outcomes and sub-group analyses, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

Economic evidence

Included studies

A global health economic search was undertaken to cover all the review questions considered in this guideline. Three economic studies were identified which were relevant to this question (Mohiuddin 2014; Fortnum 2014; Bruce 2015).

See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of included economic evidence

See Table 3 for the economic evidence profile of the included studies.

Table 3: Economic evidence profile of a systematic review of economic evaluations of ventilation tubes for managing otitis media with effusion (OME) with associated hearing loss in children under 12 years?

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effectivenss	
NICE guideline model 2023	Potentially serious limitations[1,2,3]	Directly applicable	Study employed a Markov decision-analytic model with a 2-year time horizon	Hearing Aids £959 (HA v No Int) VT £3,395 VT plus ads £3,926	Hearing Aids 0.05 QALYs (HA v No Int) VT 0.17 QALYs VT plus ads 0.20 QALYs	Hearings Aids £17,738 per QALY gained VT £19,971 per QALY gained VT plus ads £19,630 per QALY gained	In the base case analysis, the probability of each strategy being cost-effective at a cost-effectiveness threshold of £20,000 per QALY was: No intervention 7%; Hearing aids 26%; VT 26%; VT plus ads 41% Sensitivity analyses showed that the model conclusions were highly sensitive to changes to input parameters and model assumptions
Mohiuddin 2014 VT for the management of persistent bilateral OME in children	Potentially serious limitations [4]	Directly applicable	Decision analytic model	VT £564 HAs + VT £687	VT 0.111 QALYs HAs + VT -0.78 QALYS	VT £5,086 per QALY (VT v HA)	90% probability VT would be cost-effective relative to hearing aids at £20,000 per QALY
Fortnum 2014 Management of OME in Children with Down Syndrome	Potentially serious limitations [4,5]	Potentially serious limitations	Decision analytic model	HA £154 (HA v WW) Surgery £881	HA 0.005 QALYs (HA v WW) Surgery -0.02 QALYs	HA £34,399 per QALY (HA v WW)	None reported

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs	Effect	Cost effecti venss	
				(Surgery v HA)	(Surgery v HA)		
Bruce 2015 Management of OME in children with cleft palate	Potentially serious limitations [4]	Directly applicable	Decision analytic model	HA £643 (HA v DN) VT £848 (VT v HA) HA + VT £578 (HA+VT v VT)	HA 0.0489 QALYs (HA v DN) VT 0.1157 QALYs (VT v HA) HA+VT -0.0818 QALYs (HA+VT)	VT £9,053 per QALY (VT v HA)	There was a 63% probability that VT was the most cost-effective strategy at a £20,000 per QALY threshold

[1] No comparative evidence was identified for differences in health-related quality of life between the different interventions and the model assumes equivalent benefit, but model conclusions are sensitive to this assumption
[2] It was not possible to synthesise studies reporting the relative treatment effect of surgery on OME persistence and there was wide variation in the reported relative treatment effect sizes in the included studies
[3] There was wide variation in the included studies on the natural history of OME and model conclusions were sensitive to different assumptions
[4] The model results are likely to be sensitive to the utility gain per unit increase in hearing gain and there is uncertainty with respect to the assumptions made and to the hearing gain achieved as a result of intervention
[5] No probabilistic sensitivity analysis
DN = Do nothing; HA = Hearing aids; OME = Otitis media with effusion; QALYs = Quality Adjusted Life Years; VT = Ventilation tubes; WW = Watchful waiting

Economic model

An original cost utility analysis was developed to compare no intervention, hearing aids, grommets alone and grommets with adjuvant adenoidectomy for children who have OME with hearing loss. The model makes no distinction between unilateral and bilateral OME. The model is summarised below with full details provided in appendix I.

For the no intervention and hearing aid strategies a decision analytic cohort Markov model was used to estimate the cost and QALYs for children with OME over a two-year time horizon after completion of a period of 3 months watchful waiting after diagnosis. A Markov model structure was also utilised for the surgical strategies but a patient level Markov simulation was used to provide “memory” of the duration that grommets have been in place. This is difficult to capture in a conventional Markov cohort as the probability of extrusion will differ according to the time since insertion which will differ depending on whether the grommet is a first or reinsertion. This patient level Markov simulation involved sampling hypothetical patients through the model to estimate mean costs and QALYs across the sample cohort. Markov transitions between different health states occurred at the end of weekly Markov cycles.

OME is usually a time limited condition which spontaneously resolves over time. The Cochrane review provided evidence on the impact of OME persistence, and this was used to estimate clinical effectiveness in the analysis, with evidence on the natural history of spontaneous resolution of OME forming the baseline in the absence of surgical intervention. This baseline formed the basis of the Markov transition for both hearing aid and no intervention strategies.

In addition to the immediate costs of treatment the model also included subsequent related health service contacts that occur as a result of regular follow up and review. Probabilities of surgical complications and other events that could impact on strategy costs and health related quality of life were also included.

In the absence of any quantitative comparative data, it was assumed that hearing aids and grommets, either alone or with adjuvant adenoidectomy, would provide the same utility gain from mitigating the impact of hearing loss. It was also assumed that spontaneous resolution of OME with hearing loss would return health state utility to normal.

Both deterministic and probabilistic analyses were undertaken. Probabilistic sensitivity analysis involved repeated Monte Carlo simulations in which model parameters were sampled from a pre-specified probability distribution. In addition to the base case analysis, several additional analyses were undertaken to address alternative assumptions with respect to the natural history of OME with hearing loss and relative treatment effect. One-way sensitivity analysis was performed for variables that are treated as fixed in the probabilistic analysis in order to gauge their importance in driving model conclusions in the context of any uncertainty with respect to their true value.

The results provide evidence that intervention for OME with hearing loss is cost-effective but give a much less clear indication as to whether hearing aids, grommets alone or grommets with adjuvant adenoidectomy is the most cost-effective alternative. None of the interventions consistently achieved a 50% probability of being the most cost-effective at a cost-effectiveness threshold of £20,000 to £30,000 per QALY in the probabilistic sensitivity analyses. In the various scenario and sensitivity analyses, the rate of spontaneous resolution of OME given by the natural history and the relative treatment effect size were both found to have an important bearing on the model's conclusions and only low-quality evidence with considerable variation and uncertainty was available to inform the model in these respects.

The model has several important limitations and uncertainties and needs to be interpreted carefully in the context of these caveats. The model suggests that intervention substantially increases costs compared to no intervention although costs are restricted to an NHS and personal social services perspective and other educational and developmental costs may be incurred due to on-going hearing loss. Nevertheless, the results of the model generally suggested that some form of intervention was likely to be cost-effective and support the recommendations made by the committee.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

The primary outcomes were hearing, disease-specific quality of life, and persistent perforation. The committee agreed these outcomes were critical: hearing is a direct measure of any differential effectiveness associated with grommet insertion; disease-specific quality of life is a measure of well-being which may capture long-term health-related outcomes associated with the effectiveness of interventions; and persistent perforation would capture the risk of this adverse event which can happen as a result of grommet insertion.

All other outcomes listed in the protocol (presence/ persistence of OME; adverse events; receptive language skills; expressive language skills; cognitive development; psychosocial outcomes; listening skills; generic health-related quality of life; parental stress; vestibular

function; number of doctor-diagnosed acute otitis media (AOM) episodes) were agreed to be important outcomes by the committee. The committee agreed that presence or persistence of OME after grommet insertion directly measures the effectiveness of the intervention, and that adverse events other than persistent perforation (including harmful tympanic membrane changes such as atrophy, tube-related adverse events such as tube blockage, and patient-related complications such as vomiting), that are relatively common after grommet insertion, were important outcomes because they capture the risks associated with the intervention. OME and related hearing loss can be associated with impairment of receptive and expressive language skills, cognitive development, psychosocial outcomes, listening skills, and vestibular function, which could impact on the child's development, and therefore the committee agreed these were important outcomes. The committee also agreed parental stress levels were important in order to capture whether grommet insertion is successful at reducing the stress that can be associated with a child having OME, and generic health-related quality of life was important because this would measure the well-being of the child more generally than disease-specific scales. The number of doctor-diagnosed AOM episodes was agreed to be an important outcome because grommet insertion may have a protective role for recurrent AOM.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology and the evidence for outcomes identified in this review ranged from very low to low quality, in most cases due to high or moderate risk of bias and serious or very serious imprecision. Some outcomes were also downgraded for serious or very serious indirectness (for example due to strict definitions of normal hearing used, variation in interventions used, or duration of OME prior to recruitment being measured cumulatively rather than as a continuous episode), and for two outcomes, publication bias was strongly suspected.

The quality of the included studies likely reflected the era these studies were conducted in, because they were run when reporting standards were less defined. Therefore, despite the GRADE findings, the trials were conducted with rigour, and it is therefore unlikely that any newer trials adhering to current reporting standards would have different findings. The committee agreed with this assessment.

Benefits and harms

There was very low quality evidence that early grommet insertion lead to improved final hearing thresholds in the short-term when compared to watchful waiting, but no evidence of an important difference in the medium or long term, or of an important difference in the rate of return to normal hearing. This evidence was supported by the fact that there was also no evidence of an important difference in terms of return to normal hearing, change in hearing threshold, or final hearing threshold in the medium term when compared to no treatment. There was additionally no important difference for final hearing threshold in the short or medium term when compared to non-surgical treatment or to cold-steel myringotomy. There was also no evidence of important differences for most of the important outcomes specified above that may be associated with hearing loss, such as comprehensive, receptive and expressive language, cognitive development, or psychosocial outcomes. The committee noted that there was uncertainty in the importance of the outcomes for those which found no evidence of an important difference, and also agreed that the evidence comparing hearing thresholds between grommet insertion and no treatment was limited by the length of follow-up for hearing outcomes; people are more likely to experience spontaneous resolution of OME without treatment as time increases and most of the evidence reported was for medium-term outcomes. Therefore, this might have contributed to the minimal, non-significant differences in hearing. The committee agreed the critical period to consider for hearing outcomes is in the short-term, because a negative impact on hearing levels even for short periods of time can significantly impact a child's development, and it is therefore

important to negate these as soon as possible rather than waiting for spontaneous resolution. Clinicians would therefore expect to see the greatest benefits within the first 6 months post-grommet insertion. Additionally, very low to low quality evidence showed that grommet insertion had an important benefit in terms of persistence of OME in the short-term when compared to no treatment or to thermal myringotomy, and at medium-term follow-up when compared to laser myringotomy or watchful waiting. The committee agreed that the evidence regarding hearing-related outcomes is the most important to consider when evaluating the efficacy of grommet insertion, however the additional evidence regarding persistence of OME, some of which was slightly better quality, was reassuring because according to the committee's knowledge and expertise, resolution of OME usually results in improved hearing. The committee also discussed the fact that the populations included in the studies did not reflect the populations typically seen in clinical practice because of the ages of the participants: participants had an average age of 5 years across all included studies, whereas in the committee's experience children would usually receive grommets for treatment of OME much earlier, around the age of 3 years. In addition, to meet the criteria for inclusion into the studies, participants were required to have had persistent OME for at least 3 months before receiving grommets. The committee noted that as a result of this, by the time grommets were inserted, all children included in the studies would already have experienced a period of watchful waiting. This would have had an important impact on hearing outcomes because longer periods of follow-up would naturally result in only minimal hearing differences between groups, as discussed above. The committee agreed that these factors might account for why the evidence did not necessarily correspond with their experience that grommet insertion tends to result in a much larger improvement in hearing than was shown in the evidence.

Very low to low quality evidence showed that, at long-term follow-up, grommet insertion was additionally associated with the important harm of complications like tympanosclerosis when compared to no treatment, myringosclerosis when compared to non-surgical treatment, otorrhoea and persistent perforation when compared to cold-steel myringotomy, and segmental atrophy when compared to watchful waiting. The committee were not concerned about the risk of atrophy as it was thought that this reflected localised atrophy at the site of the grommet rather than atelectasis of the tympanic membrane which would be a more serious complication that, in the committee's experience, would be less likely to occur following grommet insertion due to reduced pressure on the tympanic membrane. Similarly, in their experience, myringosclerosis doesn't tend to cause symptoms in the child. However, the committee agreed persistent perforation and otorrhoea were particularly important because they could result in further complications down the line, such as impacting the child's development. The committee did note there was uncertainty in the importance of the outcome for otorrhoea when comparing grommets and cold-steel myringotomy, but agreed the effect estimate was large enough to cause concern despite the 95% CI crossing the line of no effect. It is therefore important to weigh up the potential benefits of grommet insertion, particularly resolution of OME and the resulting improvements in hearing, versus the risk of adverse events, when considering this intervention for children with OME.

Overall, the committee agreed that grommet insertion should be considered for treatment of children with OME only in circumstances where the OME has resulted in hearing loss, due to the risk of hearing loss impacting developmental outcomes. This was based on the available evidence regarding hearing and resolution of OME outcomes, and supplemented with the committee's knowledge and experience. It was also noted by the committee that when comparing grommet insertion to watchful waiting, many of the participants in the latter group in these studies did receive grommets later, even if they were originally randomised to watchful waiting, which again may have contributed to the minimal hearing differences between groups. The committee agreed that despite the limited evidence, in their experience any hearing-related improvements – even minimal or only in the short-term – can have a significant impact on the lived experience of both children and their parents and carers and might outweigh the potential risks associated with grommet insertion. However, the committee could not make a stronger recommendation due to the limited evidence regarding

benefits to hearing. The committee agreed that in situations where OME is not having an impact on the child's hearing there is not as urgent a need to consider surgery, regardless of whether the OME is persistent or transient, in light of the risks associated with grommet insertion. The committee therefore could not recommend grommet insertion for children without hearing loss. The committee discussed the fact that in all included studies, grommet insertion was only conducted after 3 months of persistent OME, and therefore whether this should be reflected in the recommendations. However, they agreed based on their knowledge and experience that this time period is not rooted in evidence that waiting 3 months before inserting grommets has any impact on outcomes.

The evidence regarding adverse events associated with grommet insertion indicate it is important to acknowledge the risk of complications when considering this intervention. In the committee's experience, in current practice these complications are not routinely discussed with parents and carers before committing to treatment. The committee agreed that not doing so impedes family members' ability to make informed decisions regarding their child's care. Both benefits and risks of grommet insertion should be clearly communicated to parents and carers when considering this intervention, to enable informed decision-making and ensure they are prepared if adverse events do occur. Further details on recommendations about providing information on risks associated with surgery in general are provided in Evidence Review N.

The committee discussed whether a separate recommendation should be made for children with Down's syndrome or craniofacial anomalies. The committee discussed their experience that there tends to be a variation in practice whereby grommet insertion is offered to some children with Down's syndrome and some children with Down's syndrome are not offered this intervention. The committee were aware that children with Down's syndrome are more likely to have narrow ear canals which can make inserting grommets more difficult and that this population may be more likely to have persistent or recurrent OME than children without craniofacial anomalies. The committee discussed the fact that recommending grommet insertion for all children with Down's syndrome or craniofacial anomalies without sufficient evidence on the benefits and harms for this group could result in an important harm, such as significant surgical complications, adverse events, or repeat grommet insertion. It was also unclear whether grommet insertion would provide important benefits to children with Down's syndrome and craniofacial anomalies because the included studies tended to either these populations or not mention them. Therefore, the committee agreed that, in the absence of specific evidence on the benefits and harms of grommet insertion for these populations, an additional recommendation could not be made. The committee agreed that any decisions made regarding grommet insertion should be made after having considered all potential risks and benefits of this intervention for the individual.

The committee agreed that the lack of evidence on the effectiveness of grommets for children with craniofacial anomalies or Down's syndrome limited their ability to recommend grommets for these populations, and that research for these populations could impact whether grommets are recommended for these children in the future. They also agreed that further research into clinical and cost-effectiveness of grommets compared to hearing aids for all children with OME-related hearing loss could help strengthen future recommendations, because there was no available evidence for this comparison. Therefore, the committee made 2 research recommendations.

Cost effectiveness and resource use

An included study (Fortnum 2014) suggested that watchful waiting was the most cost-effective strategy for children with Down's syndrome when compared to hearing aids and surgical interventions. The committee noted that the authors of this study highlighted the limitations of the available evidence for this analysis. Although the interventions produced a higher QALY gain they did so at ICERs of £34,399 per QALY and £422,114 per QALY respectively, which is not generally considered to represent good value for money.

Therefore, this reinforced the committee in their view that a recommendation for grommet insertion for children with Down's syndrome was not supported.

A study (Bruce 2015) suggested that grommet insertion could be cost-effective for children with cleft palate. An ICER of £9,053 for grommets relative to do nothing was reported, with grommets also having extended and strict dominance compared to hearing aids and hearing aids plus grommets respectively. However, the study reported limitations with the current evidence and stated that further information was required to inform this treatment choice. The committee considered that this supported their research recommendation for the effectiveness of grommets for managing OME with associated hearing loss in children with craniofacial anomalies.

Mohiuddin (2014) reported the results of an economic evaluation which found that grommet insertion for persistent bilateral OME with hearing loss was cost-effective relative to hearing aids and hearing aid plus grommet insertion strategies. The ICER for grommet insertion relative to hearing aids was £5,086 per QALY gained relative to hearing aids. However, this study concluded that further research is needed to inform treatment decisions.

The committee also considered an original economic evaluation undertaken for the guideline to compliment the Cochrane review. This analysis compared no intervention, hearing aids, grommet insertion alone and grommet insertion with adjuvant adenoidectomy. It found that grommet insertion was generally more cost-effective than no intervention, but that grommet insertion alone had comparable cost-effectiveness estimates and probability of being cost-effective relative to hearing aids and grommet insertion with adjuvant adenoidectomy. The analysis found that the cost-effectiveness of the various strategies was sensitive to assumptions made with respect to relative treatment effect and the natural history of OME with hearing loss. The committee reasoned that this analysis supported their recommendation that grommet insertion should be considered for OME with hearing loss in children alongside other management options.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1 and 1.6.2, the research recommendation on the clinical and cost-effectiveness of grommets for managing OME-related hearing loss in children under 12 years, and the research recommendation on the effectiveness of grommets for managing OME with associated hearing loss in children with craniofacial anomalies or Down's syndrome.

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Effectiveness

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Appendices

Appendix A Review protocol

Review protocol for review question: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

See the Cochrane review protocol, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

See Appendix 1 and Appendix 2 of the Cochrane review, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

Economic literature search strategy

A global, population-based search was undertaken to find economic evidence covering all parts of the guideline.

Database: MEDLINE – OVID interface

Date last searched: 09/11/2022

#	Searches
1	otitis media with effusion/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	Economics/
5	Value of life/
6	exp "Costs and Cost Analysis"/
7	exp Economics, Hospital/
8	exp Economics, Medical/
9	Economics, Nursing/
10	Economics, Pharmaceutical/
11	exp "Fees and Charges"/
12	exp Budgets/
13	budget*.ti,ab.
14	cost*.ti.
15	(economic* or pharmaco?economic*).ti.
16	(price* or pricing*).ti,ab.
17	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
18	(financ* or fee or fees).ti,ab.
19	(value adj2 (money or monetary)).ti,ab.
20	or/4-19
21	exp models, economic/
22	*Models, Theoretical/
23	*Models, Organizational/
24	markov chains/
25	monte carlo method/
26	exp Decision Theory/
27	(markov* or monte carlo).ti,ab.
28	econom* model*.ti,ab.
29	(decision* adj2 (tree* or analy* or model*)).ti,ab.
30	or/21-29
31	20 or 30
32	3 and 31
33	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
34	32 not 33
35	limit 34 to english language
36	limit 35 to yr="2000 -Current"

Database: Embase – OVID interface

Date last searched: 09/11/2022

#	Searches
1	exp secretory otitis media/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2

#	Searches
4	health economics/
5	exp economic evaluation/
6	exp health care cost/
7	exp fee/
8	budget/
9	funding/
10	budget*.ti,ab.
11	cost*.ti.
12	(economic* or pharmaco?economic*).ti.
13	(price* or pricing*).ti,ab.
14	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15	(financ* or fee or fees).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	or/4-16
18	statistical model/
19	exp economic aspect/
20	18 and 19
21	*theoretical model/
22	*nonbiological model/
23	stochastic model/
24	decision theory/
25	decision tree/
26	monte carlo method/
27	(markov* or monte carlo).ti,ab.
28	econom* model*.ti,ab.
29	(decision* adj2 (tree* or analy* or model*)).ti,ab.
30	or/20-29
31	17 or 30
32	3 and 31
33	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.
34	32 not 33
35	limit 34 to english language
36	limit 35 to yr="2000 -Current"

Database: Cochrane Central Register of Controlled Trials (CENTRAL) – Wiley interface

Date last searched: 09/11/2022

ID	Search
#1	MeSH descriptor: [Otitis Media with Effusion] this term only
#2	(("glue ear" or (("middle ear" or "otitis media") near/2 effusion*) or ome or ((secretory or serious) near/2 "otitis media"))):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Economics] this term only
#5	MeSH descriptor: [Value of Life] this term only
#6	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#7	MeSH descriptor: [Economics, Hospital] explode all trees
#8	MeSH descriptor: [Economics, Medical] explode all trees
#9	MeSH descriptor: [Economics, Nursing] this term only
#10	MeSH descriptor: [Economics, Pharmaceutical] this term only
#11	MeSH descriptor: [Fees and Charges] explode all trees
#12	MeSH descriptor: [Budgets] explode all trees
#13	budget*:ti,ab
#14	cost*:ti
#15	(economic* or pharmaco?economic*):ti
#16	(price* or pricing*):ti,ab
#17	(cost* near/2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)):ab
#18	(financ* or fee or fees):ti,ab
#19	(value near/2 (money or monetary)):ti,ab
#20	{or #4-#19}
#21	MeSH descriptor: [Models, Economic] explode all trees
#22	MeSH descriptor: [Models, Theoretical] this term only
#23	MeSH descriptor: [Models, Organizational] this term only
#24	MeSH descriptor: [Markov Chains] this term only
#25	MeSH descriptor: [Monte Carlo Method] this term only
#26	MeSH descriptor: [Decision Theory] explode all trees
#27	(markov* or "monte carlo"):ti,ab
#28	(econom* next model*):ti,ab

ID	Search
#29	(decision* near/2 (tree* or analy* or model*)):ti,ab
#30	{or #21-#29}
#31	#20 or #30
#32	#3 and #31 with Cochrane Library publication date Between Jan 2000 and Apr 2022

Database: International Network of Agencies for Health Technology Assessment (INAHTA)

Date last searched: 09/11/2022

#	Searches
1	((("Otitis Media with Effusion"[mhe]) OR ((("glue ear" or (("middle ear" or "otitis media") and effusion*) or ome or ((secretory or serous) and "otitis media")))
2	1 and FROM 2000 TO 2022 AND (English)[Language]

Database: NHS Economic Evaluation Database (NHS EED) – CRD interface

Date last searched: 09/11/2022

Line	Search for
1	MeSH DESCRIPTOR Otitis Media with Effusion EXPLODE ALL TREES
2	((glue ear or ((middle ear or otitis media) and effusion*) or ome or ((secretory or serous) and otitis media))) IN NHS EED
3	#1 OR #2

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

Clinical

See Results of the search – figure 1 from the Cochrane review, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

Appendix D Characteristics of studies tables

Characteristics of studies tables for review question: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

See the Characteristics of included studies tables from the Cochrane review, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

Appendix E Data and analyses tables

Data and analyses tables for review question: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

See the Data and analyses tables from the Cochrane review, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

Appendix F Summary of findings tables

Summary of findings tables for review question: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

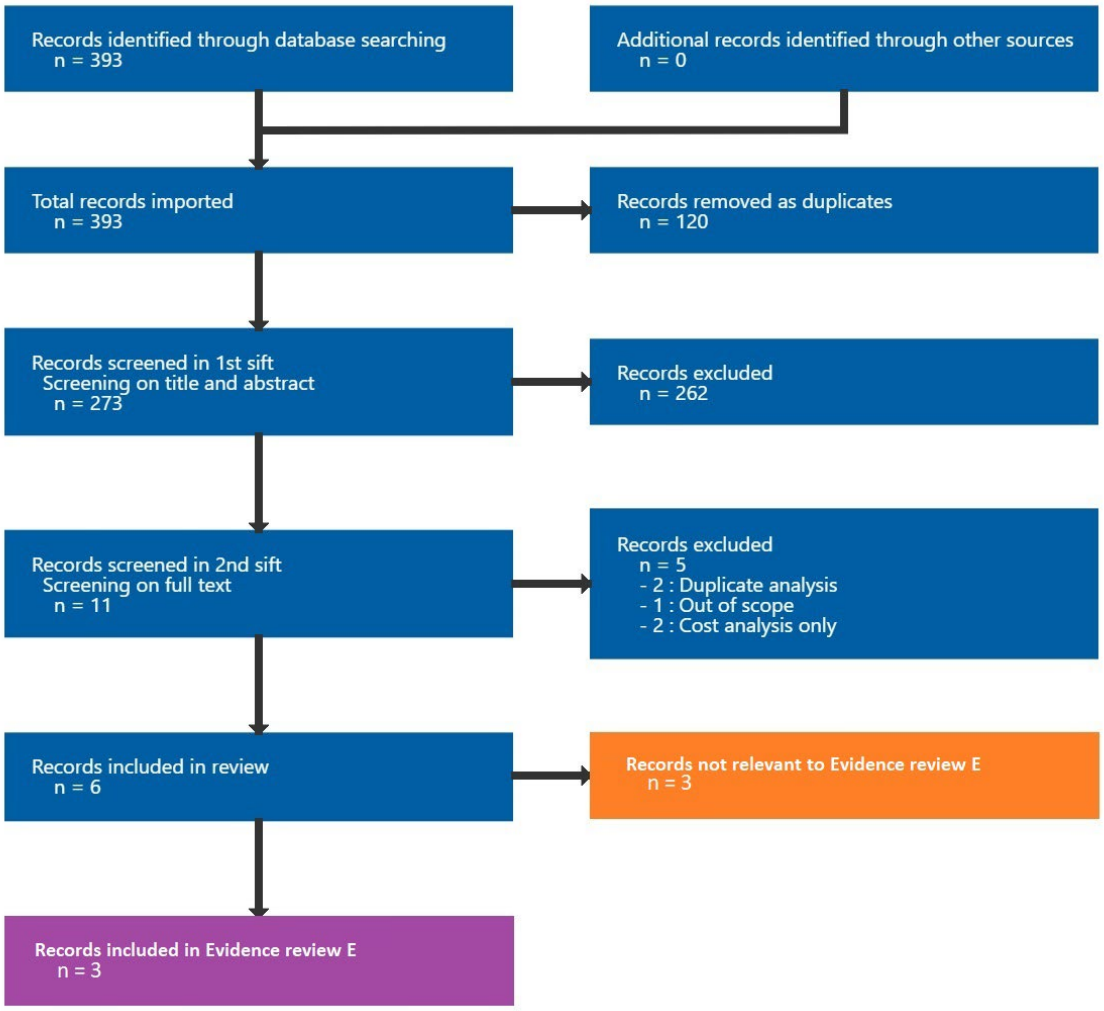
See the Summary of findings tables from the Cochrane review, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

A global search was undertaken to cover all the review questions considered in this guideline, and 3 studies were identified which was applicable to this review question (see Figure 1).

Figure 1: Study selection flowchart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

Table 4: Economic evidence tables for

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Author and year: Mohuiddin 2014 **Country:** UK **Type of economic analysis:** Cost utility analysis **Source of funding**: Not stated	**Intervention:** Ventilation tubes or hearing aids plus ventilation tubes **Comparator in detail:** Hearing aids	**Population characteristics:** Children under the age of 12 years with persistent bilateral OME **Modelling approach:** Decision analytic cohort model **Source of baseline data:** Maw R, Bawden R: Spontaneous resolution of severe chronic glue ear in children and the effect of adenoidectomy, tonsillectomy, and insertion of ventilation tubes (grommets). BMJ 1993, 306:756–760. **Source of effectiveness data:** Maw R, Bawden R: Spontaneous resolution of severe	**Mean cost:** *Hearing aids:* £1,237 *VTs*: £1,801 *HAs + VTs:* £2,498 **Primary measure of outcome**: QALYs A utility value of 0.00874 (95% CI: 0.005 to 0.012) per unit increase in dBHL following the approach used in the NICE CG60 guideline **Mean QALY:** *Hearing aids:* 0.107 QALYs *VTs*: 0.218 QALYs *HAs + VTs:* 0.139 QALYs	**ICERs:** VTs v HAs £5,086 per QALY VTs v HAs + VTs Dominant **Probability of being cost effective:** VTs had a 58% probability of being cost-effective at a cost-effectiveness threshold of £20,000 per QALY	**Currency:** GBP **Cost year:** 2010-11 **Time horizon:** 24 months **Discounting:** 3.5% per annum **Applicability:** Directly applicable **Limitations:** Potentially serious limitations **Other comments:** The relationship between health state utility and hearing and the treatment effect on dBHL were identified as the key uncertain parameters.

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		chronic glue ear in children and the effect of adenoidectomy, tonsillectomy, and insertion of ventilation tubes (grommets). BMJ 1993, 306:756–760. **Source of cost data:** Published literature and expert opinion **Source of unit cost data:** NHS Reference Costs, PSSRU			
Author and year: Fortnum 2014 **Country:** UK **Type of economic analysis:** Cost utility analysis **Source of funding**: National Institute for Health Research (NIHR)	**Intervention:** Initial treatment with either ventilation tubes or hearing aids **Comparator in detail:** Initial watchful waiting	**Population characteristics:** 3-year-old Children with Down syndrome, suffering from chronic OME and hearing loss **Modelling approach:** Decision analytic cohort model **Source of baseline data:** Dahle A, McCollister F. Hearing and	**Mean cost:** *Initial WW:* £1,303 *Initial HAs*: £1,457 *Initial VTs:* £2,338 **Primary measure of outcome**: QALYs A utility value of 0.00874 (95% CI: 0.005 to 0.012) per unit increase in dBHL following the appoach used	**ICERs:** HAs v WW £34,399 per QALY VTs v HAs Dominated **Probability of being cost effective:** Not reported	**Currency:** GBP **Cost year:** 2011-12 **Time horizon:** 24 months **Discounting:** 3.5% per annum **Applicability:** Directly applicable **Limitations:** Potentially serious limitations

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		otologic disorders in children with Down syndrome. Am J Ment Defic 1986;90:636–42 **Source of effectiveness data:** Assumed that normal hearing is restored by surgery or a hearing device **Source of cost data:** NICE CG60 **Source of unit cost data:** NHS Reference Costs, PSSRU	in the NICE CG60 guideline **Mean QALY:** *Initial WW:* 0.131 *Initial HAs*: 0.136 *Initial VTs:* 0.134		**Other comments:** The authors note that most of the model parameters are determined by expert opinion, indicating the limited evidence base
Author and year: Bruce 2015 **Country:** UK **Type of economic analysis:** Cost utility analysis **Source of funding**: National Institute for Health Research	**Intervention:** Ventilation tubes, hearing aids or hearing aids plus ventilation tubes **Comparator in detail:** Do nothing	**Population characteristics:** Children with cleft palate under the age of 12 years with persistent bilateral OME **Modelling approach:** Decision analytic cohort model **Source of baseline data:**	**Mean cost:** *DN* £592 *Hearing aids:* £1,235 *VTs*: £2,083 *HAs + VTs:* £2,661 **Primary measure of outcome**: QALYs	**ICERs:** VTs v HAs Extended dominance VTs v DN £9,053 per QALY VTs v HAs + VTs Dominant **Probability of being cost effective:**	**Currency:** GBP **Cost year:** 2010-11 **Time horizon:** 24 months **Discounting:** 3.5% per annum **Applicability:** Directly applicable

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
(NIHR) and the Healing Foundation		Maw R, Bawden R: Spontaneous resolution of severe chronic glue ear in children and the effect of adenoidectomy, tonsillectomy, and insertion of ventilation tubes (grommets). BMJ 1993, 306:756–760. **Source of effectiveness data:** Maw R, Bawden R: Spontaneous resolution of severe chronic glue ear in children and the effect of adenoidectomy, tonsillectomy, and insertion of ventilation tubes (grommets). BMJ 1993, 306:756–760. **Source of cost data:** Published literature and expert opinion **Source of unit cost data:** NHS Reference	A utility value of 0.00874 (95% CI: 0.005 to 0.012) per unit increase in dBHL following the approach used in the NICE CG60 guideline **Mean QALY:** *DN* 0.0528 *Hearing aids:* 0.1017 *VTs*: 0.2175 *HAs + VTs:* 0.1357	VTs had a 63% probability of being cost-effective at a cost-effectiveness threshold of £20,000 per QALY	**Limitations:** Potentially serious limitations **Other comments:** Significant uncertainty surrounding the estimates of hearing-level parameters used for quantifying the QALYs was highlighted by the study authors

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Costs, PSSRU			

CI = Confidence interval; dBHL = Decibels hearing level; DN = Do nothing; GBP = British pound sterling; HA = Hearing aids; OME = Otitis media with effusion; PSSRU = Personal Social Services Research Unit; QALYs = Quality Adjusted Life Years; VT = Ventilation tubes; WW = Watchful waiting

Appendix I Economic model

Economic model for review question: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

Cost-utility analysis to compare ventilation tubes with and without adenoidectomy, hearing aids and no intervention for the management of OME with associated hearing loss in children under 12 years?

Introduction

A range of interventions are available for OME, but it has proved difficult to standardise management despite the publication of a number of national guidelines (Simon 2018). Decision making is complicated by the fact that OME is a common, but usually mild childhood condition, that normally resolves spontaneously. However, it can result in prolonged hearing loss for some children with important adverse impacts on health-related quality of life and childhood development. Symptoms vary in severity and, in the absence of strong predictors of persistence, it is difficult to identify children who are most likely to benefit from active treatment.

NICE surveillance identified studies that could potentially change existing NICE guidance for the management of OME and therefore this review question was highlighted as a priority for original economic analysis, especially as the included economic studies from a literature search were published several years ago.

Methods

Setting and population

The model population was children aged 6 months to 12 years with otitis media with effusion (OME) following 3 months of watchful waiting after initial diagnosis. It is assumed that diagnosis identifies children who do not have other co-existing causes of hearing loss and those children are excluded from the model population. Management of the OME is provided in NHS settings. The model makes no distinction between unilateral and bilateral OME.

Model structure

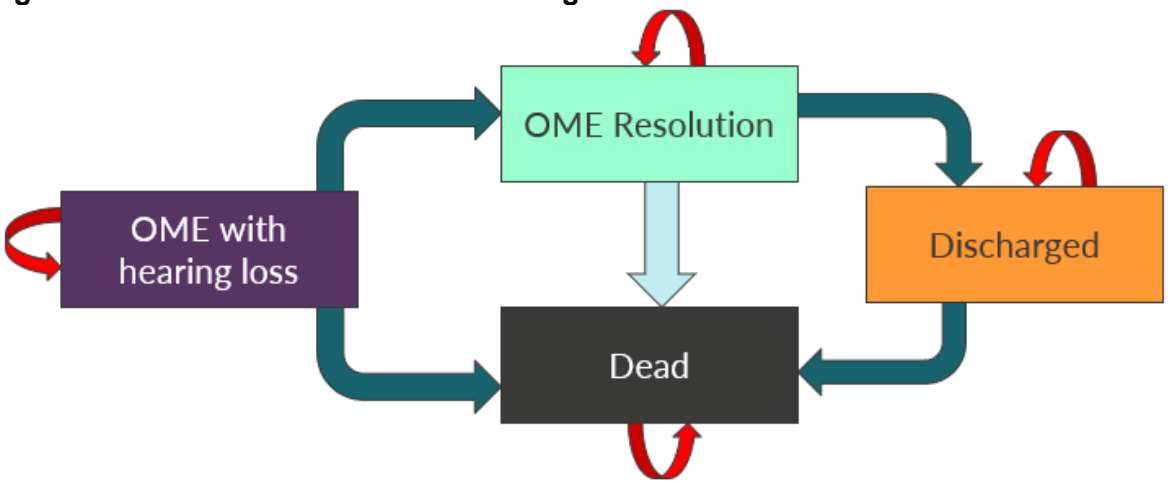
A decision analytic Markov model was developed in Microsoft Excel® to assess the cost-utility of ventilation tubes with and without adenoidectomy, hearing aids and no intervention for the management of OME. Probabilities attached to decision tree branches were derived where possible from the Cochrane review of the clinical evidence undertaken for this guideline. The time frame of the analysis was 2 years (104 weeks) with Markov transitions between different health states occurring in weekly Markov cycles. The model structure for the different interventions is described in more detail below.

i. Hearing aids

A schematic of the Markov model for hearing aid is shown in Figure 2. A cohort approach was adopted where the proportion of children in a particular health state at any moment in time was estimated based on the Markov transition probabilities. The effectiveness of hearing aids was estimated from their beneficial impact on hearing levels whilst the child has

OME. In the Cochrane review undertaken for this guideline there was no comparative estimates of treatment effects relative to alternative management options.

Figure 2: Schematic of the Markov hearing aid model



Hearing aids are inserted at the end of the watchful waiting period and children then transition between the following health states in weekly cycles:

a) OME with hearing loss
b) OME resolution
c) Discharged
d) Dead

All children start in the state of "OME with hearing loss" and any transition to "OME resolution" is determined by the natural history "engine" used for spontaneous resolution of OME over time. Transition to a state of "discharged" from "OME resolution" occurs following audiological review when it is assumed that the absence of OME with hearing loss is confirmed. The model encapsulates all-cause mortality and therefore in any week there is a very small probability of transition to an absorbing "Dead" health state.

Figure 3, Figure 4 and Figure 5 shows the decision tree elements within each weekly Markov cycle in more detail.

The initial costs of the hearing aids include the cost of a hearing aid, mould (air conduction hearing aids) and fitting. It was assumed that the intervention includes the cost of one hearing aid repair kit and, for children not discharged, that there are weekly costs for new hearing aids batteries. It was also assumed that there are costs associated with on-going audiological review. The model also accounted for the possibility of hearing aid loss or breakage and the costs of replacement. No costs are incurred for children who are in the "discharged" health state. The model also allows for an increase in 'downstream' costs arising from higher incidence of episodes of acute otitis media in children whose OME is not surgically treated, comprising a GP visit and medication.

QALYs were estimated based on the health state in a given cycle and the health state utilities assigned according to levels of hearing with a hearing aid, OME resolution (normal hearing) and mortality.

Figure 3: OME with hearing loss weekly Markov cycle decision tree structure

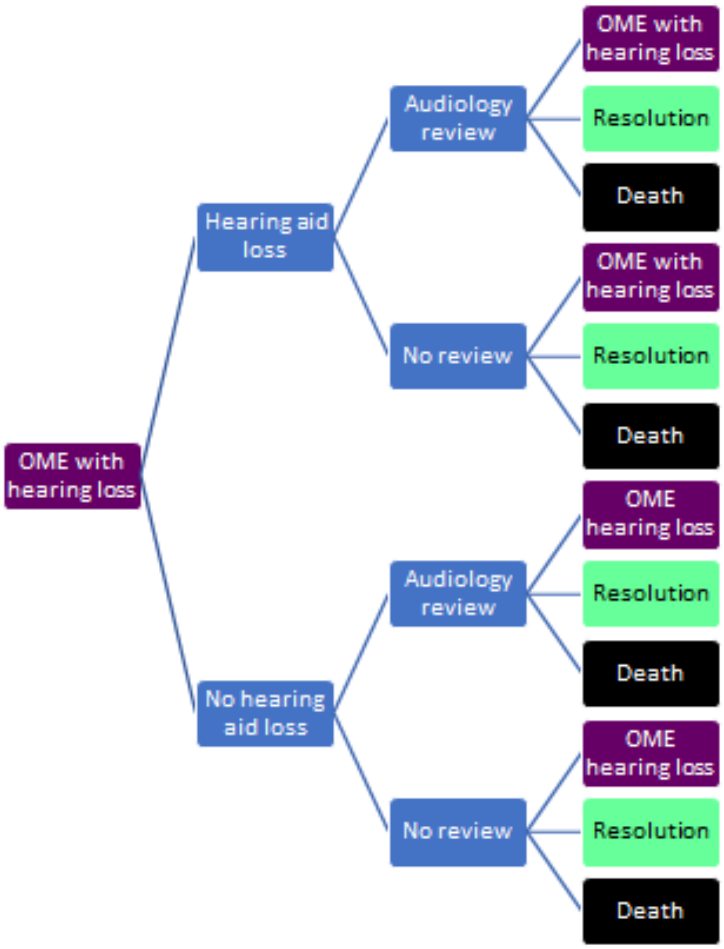


Figure 4: OME resolution weekly Markov cycle decision tree structure

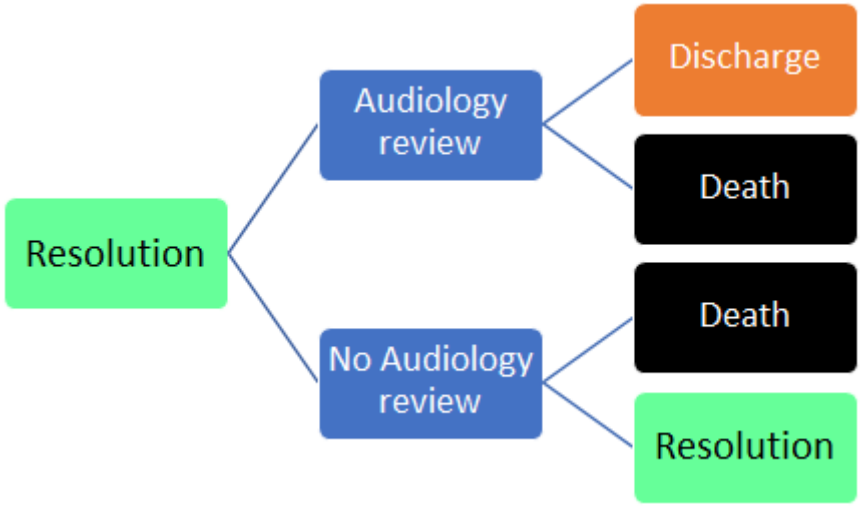
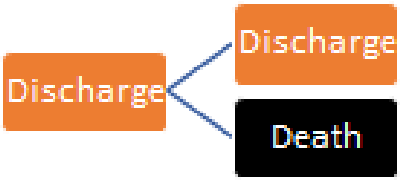


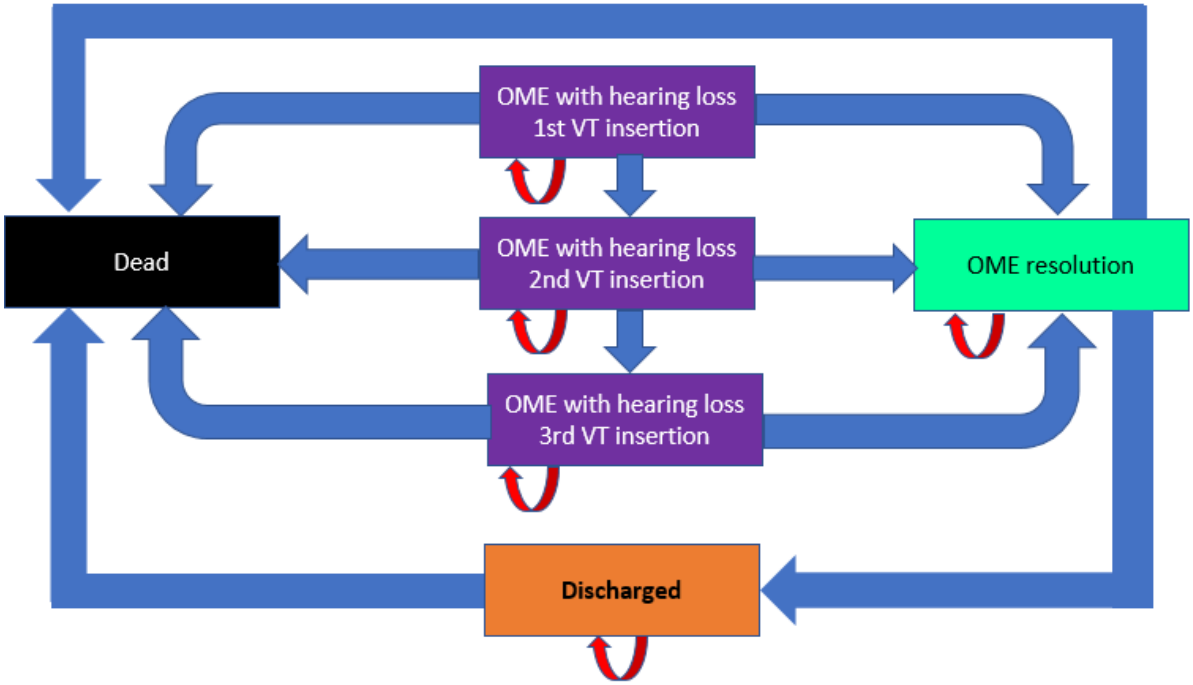
Figure 5: Discharge weekly Markov cycle decision tree structure



ii. Ventilation tubes and ventilation tubes plus adenoidectomy

A representation of the Markov model structure for the surgical management options of ventilation tubes and ventilation tubes plus adenoidectomy is illustrated in Figure 6. The effectiveness of surgery has 2 aspects in the model. First is the improvement in hearing that the child derives from the VT (with or without adenoidectomy) relative to no intervention and second, using estimates of relative treatment effect derived from the Cochrane review, a change in OME persistence over time.

Figure 6: Schematic of the Markov surgical management model



One of the known limitations of cohort Markov models is a lack of "memory" for previous health states. This was important in this context given that the probability of VT extrusion depended on the time since surgery. In a cohort Markov approach the patients in the "VT insertion" health state could have variable times since surgery because the model allowed for VT reinsertion. Therefore, for ease of computation, a patient level Markov simulation approach was adopted to model the costs and QALYs of surgical management interventions. This involved simulating a sample of individual patients through the Markov model and aggregating the costs and QALYs for each patient in order to estimate the mean costs and QALYs associated with each intervention over a hypothetical cohort. At any particular moment in time, in the patient level Markov simulation, a child can only be in one particular health state with this determined stochastically according to the Markov transition probabilities.

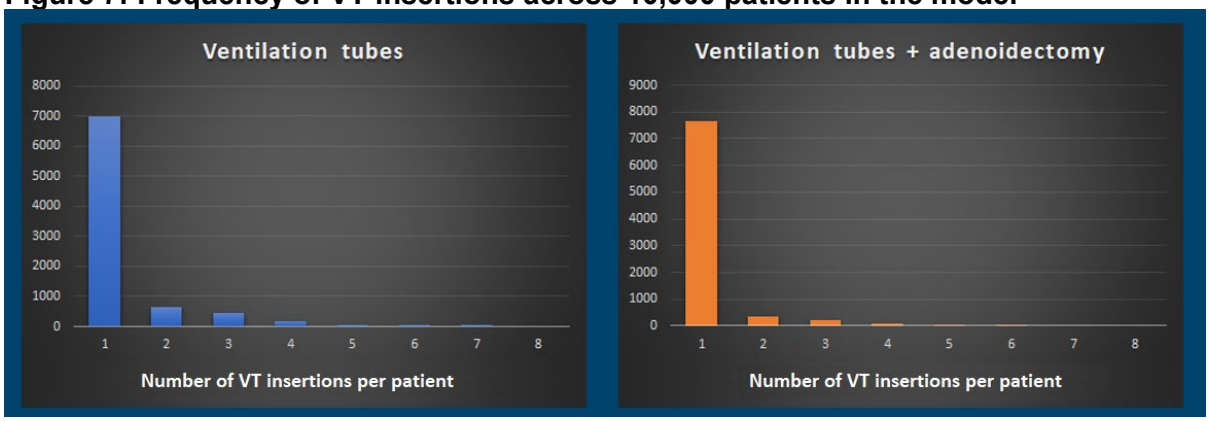
Ventilation tubes with or without adenoidectomy are inserted at the end of a period of watchful waiting period. The various health states are listed below and the individual simulated child transitions between these states at the end of weekly cycles:

a) VT insertion
b) VT in situ
c) OME persisting no VT
d) OME resolution no VT
e) Discharged
f) Death

The individual simulated child starts in the state of “VT insertion” in the first Markov cycle and will then usually transition to the state of “VT in situ”, although the model also factors in the very small risk of general anaesthetic mortality. The risk of complications are all captured in the cycle following VT insertion as shown in Figure 8 below and are not assigned unique health states. This was a simplifying assumption as some complications such as otorrhoea, for example, may emerge over time but the important point was to capture the overall cost and any QALY loss of such complications without adding to model complexity. Estimates for the probability of surgical complications were estimated from the Cochane review undertaken for this guideline where possible.

In any week, there is a probability that a ventilation tube may be extruded and in that case the transition to other states will depend on other temporal factors. If, after extrusion, OME recurs and then the child transitions to the state of “OME persisting no VT”. In which case, the child will have another VT insertion. The model does not assume a maximum number of reinsertions, but the committee were satisfied that the frequency distribution of reinsertions across 10,000 patients in the model (see Figure 7) approximated clinical practice.

Figure 7: Frequency of VT insertions across 10,000 patients in the model



If OME does not recur after extrusion, the child will then move into the “OME resolution state” pending their next ENT review where they transition into the discharged state where no further costs are incurred. The probability of a child having OME after VT extrusion at a particular moment in time is estimated according to the natural history “engine” adjusted by a relative treatment effect. The model assumes that the probability of extrusion in any given week is independent of the probability that OME will recur. A probability for surgical removal of VT is included for the “VT in situ” health state. Whilst in practice this may usually be related to complications such as otorrhoea, this was not done in this analysis as it would greatly add to model complexity and is rare. The simplified approach was used to capture the “downstream” costs of the complication leading to VT removal but did not affect transitions to other Markov health states.

As with the hearing aid component of the model, all-cause mortality is factored into the Markov cycles and therefore it is possible for a simulated child to experience death in any cycle albeit, reflecting their age, with a very small probability.

Figure 8, Figure 9, Figure 10 and Figure 11 depict the decision tree for the weekly Markov cycles for each of the health states. Costs are allocated for surgical interventions including VT removal, complications and ENT (ear, nose and throat) review. QALYs were estimated according to hearing levels with VT, with or without adenoidectomy, where OME was not resolved, normal hearing where OME was no longer persisting (with or without VT in place)

and mortality. In addition, the model could account for any disutility associated with complications as part of a sensitivity analysis.

Figure 8: VT insertion weekly Markov cycle decision tree structure

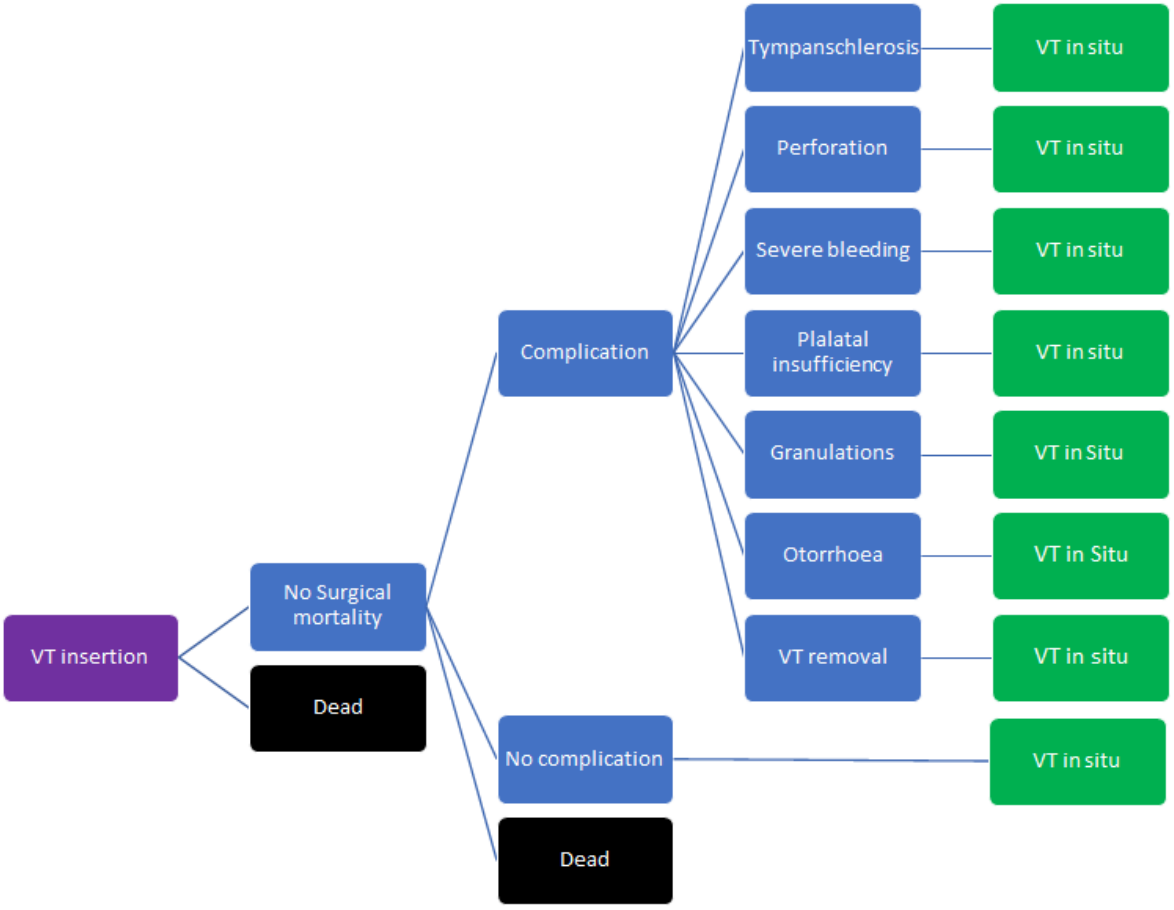


Figure 9: VT in situ weekly Markov cycle decision tree structure

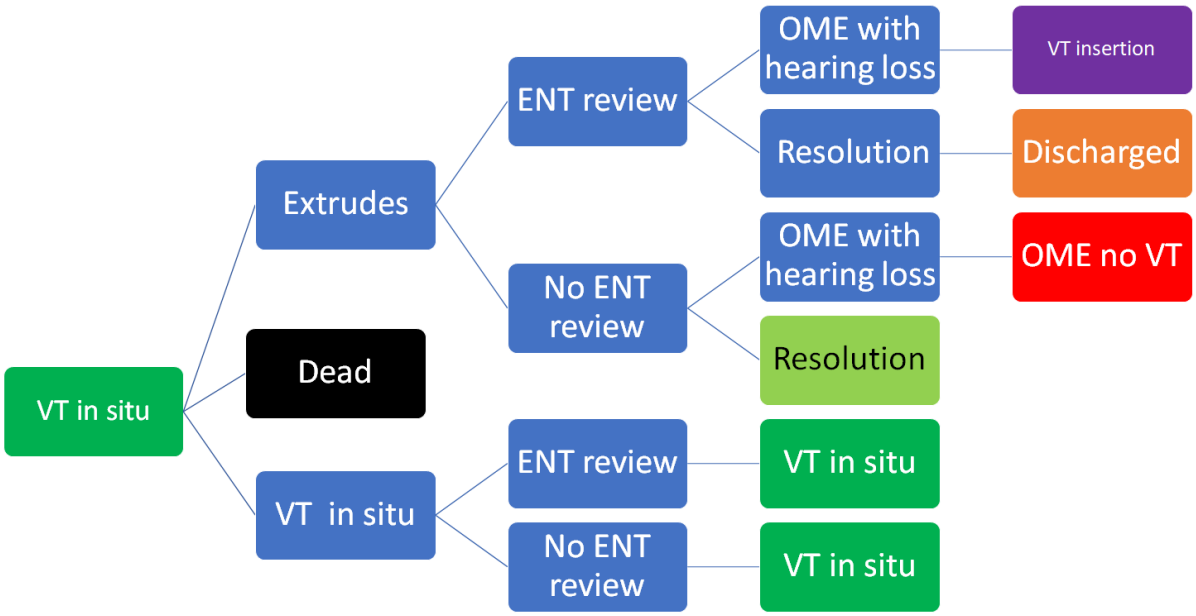


Figure 10: OME resolution no VT weekly Markov cycle decision tree structure

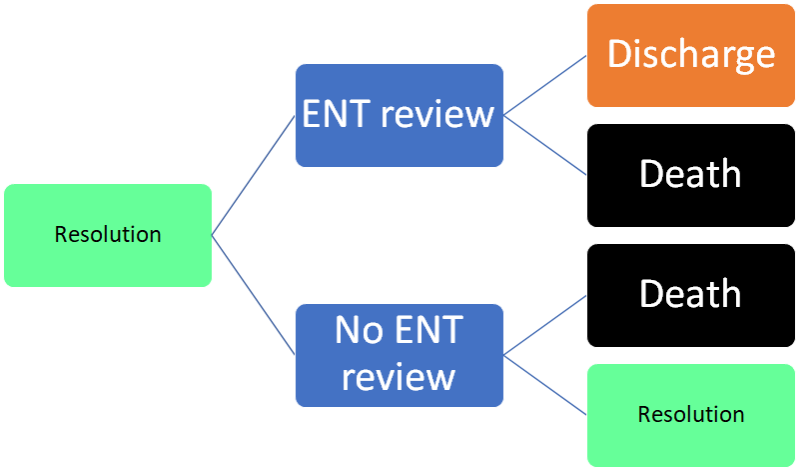


Figure 11: OME no VT weekly Markov cycle decision tree structure

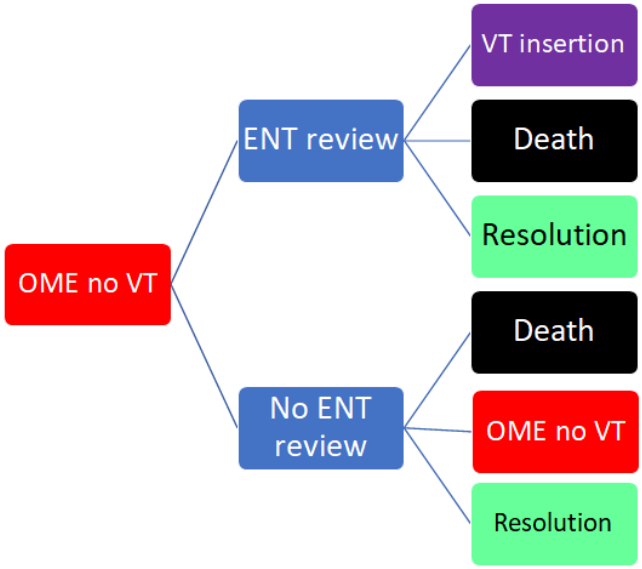
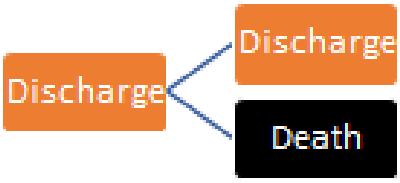


Figure 12: Discharge weekly Markov cycle decision tree structure



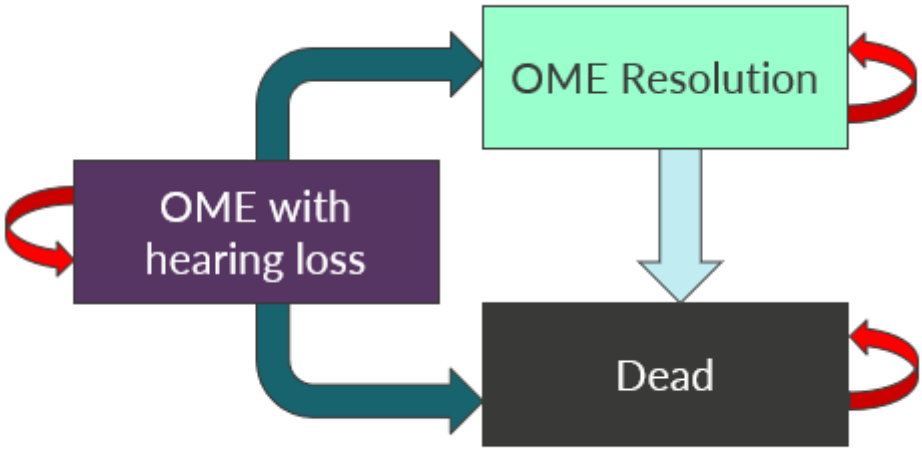
iii. No intervention

The model structure for no intervention was similar to that for hearing aids as hearing aids also do not impact on the natural history of the condition. The schematic of the Markov model for no intervention is shown in Figure 13.

As with hearing aids a cohort approach was adopted where the proportion of children in a particular health state at any moment in time is estimated based on the Markov transition probabilities between different states over time. The health state for no intervention are as follows:

a) OME with hearing loss
b) OME resolution
c) Dead

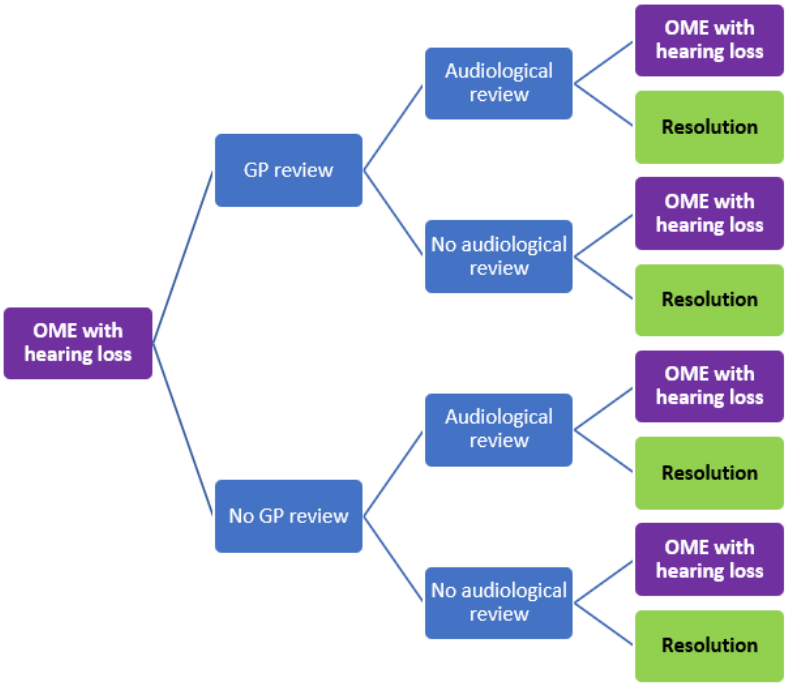
Figure 13: Schematic of the Markov no intervention model



All children start in the state of "OME with hearing loss" and any transition to "OME resolution" is determined by the natural history "engine" used for spontaneous resolution of OME over time. As for other interventions all-cause mortality is factored into the analysis through transitions to an absorbing "Dead" health state.

The decision elements within each weekly Markov cycle are illustrated in Figure 14. As in the 2008 NICE guideline on OME it was assumed that children with persistent OME will have on-going contact with health services and so periodic GP and audiological appointments are included. The model also allows for an increase in 'downstream' costs arising from higher incidence of episodes of acute otitis media in children whose OME is not treated comprising a GP visit and medication.

Figure 14: No intervention weekly Markov cycle decision tree structure



Effectiveness and Markov transition probabilities

Baseline

OME is usually a time limited condition which spontaneously resolves for most children. This natural history reflects the baseline from which to compare intervention as any detrimental impact of OME on health-related quality of life will be a function of the duration of OME in addition to the beneficial impact that intervention has on health-related quality of life due to hearing loss.

The model can be run for a number of alternative natural history models, and these are used as the "engine" to estimate a weekly probability of OME resolution in the Markov cycles and the transition to different health states over time.

These alternative natural history models are described below.

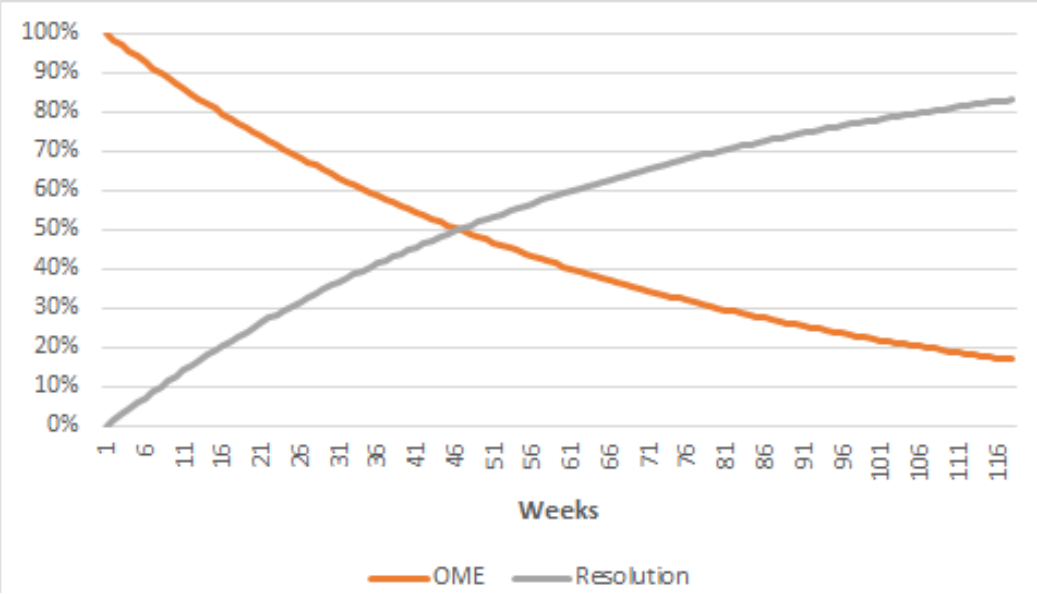
a. Natural history model 1

This model was based on the 2008 NICE guideline on OME where it was estimated that 75% of OME cases would resolve spontaneously after 21 months (91 weeks). For this analysis we have assumed that this resolution is from the start of the watchful waiting period. It was additionally assumed that the weekly probability of OME resolution would be constant over time which was calculated as shown below:

Weekly probability = 1-EXP ((LN (1-0.75))/91) = 1.5%

This gives a natural history of OME resolution as shown in Figure 15 below. This natural history model was used in the base case analysis.

Figure 15: Spontaneous OME resolution over time for natural history model 1



b. Natural history models 2 - 5

These models were based on the clinical evidence review undertaken for this guideline (see Evidence review D). Numerous studies were included for this review, but the quality was generally low, and the evidence showed a wide variation in persistence in the rates of OME causing hearing loss. Therefore, for the purpose of sensitivity analysis, 2 studies with faster resolution than the base case and 2 studies with slower resolution were chosen. These 4 studies are listed in Table 5 below. These natural history models are graphed in Figure 16, Figure 17, Figure 18 and Figure 19. As for natural history model 1, the same formula was used to calculate a weekly probability of OME resolution, assumed to be constant over the model timeframe.

Table 5: Summary of natural history models used in sensitivity analysis

Name	Study	Resolution period (weeks)	Resolution	Weekly resolution probability
NH2	O'Shea 1980	13	50.0%	5.2%
NH3	O'Shea 1982	52	29.2%	0.7%
NH4	Francis 2018	26	11.6%	0.5%
NH5	O'Shea 1980	52	77.1%	2.8%

Figure 16: Spontaneous OME resolution over time for natural history model 2 (NH2)

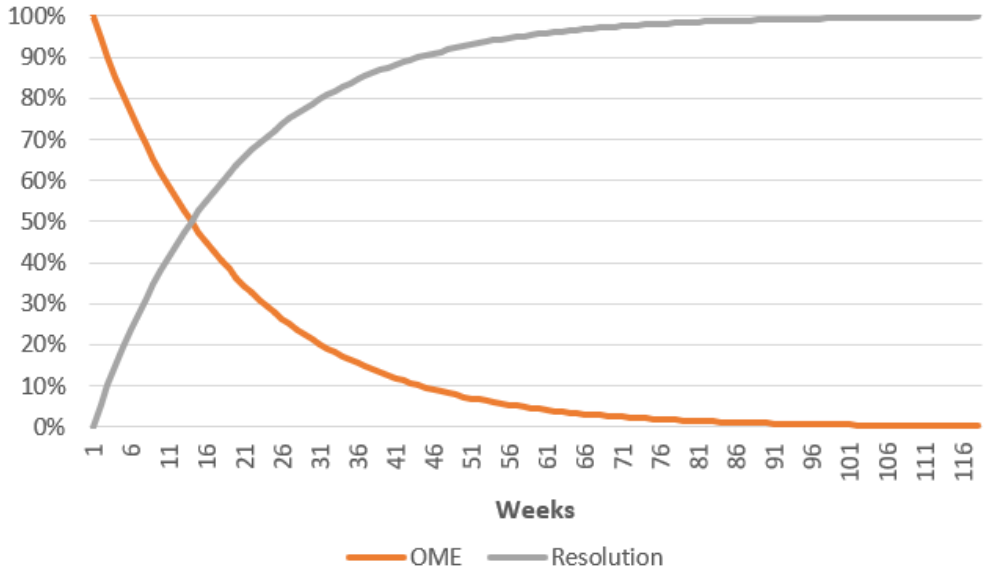


Figure 17: Spontaneous OME resolution over time for natural history model 3 (NH3)

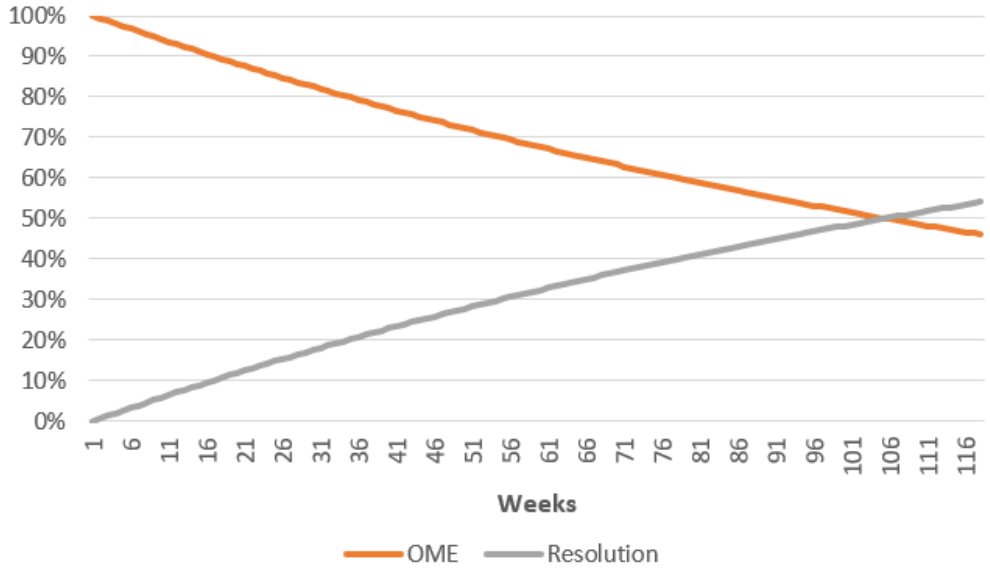


Figure 18: Spontaneous OME resolution over time for natural history model 4 (NH4)

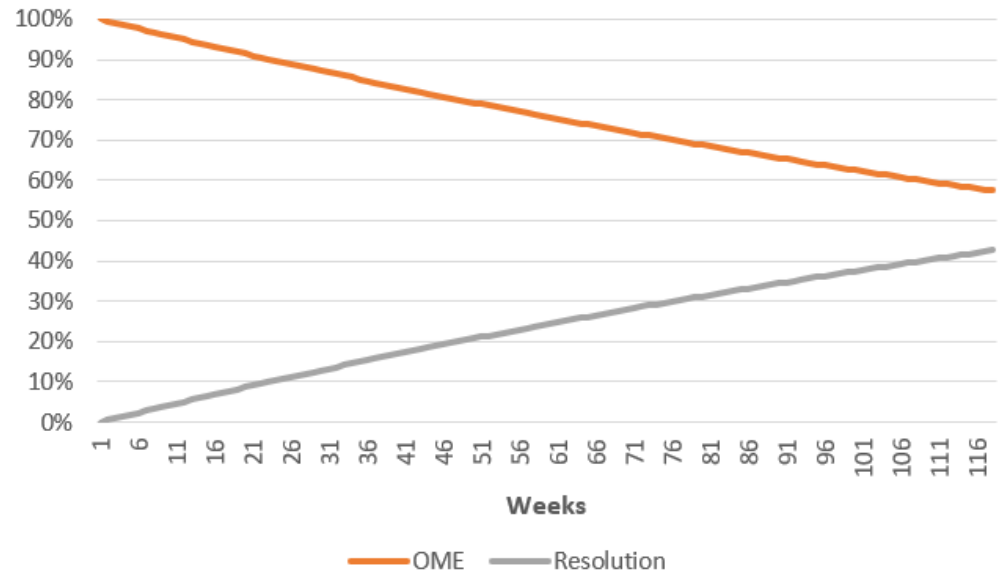
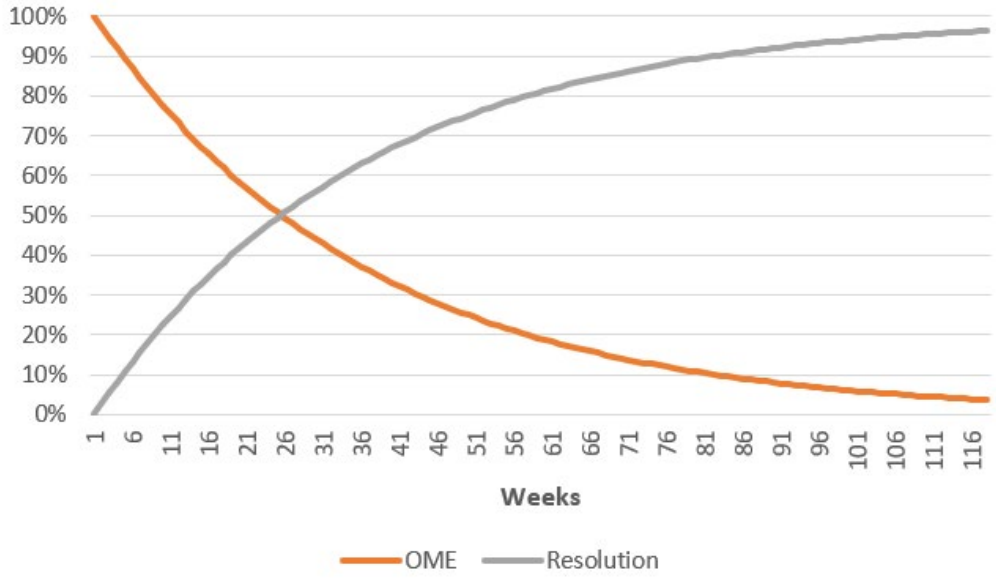


Figure 19: Spontaneous OME resolution over time for natural history model 5 (NH5)



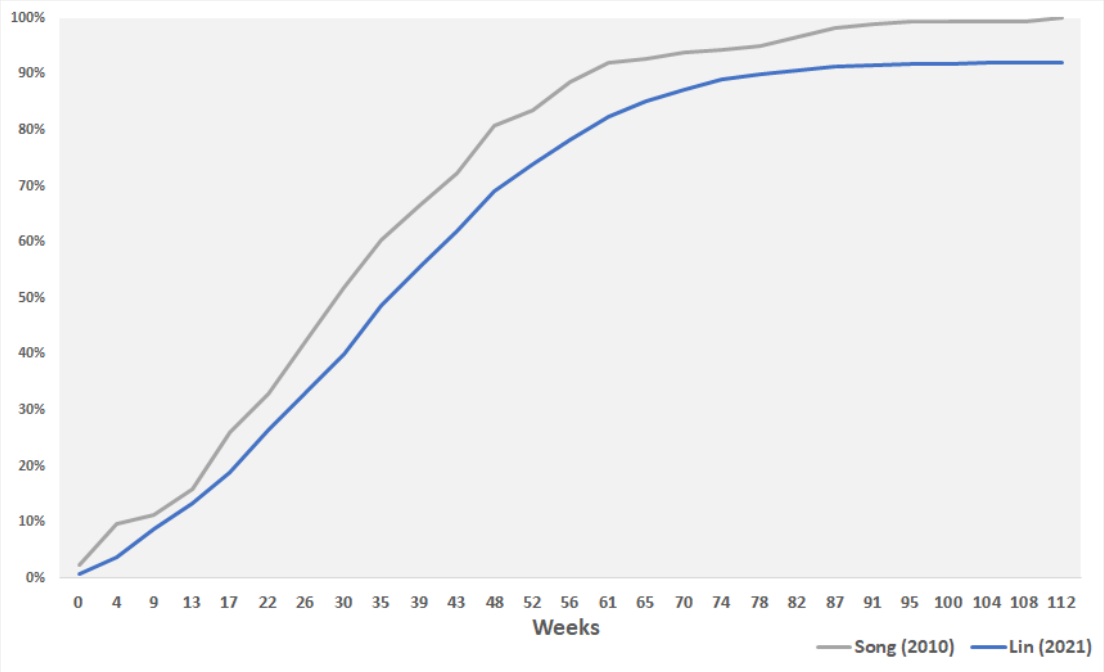
Ventilation tube extrusion

Lin (2021) reported a mean time of 221.3 days (standard deviation 159.9 days) to the extrusion of ventilation tubes in children and a normal distribution was applied to this data in order to estimate the proportion of ventilation tubes extruded by weeks since insertion.

The cumulative distribution function for this data is plotted on Figure 20. Also, plotted is the cumulative frequency of VT extrusion reported by Song (2010) in paediatric patients. Comparing the two gives some indication of the reasonableness of assuming a normal distribution to the Lin (2021) parameters as the actual distribution is likely to be right skewed.

The model assumes the same probability distribution for time to extrusion for any subsequent VT insertion.

Figure 20: Proportion of VT extruded by weeks since insertion



Relative treatment effect

The model estimates the probability that OME will recur following VT insertion, with and without adenoidectomy, using data on the outcome of OME persistence reported in the Cochrane review undertaken for this guideline. The results are summarised in Table 6 below. The relative risks were applied to the baseline probabilities of persistence and a weekly probability of OME persisting was estimated using the same formula as for the baseline values.

Table 6: Relative treatment effect reported for the persistence of OME in the systematic review undertaken for this guideline

Study	Comparator	Intervention	Relative Risk	Lower 95% CI	Upper 95% CI
Rach 1991	No treatment	VT	0.30	0.14	0,65
Dempster 1993	No treatment	VT	0.83	0.61	1.13
Velepic 2011	Watchful waiting	VT	0.39	0.09	1.70
Maw 1999	Watchful waiting	VT	0.52	0.37	0.71
Maw 1999, Paradise 2007	Watchful waiting	VT	1.19	0.82	1.72
Maw 1999	Watchful waiting	VT	0.99 [a]	0.35	2.83
Jabeen 2019	Bilateral VT	Bilateral VT + Ads	0.14	0.06	0.37
Hao 2019	Bilateral VT	Bilateral VT + Ads	0.92	0.68	1.23
Gates 1989	Bilateral VT	Bilateral VT + Ads	0.96	0.86	1.07

Study	Comparator	Intervention	Relative Risk	Lower 95% CI	Upper 95% CI
Maw 1983	VT	VT + Ads	0.58	0.38	0.91
Maw 1983, Dempster 1993	VT	VT + Ads	0.57	0.38	0.86
Maw 1983	VT	VT + Ads	0.67	0.35	1.29
Gates 1989	No treatment/ Watchful waiting	VT + Ads	0.91	0.82	1.01

(a) Odds ratio

These data compare 3 strategies (no intervention, VT alone and VT plus adenoidectomy) and the model requires that 2 studies be chosen to measure the relative treatment effect of either:

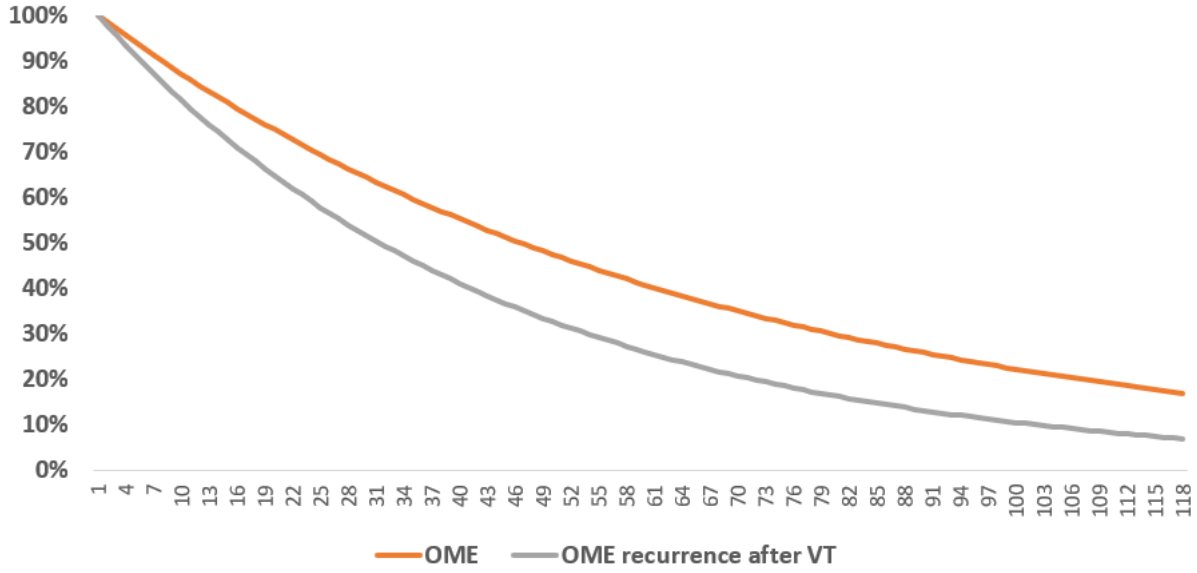
- VT versus no treatment and VT versus VT plus adenoidectomy
- VT plus adenoidectomy versus no treatment and VT versus VT plus adenoidectomy

However, as no network meta-analysis was undertaken, Bucher's method (Bucher 1997) was used in order to estimate the indirect treatment effect of either VT plus adenoidectomy versus no treatment in the first case or VT versus no treatment in the second case.

For illustrative purposes only, Rach 1991 and Jabeen 2019 were selected for the base case analysis. The impact of different treatment effect size was estimated in sensitivity analysis.

The relative treatment effect is then applied to the natural history OME resolution rate to give the risk of OME recurrence after VT extrusion across the timeframe of the analysis. An example is shown in Figure 21 below using a relative risk of 0.52 taken from Maw (1999) and Natural History Model 1 when comparing VT to watchful waiting.

Figure 21: Chart to indicate risk of OME recurrence following VT extrusion compared to OME persistence in the absence of intervention



Model probabilities

Table 7 outlines the probabilities associated with complications of surgery and other events that may incur costs or have implications for health-related quality of life.

Table 7: Model probabilities

Outcome	Probability	Distribution	Parameters	Source
Granulations	4.2%	Beta	α = 37, β = 850	Kay 2001
Ear perforations (1st insertion)	2.2%	Beta	α = 178, β = 7,929	Kay 2001
Ear perforations (1st insertion)	16.6%	Beta	α = 577, β = 2,799	Kay 2001
Severe bleeding	1.0%	Fixed	N/A	CG60
Perforations needing tympanoplasty	30%	Fixed	N/A	Guideline committee
Severe bleeding|hospitalia stion	0.4%	Fixed	N/A	CG60
Palatal insufficiency	0.06%	Fixed	N/A	CG60
Otorrhoea	26.2%	Beta	α = 1,439, β = 4,052	Kay 2001
Tympanosclerosis	38.9%	Fixed	N/A	Dempster 1993
Surgical mortality	0.001%	Fixed	N/A	Great Ormond Street [a]
VT removal	1.0%	Fixed	N/A	Guideline committee
Weekly loss/breakage of hearing aid	0.31%	Fixed	N/A	CG60
Proportion air conduction hearing aids	95%	Fixed	N/A	Guideline committee [b]
Hearing aid adherence	90.9%	Fixed	N/A	Mohiuddin 2014

(a) https://www.gosh.nhs.uk/your-hospital-visit/coming-gosh-day-or-inpatient-admission/your-childs-general-anaesthetic/#:~:text=The%20risk%20of%20death%20due,risks%20may%20be%20substantially%20higher (Accessed 01/02/2023).

(b) The remaining are bone conduction hearing aids

Costs and resource use

In accordance with NICE methodology a NHS and Personal Social Services (PSS) perspective was adopted for this analysis (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf). Costs were based on a 2021-22 price year. The model input cost parameters are given in Table 8. Any costs occurring after 1-year were discounted at an annual rate of 3.5% in line with NICE methods.

Table 8: Model unit cost parameters

Variable	Value	Distribution	Parameters	Source
Bone conduction hearing aid	£2,766	Normal	μ=£2,766, σ_M = £602	National Schedule of NHS Costs (2020-21) [a]
Air conduction hearing aid	£175	Normal	μ=£175, σ_M = £18	National Schedule of NHS Costs (2020-21) [b]
Hearing aid fitting	£220	Normal	μ=£220, σ_M = £22	National Schedule of NHS Costs (2020-21) [c]

Variable	Value	Distribution	Parameters	Source
Hearing aid mould	£35	Fixed	N/A	https://www.chears.co.uk/wp-content/uploads/2021/06/Hearing-aid-prices-March-2021.pdf
Hearing aid battery	£0.22	Fixed	N/A	https://www.hearingaidaccessories.co.uk/ (accessed 01/02/2023)
Audiology review	£169	Normal	μ=£169, σ_M = £16	National Schedule of NHS Costs (2020-21) [d]
Hearing aid repair kit	£25	Fixed	N/A	Guideline Committee
Ventilation tube insertion	£2,221	Normal	μ=£2,221, σ_M = £108	National Schedule of NHS Costs (2020-21) [e]
Ventilation tube plus adenoidectomy	£3,389	Normal	μ=£3,389, σ_M = £1,389	National Schedule of NHS Costs (2020-21) [f]
Removal of ventilation tube	£2,221	Normal	μ=£2,221, σ_M = £108	National Schedule of NHS Costs (2020-21) [e]
ENT first consultation	£195	Normal	μ=£195, σ_M = £15	National Schedule of NHS Costs (2020-21) [g]
ENT follow-up consultation	£184	Normal	μ=£148, σ_M = £12	National Schedule of NHS Costs (2020-21) [h]
Medication	£6.01	Fixed	N/A	BNF 2022 https://bnf.nice.org.uk/drugs/ciprofloxacin/medicinal-forms/#ear-drops [i]
GP consultation	£39	Fixed	N/A	PSSRU 2021 https://kar.kent.ac.uk/92342/
Palatoplasty	£2,955	Normal	μ=£2,955, σ_M = £333	National Schedule of NHS Costs (2020-21) [j]
Tympanoplasty	£5,048	Normal	μ=£5,048, σ_M = £243	National Schedule of NHS Costs (2020-21) [k]
Surgical arrest of bleeding	£2,011	Normal	μ=£2,011, σ_M = £213	National Schedule of NHS Costs (2020-21) [l]
High Dependency Unit per day	£1,529	Normal	μ=£1,529, σ_M = £209	National Schedule of NHS Costs (2020-21) [m]
Intensive Care Unit per day	£8,265	Normal	μ=£8,265, σ_M = £1,898	National Schedule of NHS Costs (2020-21) [n]

(a) Currency code: DEV05; High cost devices
(b) Currency Code: AS07; Community Health Services, Audiology
(c) Currency Code: AS02; Community Health Services, Audiology
(d) Currency Code: WF01C; Consultant Led, Audiology
(e) Currency Code: CA35B; Day case
(f) Currency Code: CA81C; Day case, Complex, Mouth or Throat Procedures, between 2 and 18 years
(g) Currency Code: WF01B; Consultant led, ENT
(h) Currency Code: WF01A; Consultant led, ENT
(i) One bottle of ciprofloxacin ear drops
(j) Currency Code: CA83C; Day case, Major, Mouth or Throat Procedures, 18 years and under
(k) Currency Code: CA32B; Day case
(l) Currency Code: CA23Z; Day case, Intermediate nose procedures
(m) Currency Code: XB01Z; Paediatric Critical Care, Advanced Critical Care 5
(n) Currency Code: XB01Z; Paediatric Critical Care, Advanced Critical Care 5

For the hearing aid intervention, it was assumed that after a period of watchful waiting all children whose OME with hearing loss had not resolved (the model population) would incur

the costs of a hearing aid fitting, the cost of the hearing aid itself, a hearing aid mould, and a one-off hearing aid repair kit. In the event of hearing aid loss or breakage these costs would be reincurred. It was assumed that batteries needed to be replaced weekly and that, as in the 2008 NICE guideline on OME, moulds would be replaced every 13 weeks. Finally, the cost of the hearing aid intervention included periodic audiological review. The schedule of these reviews could be adjusted in the model to reflect variations in clinical practice with the alternatives shown in Table 9 with the week denoting the time elapsed since the end of the watchful waiting period. The review schedule denoted by option 1 was used in the base case analysis.

Table 9: Alternative audiological review schedule options for children with OME and hearing aids

Appointment number	Option 1 (week)	Option 2 (week)	Option 3 (week)	Option 4 (week)	Option 5 (week)	Option 6 (week)	Option 7 (week)
1	13	12	26	8	8	8	8
2	39	24	52	21	21	20	34
3	65	36	78	34	47	32	60
4	91	48	104	47	73	44	86
5	117	60		60	99	56	112
6		72		73		68	
7		84		86		80	
8		96		99		92	
9		108		112		104	
10						116	

Reflecting the recommendations made in this guideline it was assumed that children receiving a surgical intervention would be followed up at 6 weeks and 1-year post surgery. It was also assumed that children given no intervention would still have 2 GP visits and 1 audiological review per annum if their OME had not resolved.

Health State utilities and QALYs

The health state utility for healthy children (those without hearing loss) was taken from UK population norms in people aged under 25 years old (Kind, 1999). Following the NICE guidance on Hearing loss in adults: assessment and management (NG98) it was assumed that hearing loss results in a 0.19 reduction in health state utility compared to that of healthy children and that the use of hearing aids would confer a health state utility gain of 0.06 to children with hearing loss, the difference between health state utility from hearing loss with hearing aids and hearing loss without intervention. The model assumed an identical health state utility gain with surgical intervention as with hearing aids. These health state utilities are summarised in Table 10.

Table 10: Health state utilities according to hearing status

Hearing status	Health state utility	Source
Normal hearing	0.94	Kind 1993
Hearing loss without intervention	0.75	NG98
Hearing loss with hearing aids	0.81	NG98
Hearing loss with ventilation tubes	0.81	Guideline committee
Hearing loss with ventilation tubes and adenoidectomy	0.81	Guideline committee

Using the values in Table 10 it is possible to assign a health state utility to each of the Markov states in the model as shown in Table 11. It was difficult to quantify uncertainty with respect to health state utility and therefore parameter values were treated as fixed in the probabilistic analysis. However, it was recognised that considerable uncertainty exists with respect to these estimates, and this was addressed through sensitivity analysis (see Table 30 and Table 31).

Table 11: Health state utilities for the various Markov health states

Markov state	Intervention	Health state utility
OME with hearing loss	No intervention	0.75
OME resolution	No intervention	0.94
OME with hearing loss	Hearing aids	0.81
OME resolution	Hearing aids	0.94
Discharged	Hearing aids	0.94
VT insertion	VT alone|VT plus adenoidectomy	0.81
VT in Situ (OME not resolved)	VT alone|VT plus adenoidectomy	0.81
VT in Situ (OME resolved)	VT alone|VT plus adenoidectomy	0.94
OME persisting no VT	VT alone|VT plus adenoidectomy	0.75
OME resolution no VT	VT alone|VT plus adenoidectomy	0.94
Death	All	0.00

In the base case analysis, no QALY loss was assigned to complications or adverse events (otorrhoea, ear perforations, granulations, severe bleeding, tympanosclerosis or palatal insufficiency). This was because it was assumed that treatment of the complication would mean that any health state utility loss resulting from complications and adverse events would only be experienced for a very short time. Furthermore, the more serious complications where this assumption may be questioned only affect a very small proportion of children and the absolute effect of relaxing this assumption would be negligible. Sensitivity analysis was undertaken to verify that the base case assumption was unlikely to affect model conclusions.

Health state utilities occurring in the 2nd year of the model were discounted at 3.5% in line with the NICE reference case outlined with NICE methodology. Net monetary benefits (NMB) are stated for a £20,000 per QALY cost-effectiveness threshold unless otherwise stated.

Sensitivity and scenario analyses

Probabilistic sensitivity analysis was undertaken to assess parameter uncertainty simultaneously across a number of model inputs. This involved running Monte Carlo simulations of the model, with many model inputs sampled from a specified probability distribution for each iteration.

A wide range of scenario analyses were undertaken to explore and quantify the extent to which conclusions about the cost-effectiveness depended on model assumptions and parameter values. These included different scenarios for the natural history of spontaneous resolution of OME and relative treatment effect. In addition, a number of one-way sensitivity analyses were undertaken for model parameters that were treated as fixed in the PSA (because it was difficult to ascertain a probability distribution) but where there existed some uncertainty with respect to the true value of the parameter. This involved changing just one parameter value whilst holding all other model inputs constant,

Results

Base case analysis

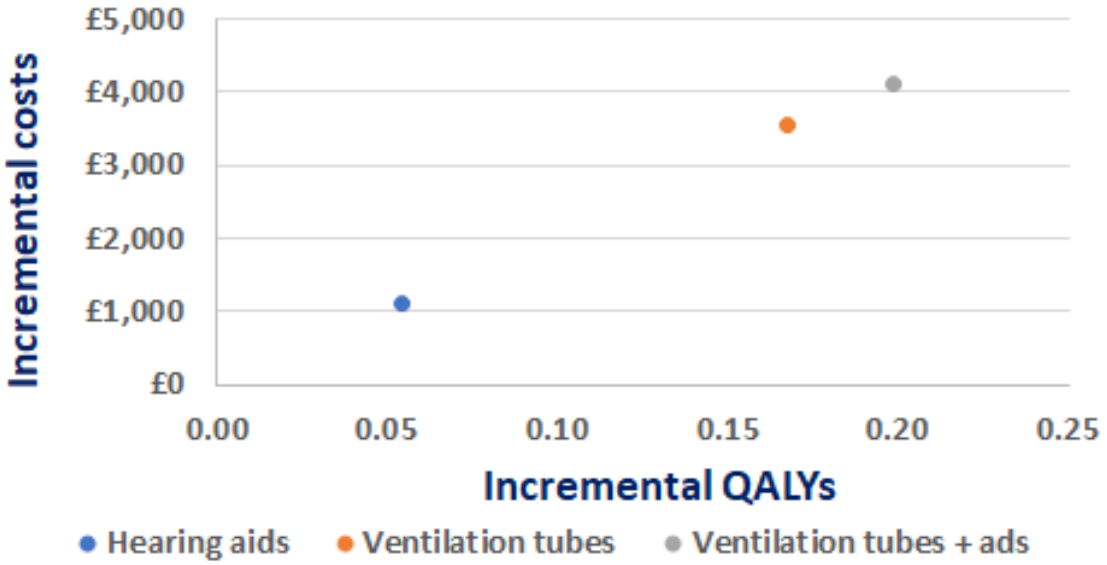
The deterministic analysis using the base case models inputs and a sample of 1,000 patients in the patient level Markov simulation, is shown in Table 12 and Figure 22. No intervention has the highest NMB but, at a cost-effectiveness threshold of £20,000 per QALY, the NMBs of all strategies are similar despite the relatively large difference in costs. This is also reinforced by the ICERs which indicate that hearing aids and ventilation tube plus adjuvant adenoidectomy are borderline cost-effective at this cost-effectiveness threshold.

Table 12: Deterministic base case analysis results

Strategy	Cost	QALYS	Incremental cost	Incremental QALYS	ICER	NMB
No intervention	£215	1.66	n/a	n/a	n/a	£32,980
Hearing Aids	£1,330	1.71	£1,114	0.05	£20,475	£32,954
VT	£3,752	1.83	n/a	n/a	Extended dominance	£32,787
VT + Ads	£4,312	1.86	£2,982	0.14	£20,728	£32,849

ICER = Incremental cost-effectiveness ratio (per QALY); NMB = Net monetary benefit; VT = Ventilation tubes; VT + ads = Ventilation tubes with adjuvant adenoidectomy

Figure 22: Cost-effectiveness plane for deterministic base case analysis relative to no intervention



The results of the probabilistic sensitivity analysis (PSA) for the base case analysis with 10,000 model simulations and using a sample of 1,000 patients for the patient level Markov simulation, are given in Table 13, Table 14 and Figure 23. Costs and QALYs are the mean across 10,000 simulations. The tables give 95% credible intervals (CrInt) for costs, QALYs and net monetary benefits. The cost-effectiveness plane is graphed in Figure 24 and the cost-effectiveness acceptability curve (CEAC) is displayed in Figure 25.

Hearing aids have the highest mean NMB at a cost-effectiveness of £20,000 cost-effectiveness threshold, although they do not have the highest probability of being the most

cost-effective intervention. At a cost-effectiveness threshold of £20,000 per QALY ventilation tubes plus adenoidectomy has a 42% probability of being the most cost-effective. This rises to 57% if a higher cost-effectiveness threshold of £30,000 per QALY is used. Despite the marginal extended dominance of ventilation tubes plus adenoidectomy over ventilation tubes alone, ventilation tubes nevertheless have a relative high probability of being cost-effective at cost-effectiveness thresholds between £20,000 to £30,000 per QALY. The CEAC demonstrates that as the valuation of QALYs increases, the probability of the surgical interventions, which provide the highest QALY's, being cost-effective increases. The probability of no intervention being most cost-effective declines rapidly with increasing monetary valuation of QALY gains but reflecting its position as the cheapest strategy, it has a 100% probability of being cost-effective when QALYs are accorded a zero monetary valuation.

Table 13: Costs and QALYs of the PSA for the base case analysis

Strategy	Cost (95% CrInt)	QALYs (95% CrInt)	Incremental cost	Incremental QALY
No intervention	£222 (£183 to £266)	1.66 (1.63 to 1.68)	N/A	N/A
Hearing Aids	£1,237 (£989 to £1,500)	1.72 (1.69 to 1.73)	£1,015	0.05
VT	£3,620 (£3,049 to £4,496)	1.83 (1.78 to 1.84)	N/A	N/A
VT + Ads	£4,162 (£1,611 to £6,770)	1.86 (1.84 to 1.86)	£2,925	0.14

Table 14: Summary outcomes of the PSA for the base case analysis

Strategy	ICER	NMB (95% CrInt)	Probability cost-effective at £20,000 per QALY	Probability cost-effective at £30,000 per QALY
No intervention	N/A	£32,999 (£32,406 to £33,568)	10%	0%
Hearing Aids	£18,775	£33,065 (£32,540 to £33,555)	21%	2%
VT	Extended dominance	£32,909 (£31,334 to £33,855)	27%	41%
VT + Ads	£20,666	£32,971 (£30,335 to £35,535)	42%	57%

Figure 23: Net monetary benefit with credible intervals (base case analysis)

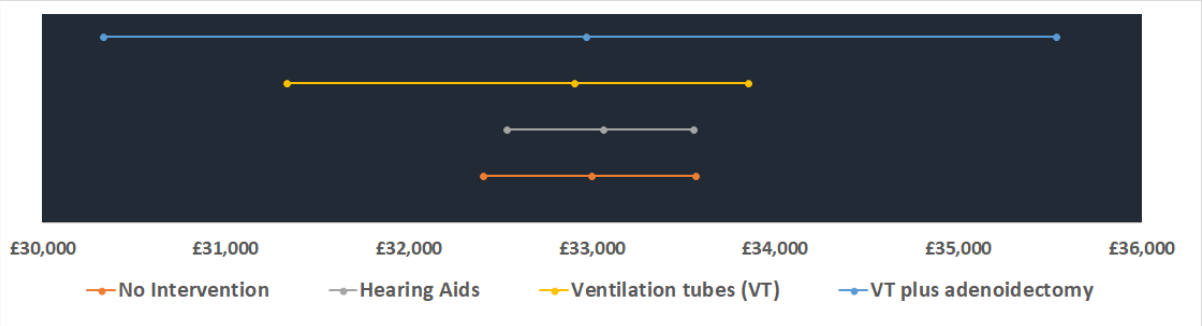


Figure 24: Cost-effectiveness plane base case PSA relative to no intervention

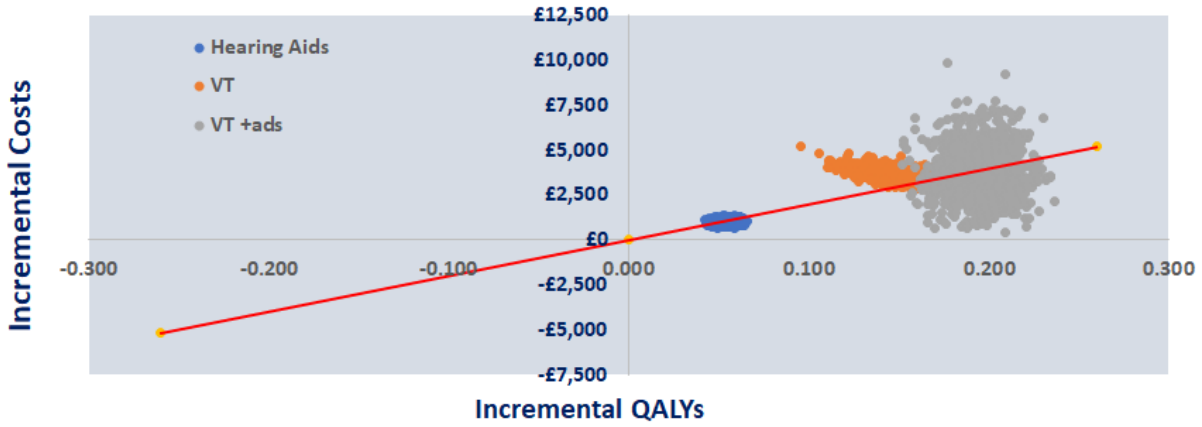
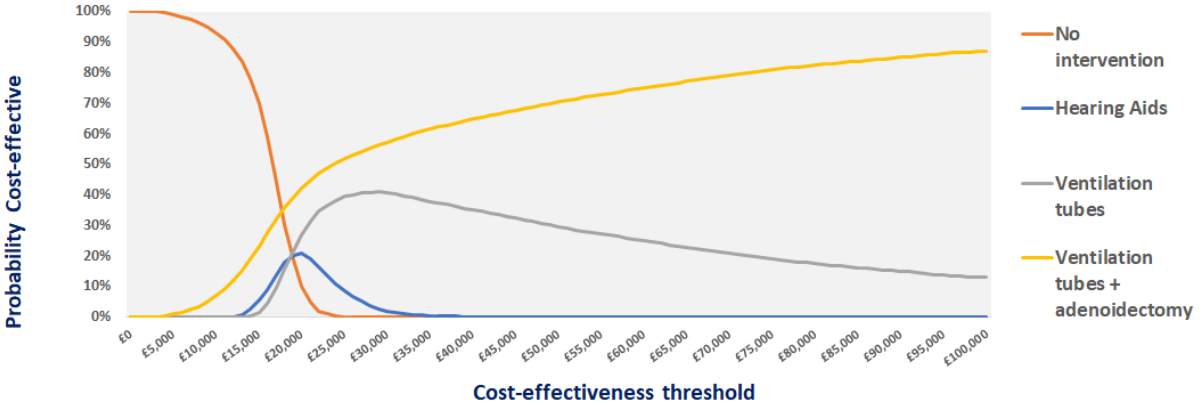


Figure 25: CEAC for base case PSA



NH2 analysis

NH2 assumes earlier spontaneous resolution of OME with hearing loss than the base case analysis. Indeed, it is the natural history model with the fastest rate of spontaneous resolution in the sensitivity analysis. The deterministic analysis for NH2, keeping all other model inputs constant at their base case value, is shown in Table 15 and Figure 26. Again, the patient level Markov simulation utilises a sample of 1,000 patients. In this analysis no intervention

has the highest NMB at a cost-effectiveness threshold of £20,000 per QALY with the ICERs for surgical interventions indicating that they would not be considered cost-effective.

Table 15: Deterministic NH2 analysis results

Strategy	Cost	QALYS	Incremental cost	Incremental QALYS	ICER	NMB
No intervention	£69	1.78	n/a	n/a	n/a	£35,522
Hearing Aids	£1,007	1.80	n/a	n/a	Extended dominance	£34,985
VT	£3,116	1.85	£3,047	0.07	£42,433	£33,911
VT + Ads	£4,051	1.86	£935	0.01	£106,386	£33,152

ICER = Incremental cost-effectiveness ratio (per QALY); NMB = Net monetary benefit; VT = Ventilation tubes; VT + ads = Ventilation tubes with adjuvant adenoidectomy

Figure 26: Cost-effectiveness plane for NH2 analysis relative to no intervention

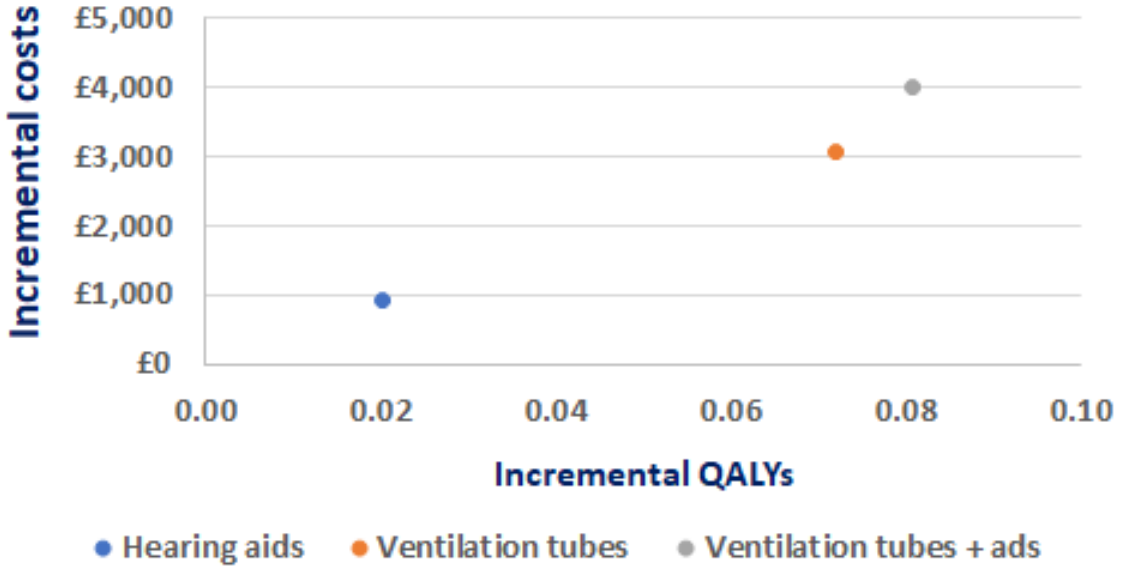


Table 16, Table 17 and Figure 27 show the PSA results for the NH2 model analysis with 1,000 model simulations and using a sample of 1,000 patients for the patient level Markov simulation. The cost-effectiveness plane is plotted in Figure 28 with the CEAC reproduced in in Figure 29. The PSA shows that no intervention has the highest NMB and the highest probability of being cost-effective. The CEAC shows that the surgical interventions are only likely to be cost-effective if the cost-effectiveness threshold is increased substantially above a level of £30,000 per QALY.

Table 16: Cost and QALYs of PSA for NH2 analysis

Strategy	Cost (95% CrInt)	QALYs (95% CrInt)	Incremental cost	Incremental QALY
No intervention	£122 (£112 to £158)	1.78 (1.73 to 1.80)	N/A	N/A
Hearing Aids	£990 (£851 to £1,154)	1.80 (1.76 to 1.81)	N/A	N/A

Strategy	Cost (95% CrInt)	QALYs (95% CrInt)	Incremental cost	Incremental QALY
VT	£2,792 (£2,413 to £3,280)	1.85 (1.83 to 1.85)	£2,670	0.07
VT + Ads	£3,787 (£1,317 to £6,371)	1.86 (1.85 to 1.86)	£995	0.01

Table 17: Summary outcomes of PSA for NH2 analysis

Strategy	ICER	NMB (95% CrInt)	Probability cost-effective at £20,000 per QALY	Probability cost-effective at £30,000 per QALY
No intervention	N/A	£35,449 (£34,522 to £36,002)	94%	73%
Hearing Aids	Extended dominance	£34,988 (£34,243 to £35,434)	0%	2%
VT	£38,078	£34,182 (£33,403 to £34,683)	0%	6%
VT + Ads	£90,609	£33,407 (£30,811 to £35,865)	6%	18%

Figure 27: Net monetary benefit with credible intervals (NH2 analysis)

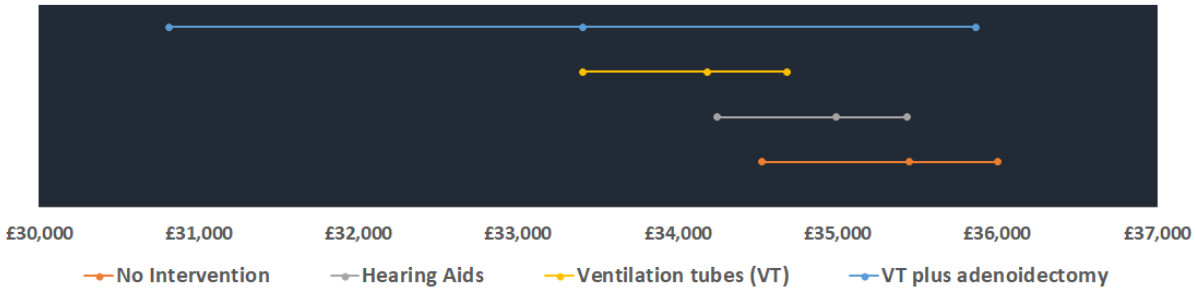


Figure 28: Cost-effectiveness plane NH2 PSA relative to no intervention

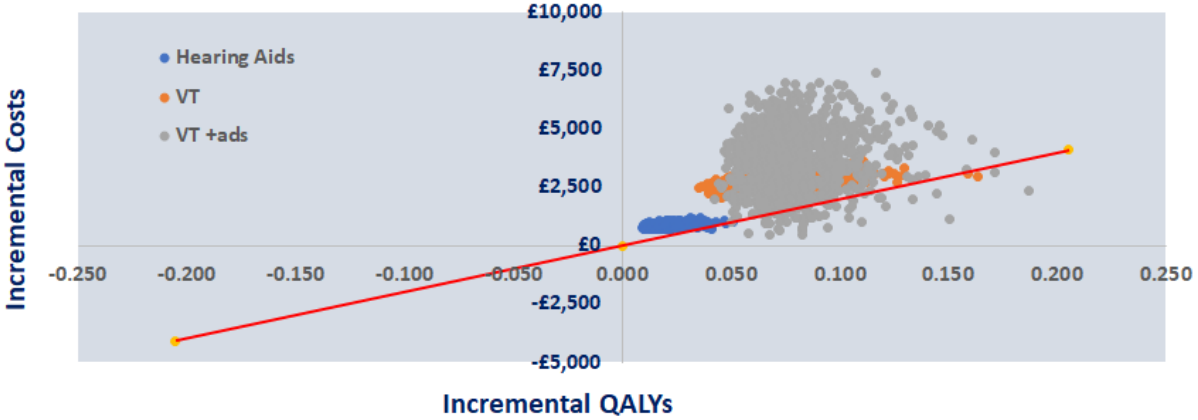
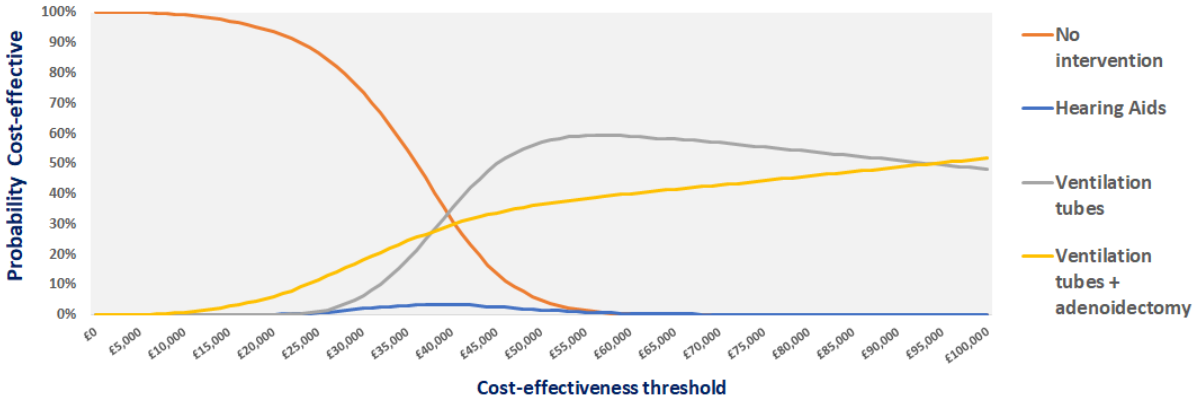


Figure 29: CEAC for NH2 PSA



NH3 analysis

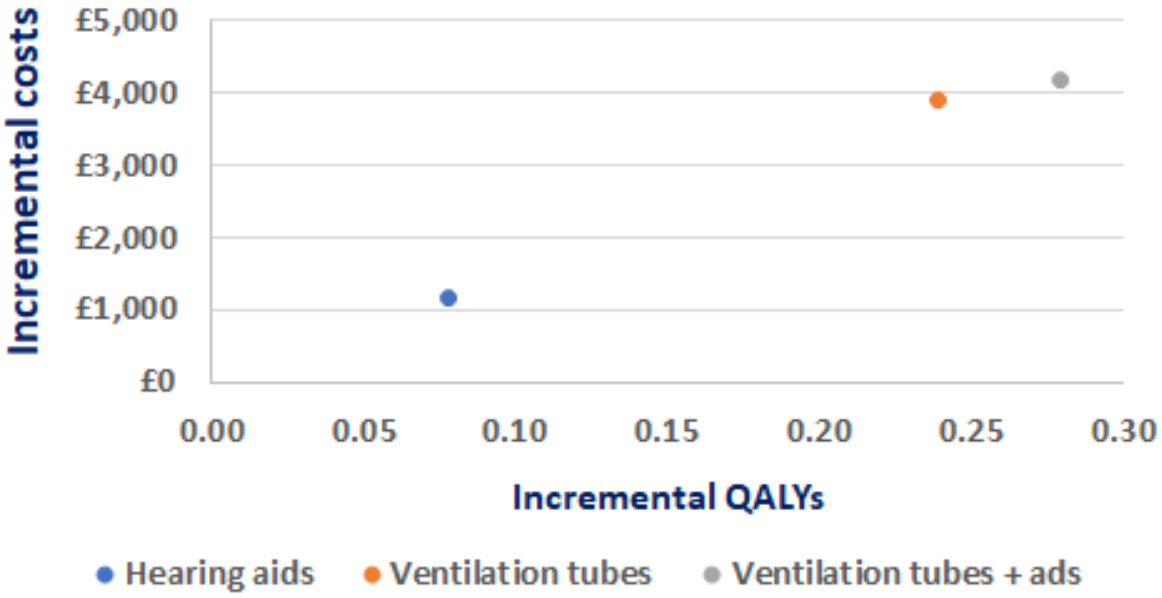
NH3 has a slower spontaneous resolution than in the base case analysis. The result of the deterministic analysis for NH3 is shown in Table 18 and Figure 30. This indicated that ventilation tubes with adjuvant adenoidectomy had the highest NMB at a cost-effectiveness threshold of £20,000 per QALY. All other interventions would be considered cost-effective relative to no intervention which has the lowest NMB.

Table 18: Deterministic NH3 analysis results

Strategy	Cost	QALYS	Incremental cost	Incremental QALYS	ICER	NMB
No intervention	£343	1.58	n/a	n/a	n/a	£31,221
Hearing Aids	£1,521	1.66	n/a	n/a	Extended dominance	£31,600
VT	£4,241	1.82	n/a	n/a	Extended dominance	£32,101
VT + Ads	£4,513	1.86	£4,170	0.28	£14,961	£32,625

ICER = Incremental cost-effectiveness ratio (per QALY); NMB = Net monetary benefit; VT = Ventilation tubes; VT + ads = Ventilation tubes with adjuvant adenoidectomy

Figure 30: Cost-effectiveness plane for deterministic NH3 analysis relative to no intervention



The PSA for the NH3 analysis with 1,000 model simulations and a sample of 1,000 patients for the patient level Markov simulation, produced the results shown in Table 19, Table 20 and Figure 31. As in the deterministic analysis, ventilation tubes plus adjuvant adenoidectomy had the highest NMB as well as a high probability of being the most cost-effective strategy. Figure 32 shows the plot of the 1,000 model iterations on a cost-effectiveness plane with the corresponding CEAC depicted in Figure 33.

Table 19: Cost and QALYs of PSA for NH3 analysis

Strategy	Cost (95% CrInt)	QALYs (95% CrInt)	Incremental cost	Incremental QALY
No intervention	£345 (£270 to £422)	1.58 (1.53 to 1.62)	N/A	N/A
Hearing Aids	£1,429 (£1,111 to £1,768)	1.66 (1.62 to 1.68)	£1,084	0.08
VT	£4,152 (£3,351 to £5,482)	1.81 (1.75 to 1.84)	N/A	N/A
VT + Ads	£4,335 (£1,776 to £7,022)	1.85 (1.83 to 1.86)	£2,906	0.20

(a)

Table 20: Summary outcomes of PSA for NH3 analysis

Strategy	ICER	NMB (95% CrInt)	Probability cost-effective at £20,000 per QALY	Probability cost-effective at £30,000 per QALY
No intervention	N/A	£31,214 (£30,333 to £32,160)	0%	0%

Strategy	ICER	NMB (95% CrInt)	Probability cost-effective at £20,000 per QALY	Probability cost-effective at £30,000 per QALY
Hearing Aids	£13,919	£31,688 (£30,943 to £32,464)	7%	0%
VT	Extended dominance	£32,043 (£29,624 to £33,401)	30%	26%
VT + Ads	£14,656	£32,747 (£30,099 to £35,308)	63%	73%

(a)

Figure 31: Net monetary benefit with credible intervals (NH3 analysis)

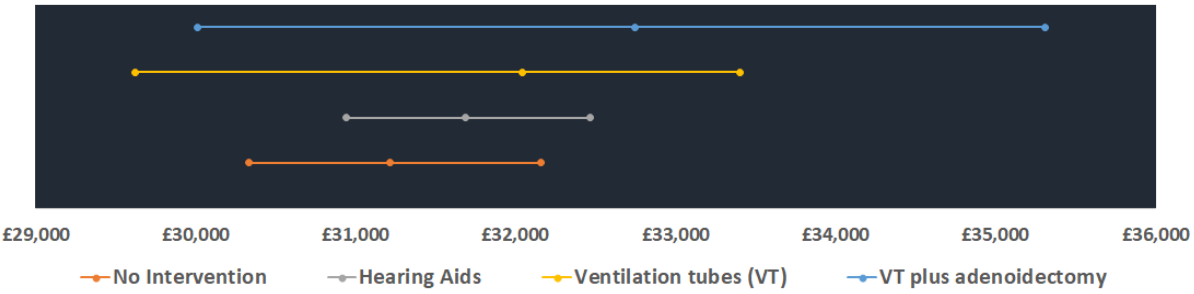


Figure 32: Cost-effectiveness plane NH3 PSA relative to no intervention

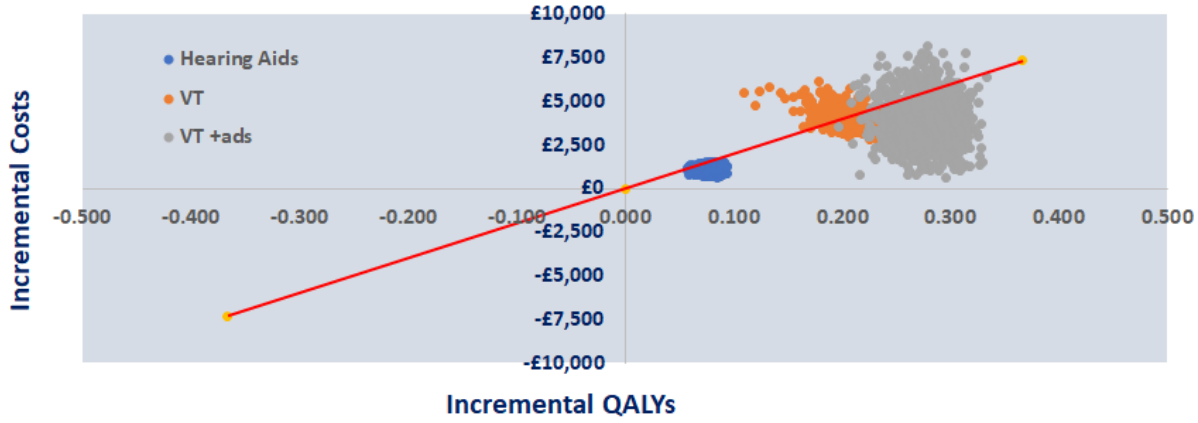
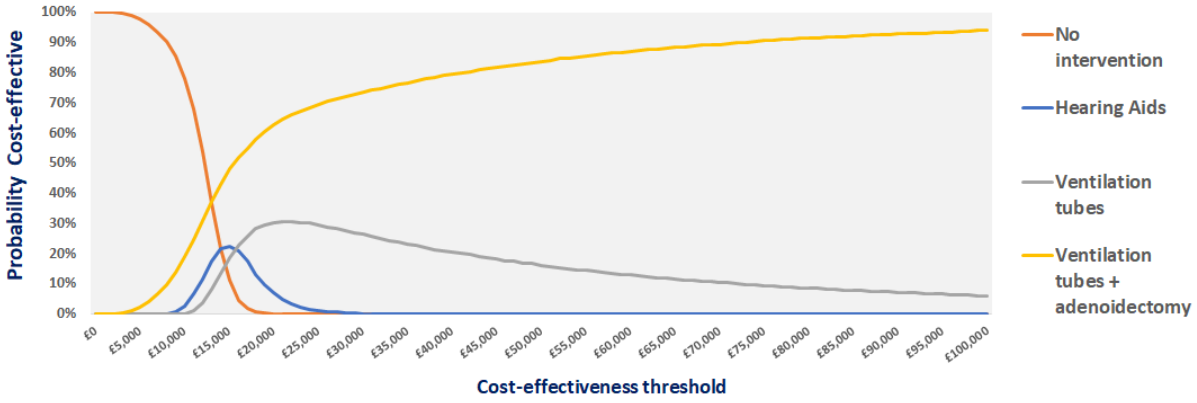


Figure 33: CEAC for NH3 PSA



NH4 analysis

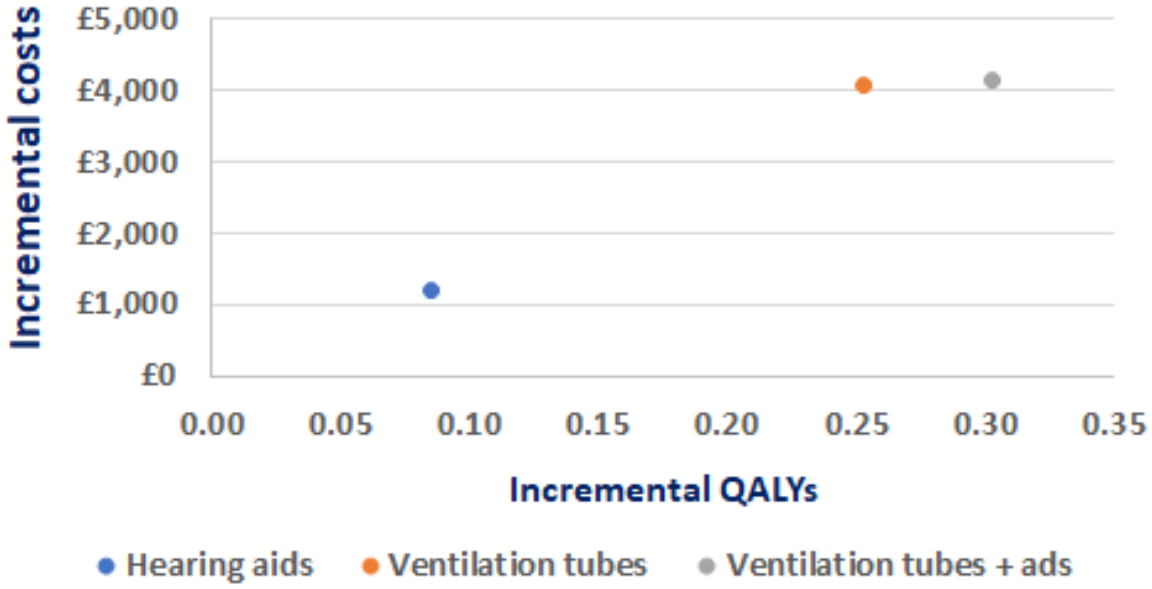
NH4 has the slowest spontaneous resolution in the sensitivity analysis of natural history. The deterministic analysis, retaining other model inputs at their base case values, is shown in Table 21 and Figure 34. The ordering results is similar to NH3 with ventilation tubes plus adjuvant adenoidectomy the most cost-effective strategy as indicated by the NMB values for a £20,000 cost-effectiveness threshold.

Table 21: Deterministic NH4 analysis results

Strategy	Cost	QALYS	Incremental cost	Incremental QALYS	ICER	NMB
No intervention	£385	1.55	n/a	n/a	n/a	£30,682
Hearing Aids	£1,576	1.64	n/a	n/a	Extended dominance	£31,190
VT	£4,437	1.81	n/a	n/a	Extended dominance	£31,680
VT + Ads	£4,498	1.86	£4,114	0.30	£13,579	£32,627

ICER = Incremental cost-effectiveness ratio (per QALY); NMB = Net monetary benefit; VT = Ventilation tubes; VT + ads = Ventilation tubes with adjuvant adenoidectomy

Figure 34: Cost-effectiveness plane for deterministic NH4 analysis relative to no intervention



1,000 model simulations for NH4 gave the results that are given in Table 22, Table 23 and Figure 35. Ventilation tubes with adjuvant adenoidectomy is the most cost-effective strategy and has a 66% probability of being the most cost-effective option at a cost-effectiveness threshold of £20,000 per QALY rising to 76% when the threshold is increased to £30,000 per QALY. The cost-effectiveness plane is graphed in Figure 36 and the CEAC is displayed in Figure 37.

Table 22: Costs and QALYs of PSA for NH4 analysis

Strategy	Cost (95% CrInt)	QALYs (95% CrInt)	Incremental cost	Incremental QALY
No intervention	£384 (£320 to £450)	1.55 (1.52 to 1.58)	N/A	N/A
Hearing Aids	£1,487 (£1,163 to £1,832)	1.64 (1.61 to 1.66)	£1,102	0.09
VT	£4,305 (£3,445 to £5,642)	1.80 (1.74 to 1.83)	N/A	N/A
VT + Ads	£4,396 (£1,719 to £7,099)	1.85 (1.83 to 1.86)	£2,909	0.22

Table 23: Summary outcomes of PSA for NH4 analysis

Strategy	ICER	NMB (95% CrInt)	Probability cost-effective at £20,000 per QALY	Probability cost-effective at £30,000 per QALY
No intervention	N/A	£30,679 (£30,055 to £31,377)	0%	0%
Hearing Aids	£12,967	£31,277 (£30,677 to £31,884)	4%	0%

Strategy	ICER	NMB (95% CrInt)	Probability cost-effective at £20,000 per QALY	Probability cost-effective at £30,000 per QALY
VT	Extended dominance	£31,794 (£29,407 to £33,273)	29%	24%
VT + Ads	£13,523	£32,671 (£29,931 to £35,395)	66%	76%

Figure 35: Net monetary benefit with credible intervals (NH4 analysis)

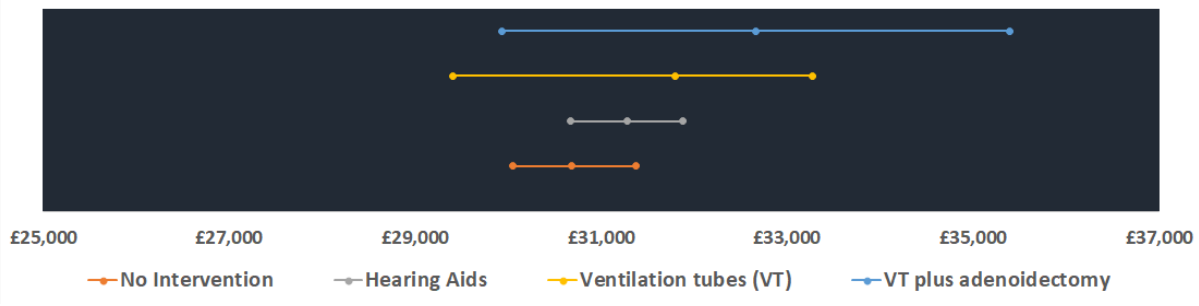


Figure 36: Cost-effectiveness plane NH4 PSA relative to no intervention

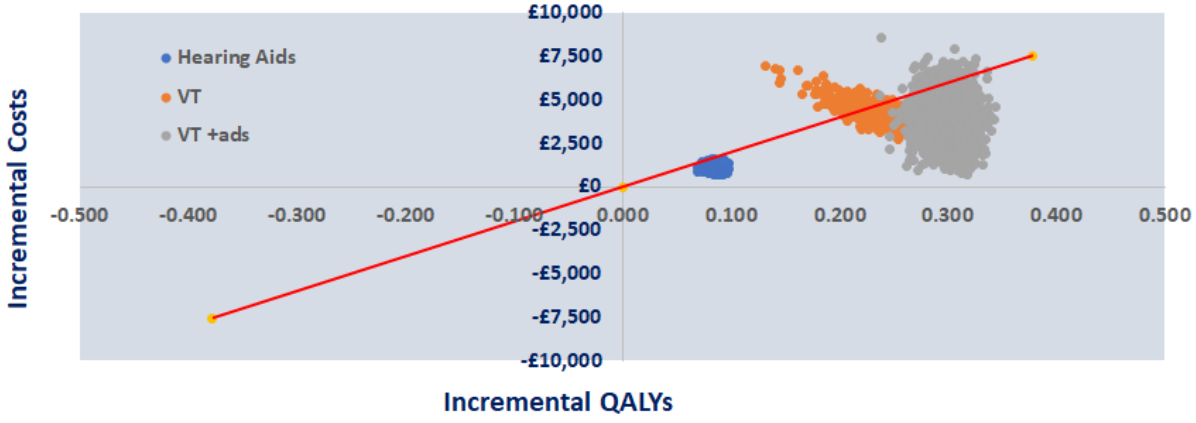
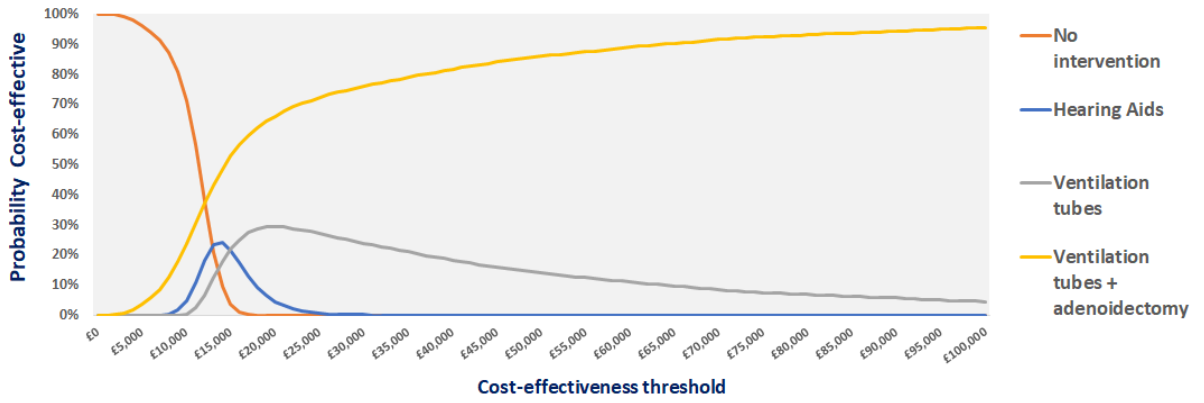


Figure 37: CEAC for NH4 PSA



NH5 analysis

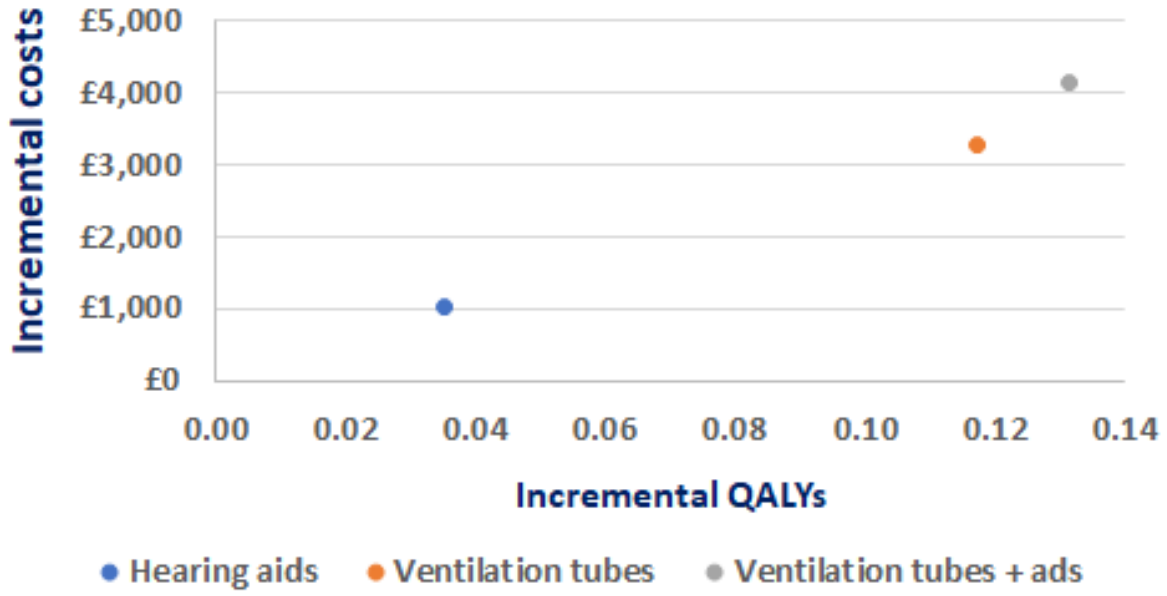
In this sensitivity analysis natural history model NH5 is selected. NH5 has faster spontaneous resolution than in the base case analysis. All other model inputs are set to their base case value. The result of the deterministic analysis is shown in Table 24 and Figure 38. No intervention is the most cost-effective option with a NMB of £34,408.

Table 24: Deterministic NH5 analysis results

Strategy	Cost	QALYS	Incremental cost	Incremental QALYS	ICER	NMB
No intervention	£125	1.73	n/a	n/a	n/a	£34,408
Hearing Aids	£1,158	1.76	n/a	n/a	Extended dominance	£34,079
VT	£3,407	1.84	£2,319	0.12	£28,048	£33,466
VT + Ads	£4,266	1.86	£772	0.01	£60,191	£32,892

ICER = Incremental cost-effectiveness ratio (per QALY); NMB = Net monetary benefit; VT = Ventilation tubes; VT + ads = Ventilation tubes with adjuvant adenoidectomy

Figure 38: Cost-effectiveness plane for deterministic NH5 analysis relative to no intervention



PSA results for NH5 with 1,000 model simulations are presented in Table 25, Table 26 and Figure 39. Costs and QALYs are the mean across 1,000 simulations. The cost-effectiveness plane is graphed in Figure 40. No intervention is the most cost-effective strategy at £20,000 per QALY but, as indicated by the CEAC in Figure 41, the probability falls rapidly with an increasing cost-effectiveness threshold such that the probability that no intervention is cost-effective at £30,000 per QALY has fallen to 9%. At a cost-effectiveness threshold of £30,000 per QALY, ventilation tubes alone and ventilation tubes have a 42% and 39% probability of being cost-effective respectively.

Table 25: Costs and QALYs of PSA for NH5 analysis

Strategy	Cost (95% CrInt)	QALYs (95% CrInt)	Incremental cost	Incremental QALY
No intervention	£144 (£117 to £186)	1.73 (1.69 to 1.76)	N/A	N/A
Hearing Aids	£1,085 (£900 to £1,297)	1.76 (1.73 to 1.78)	£941	0.03
VT	£3,170 (£2,725 to £3,777)	1.84 (1.81 to 1.85)	£2,086	0.08
VT + Ads	£4,010 (£1,465 to £6,625)	1.86 (1.85 to 1.86)	£840	0.02

(b)

Table 26: Summary outcomes of PSA for NH5 analysis

Strategy	ICER	NMB (95% CrInt)	Probability cost-effective at £20,000 per QALY	Probability cost-effective at £30,000 per QALY
No intervention	N/A	£34,420 (£33,629 to £35,098)	78%	9%
Hearing Aids	£27,041	£34,226 (£33,531 to £34,723)	2%	11%
VT	£27,298	£33,617 (£32,536 to £34,286)	2%	42%
VT + Ads	£43,791	£33,161 (£30,531 to £35,699)	18%	39%

Figure 39: Net monetary benefit with credible intervals (NH5 analysis)

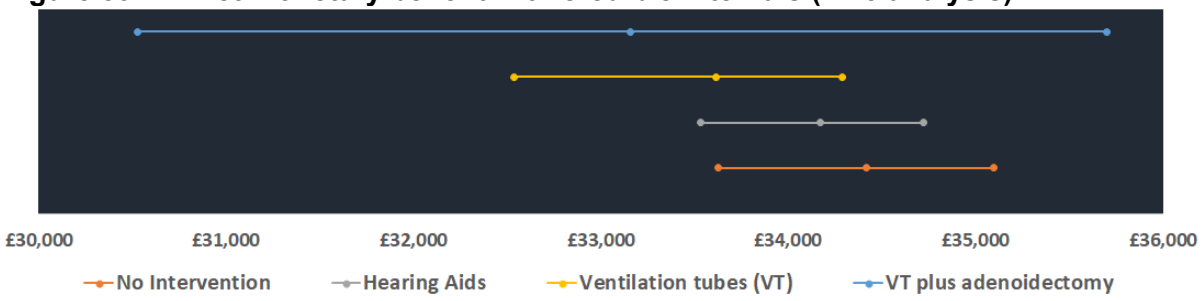


Figure 40: Cost-effectiveness plane NH5 PSA relative to no intervention

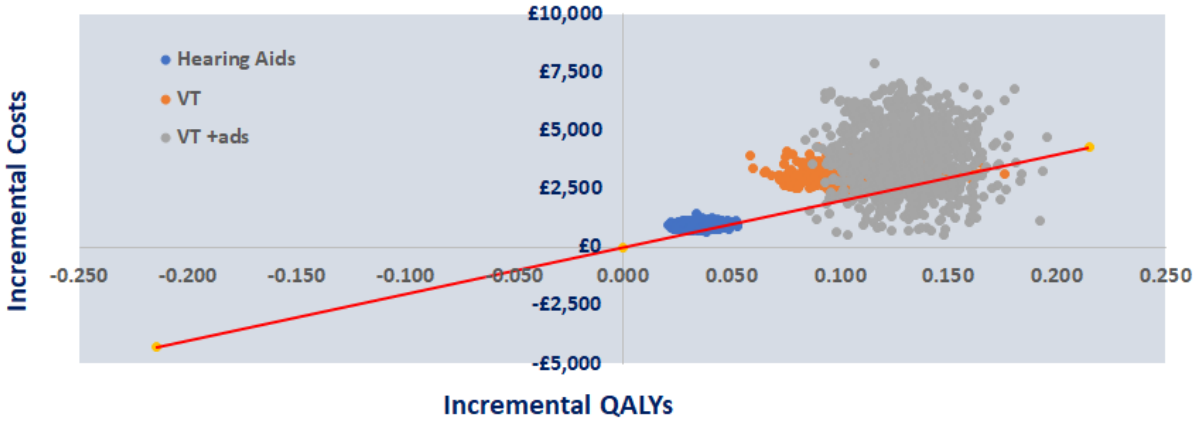
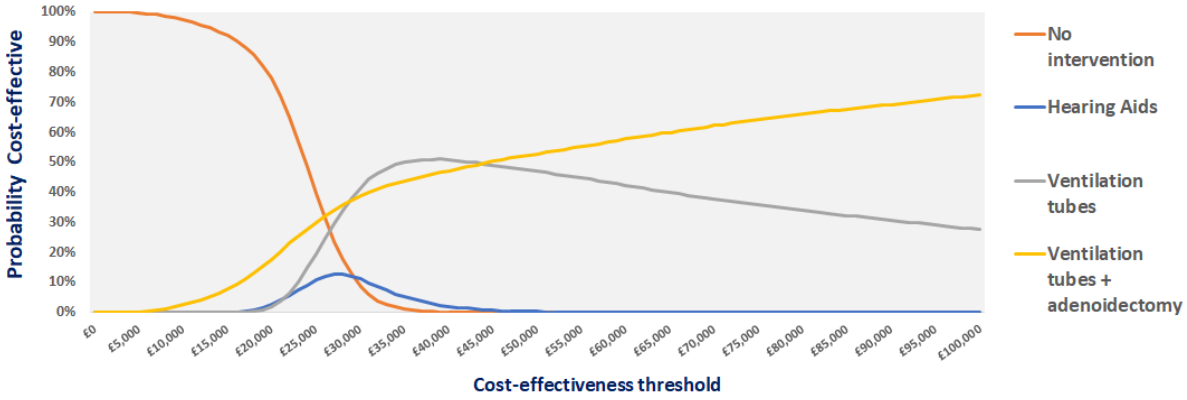


Figure 41: CEAC for NH5 PSA



Lower treatment effectiveness

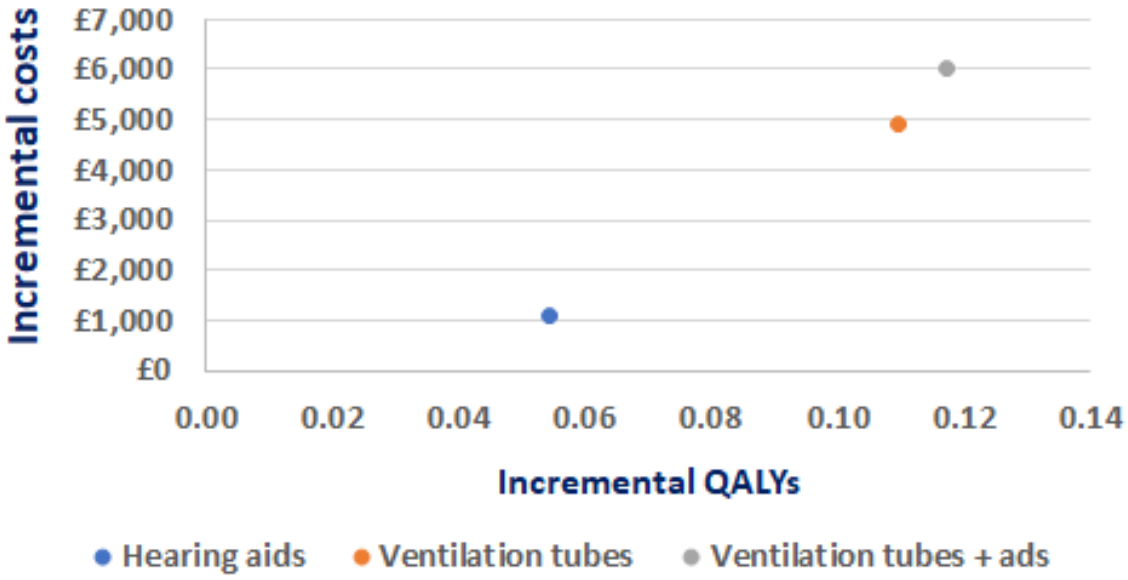
For this sensitivity analysis estimates of treatment effect were taken from Dempster (1993) and Gates (1989), with Ventilation tubes having a relative risk of persistence of 0.83 relative to no intervention and ventilation tubes plus adjuvant adenoidectomy have a relative risk of persistence of 0.96 relative to ventilation tubes alone. The deterministic results for this sensitivity analysis are tabulated in Table 27 and the associated cost-effectiveness plane is shown in Figure 42.

Table 27: Deterministic sensitivity analysis results for lower surgical treatment effect

Strategy	Cost	QALYS	Incremental cost	Incremental QALYS	ICER	NMB
No intervention	£215	1.66	n/a	n/a	n/a	£32,980
Hearing Aids	£1,330	1.71	£1,114	0.05	£20,475	£32,954
VT	£5,112	1.77	£3,782	0.06	£68,691	£30,273
VT + Ads	£6,236	1.78	£1,124	0.01	£143,516	£29,305

ICER = Incremental cost-effectiveness ratio (per QALY); NMB = Net monetary benefit; VT = Ventilation tubes; VT + ads = Ventilation tubes with adjuvant adenoidectomy

Figure 42: Cost-effectiveness plane for deterministic sensitivity analysis relative to no intervention for lower surgical treatment effect



The PSA results for this sensitivity analysis. With 1,000 simulations, involving lower estimates for surgical treatment effectiveness are presented in Table 28, Table 29 and Figure 43. This shows that hearing aids are the most cost-effective intervention at a cost-effectiveness threshold of £20,000 per QALY as denoted by the highest NMB. Hearing aids also have a very high probability of being the most cost-effective strategy between the cost-effectiveness thresholds of £20,000 to £30,000 per QALY (66% and 98% respectively). Figure 44 plots the 1,000 iterations on a cost-effectiveness plane and the CEAC for this data is presented in Figure 45. The CEAC shows that the surgical interventions have an increased probability of being cost-effective when a higher monetary value is attributed to the smaller QALY gains resulting at lower rates of treatment effectiveness.

Table 28: Costs and QALYs of PSA for lower treatment effectiveness

Strategy	Cost (95% CrInt)	QALYs (95% CrInt)	Incremental cost	Incremental QALY
No intervention	£222 (£183 to £265)	1.66 (1.63 to 1.68)	N/A	N/A
Hearing Aids	£1,237 (£984 to £1,504)	1.72 (1.69 to 1.73)	£1,015	0.05
VT	£4,851 (£4,086 to £5,669	1.77 (1.74 to 1.79)	£3,614	0.05
VT + Ads	£6,008 (£3,338 to £8,778)	1.77 (1.74 to 1.80)	£1,157	0.00

(c)

Table 29: Summary outcomes of PSA for lower treatment effectiveness

Strategy	ICER	NMB (95% CrInt)	Probability cost-effective at £20,000 per QALY	Probability cost-effective at £30,000 per QALY
No intervention	N/A	£33,003	33%	0%

Strategy	ICER	NMB (95% CrInt)	Probability cost-effective at £20,000 per QALY	Probability cost-effective at £30,000 per QALY
		(£32,409 to £33,556)		
Hearing Aids	£18,803	£33,068 (£32,545 to £33,549)	66%	98%
VT	£66,218	£30,545 (£29,193 to £31,819)	0%	0%
VT + Ads	£322,744	£29,460 (£26,450 to £32,326)	0%	2%

Figure 43: NMB with credible intervals (PSA for lower surgical treatment effectiveness)

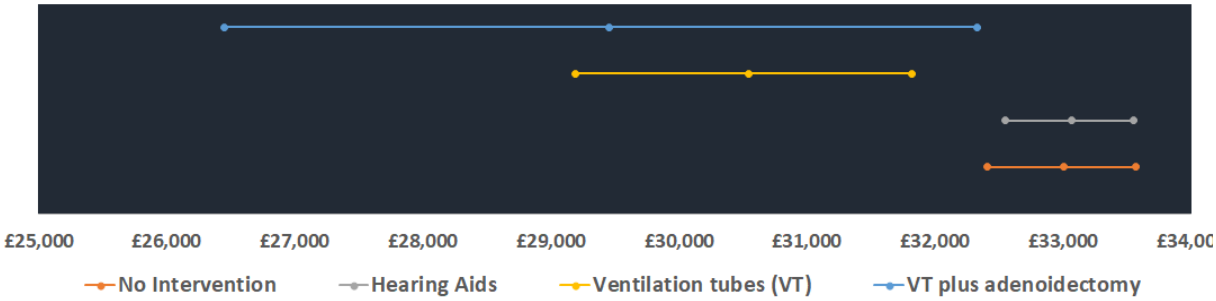


Figure 44: Cost-effectiveness plane for lower surgical treatment effectiveness PSA

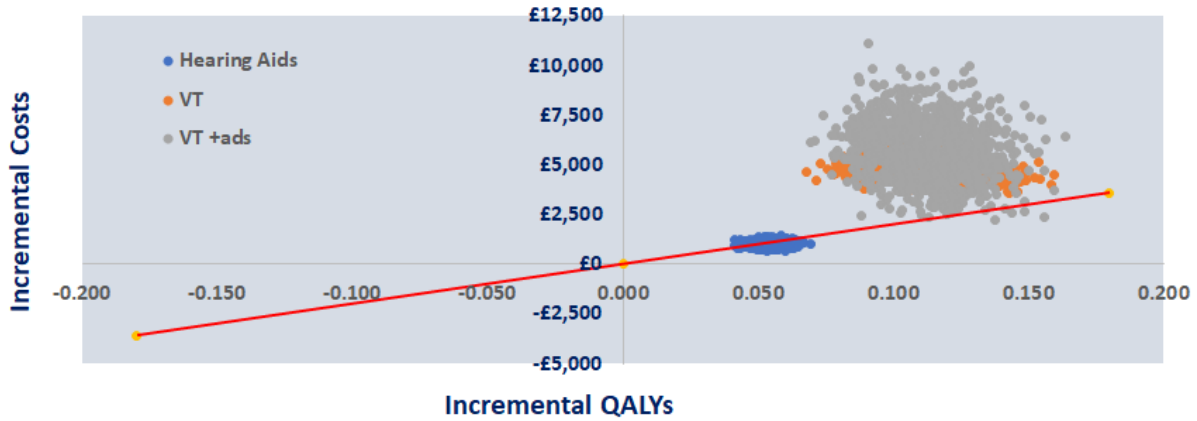
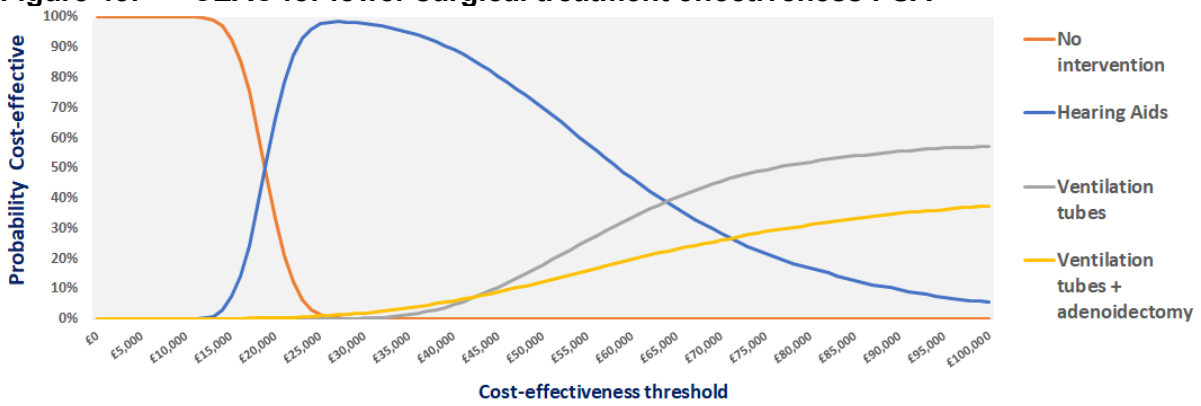


Figure 45: CEAC for lower surgical treatment effectiveness PSA



Additional sensitivity analyses

A number of additional sensitivity analyses were run for several model inputs that were treated as fixed in the probabilistic analyses. These variables were altered one at a time and a PSA of 100 simulations was run for this new input value with a sample of 1,000 children for the patient level Markov simulation. A summary of these analyses is presented in Table 30 and Table 31. The intervention that is most cost-effective, as measured by the highest NMB at cost-effectiveness threshold of £20,000 per QALY, and has the highest probability of being cost-effective, are highlighted green in the respective tables. It should be noted that some of the differences are a result of random variation, with a relatively small number of simulations, rather than the change in the input parameter. Where changes to the variable value have limited impact on the overall NMB then random variation could predominate leading to a slightly counter intuitive result when compared to the base case.

Table 30: NMB of PSA results from one-way sensitivity analysis

	Base case	Discount rate 1.5%	50% hearing aid adherence	100% hearing aid adherence	15% perforations needing tympanoplasty	45% perforations needing tympanoplasty	0.1% probability of weekly hearing aid loss	1.0% probability of weekly hearing aid loss	0.87 health state utility of treated OME	0.76 health state utility of treated OME	5 QALYs loss per case of palatal insufficiency
No intervention	£32999	£33487	£32991	£32998	£32996	£33014	£33033	£33013	£32972	£32972	£32999
Hearing Aids	£33065	£33561	£32577	£33163	£33084	£33090	£33165	£32901	£34151	£32154	£33071
VT	£32909	£33389	£32827	£32866	£32954	£32749	£32942	£32862	£33285	£32575	£32883
VT + Ads	£32971	£33629	£33139	£33100	£33158	£32940	£33031	£33125	£32950	£32856	£32744

Table 31: Probability cost-effective from one-way sensitivity analysis

	Base case	Discount rate 1.5%	50% hearing aid adherence	100% hearing aid adherence	15% perforations needing tympanoplasty	45% perforations needing tympanoplasty	0.1% probability of weekly hearing aid loss	1.0% probability of weekly hearing aid loss	0.87 health state utility of treated OME	0.76 health state utility of treated OME	5 QALYs loss per case of palatal insufficiency
No intervention	10%	10%	26%	5%	5%	10%	6%	20%	0%	39%	18%
Hearing Aids	21%	16%	0%	31%	25%	26%	26%	5%	77%	0%	20%
VT	27%	30%	27%	22%	25%	22%	26%	27%	0%	15%	26%
VT + Ads	42%	44%	47%	42%	45%	42%	42%	48%	23%	46%	36%

The sensitivity analyses indicate that hearing aid adherence and the health state utility gain from treating OME are the most important determinants of the model's conclusions amongst this group of variables.

Discussion

It is important to recognise the limitations with this analysis and there are many important uncertainties which sensitivity analyses have demonstrated are important in determining the model results. First no greater weight should be attached to what is termed the "base case" analysis as the results are best seen as representing different scenarios which whilst evidence based as far as possible also reflect the often-low quality of the evidence reviewed.

There remains considerable uncertainty with respect to the natural history and the model shows in the base case analysis and the natural history model sensitivity analyses (NH2 NH3 NH4 NH5) that this is important a determinant of cost-effectiveness. Unsurprisingly any intervention is less likely to be cost-effective as the time to spontaneous resolution falls. Conversely in NH4 which has the slowest rate of spontaneous resolution the probability of one of the surgical interventions being cost-effective is 95% at a cost-effectiveness threshold of £20000 per QALY rising to 100% at a £30000 per QALY cost-effectiveness threshold.

QALYs are used as the main measure of benefit as specified in the NICE reference case but this has required a number of assumptions and extrapolations from adult populations. First it was assumed that hearing aids or surgical intervention provided the same gain in health state utility but as far as we are aware there is no actual comparative data of hearing aids against surgical intervention for OME with hearing loss in children. Second the gain in health state utility was based on studies in adults with other causes of hearing loss than OME.

There was no evidence reviewed which compared any of the model interventions in terms of their impact on quality of life. Therefore, effectiveness was measured using persistence of OME (or recurrence after extrusion of ventilation tubes). However, it was difficult to

synthesise the many included studies and the reported relative treatment effects varied widely across studies. The sensitivity analysis showed that a lower treatment effectiveness than used in the base case analysis results in hearing aids becoming considerably more cost-effective relative to the surgical interventions.

Unless spontaneous resolution occurs at a substantially faster rate than the base case analysis, which was based on expert committee opinion, then the model provides good evidence that some form of intervention for OME with hearing loss is likely to be cost-effective. Conservative assumptions were used to estimate the health state utility gain from intervention, but higher gains have been reported (Swan 2012; Grutters 2014) which would increase the cost-effectiveness of interventions.

However, no one form of intervention is clearly better than another with the sensitivity analyses showing that the intervention with the highest NMB and highest probability of being cost-effective was sensitive to changes in model inputs and assumptions. Furthermore, the cost-effectiveness of the different alternatives often changed markedly within a cost-effectiveness threshold range of £20,000 to £30,000 per QALY, which is often used to guide committee recommendations in NICE guidance.

Although most analyses produce a higher NMB than probability of being cost-effective for ventilation tubes plus adjuvant adenoidectomy when compared to ventilation tubes this finding is highly dependent on the study used to estimate the relative treatment effect between the 2 interventions.

The relative cost-effectiveness of surgical interventions was higher for longer time to spontaneous resolution of OME with hearing loss, greater risk reduction in the persistence of OME after ventilation tube extrusion and lower hearing aid adherence. The cost-effectiveness of hearing aids was clearly often the inverse of these factors but assuming a higher health state utility gain from treatment also improved the relative cost-effectiveness of hearing aids.

Conclusion

The model suggests that intervention substantially increases costs compared to no intervention although costs are restricted to an NHS and personal social services perspective and other educational and developmental costs may be incurred due to on-going hearing loss. Nevertheless, the results of the model generally suggested that some form of intervention was likely to be cost-effective as the QALY gains were worth the additional costs incurred using a cost-effectiveness threshold of £20,000 per QALY.

However, there was considerable uncertainty over model inputs and assumptions and no single intervention appeared to be clearly the most likely to be cost-effective. Therefore, the model results supported the recommendations made by the committee.

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

Excluded effectiveness studies

See the Characteristics of excluded studies table from the Cochrane review, MacKeith 2023a at https://doi.org/10.1002/14651858.CD015215.pub2.

Excluded economic studies

Study	Code [Reason]
Baik, Grace and Brietzke, Scott (2015) How much does the type of tympanostomy tube matter? A utility-based Markov decision analysis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 152(6): 1000-6	- Out of scope
Gomez, Gabriel and Chen, Philip G (2018) Tympanostomy tube placement and ear drops: Evidence-based cost saving models. International journal of pediatric otorhinolaryngology 110: 110-113	- Cost analysis only
Hartman, M, Rovers, M M, Ingels, K et al. (2001) Economic evaluation of ventilation tubes in otitis media with effusion. Archives of otolaryngology--head & neck surgery 127(12): 1471-6	- Cost analysis only
Mohiuddin, Syed, Payne, Katherine, Fenwick, Elisabeth et al. (2015) A model-based cost-effectiveness analysis of a grommets-led care pathway for children with cleft palate affected by otitis media with effusion. The European journal of health economics : HEPAC : health economics in prevention and care 16(6): 573-87	- Duplicate analysis

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of ventilation tubes for managing OME with associated hearing loss in children under 12 years?

K.1.1 Research recommendation 1

What is the effectiveness of grommets for managing OME with associated hearing loss for children with craniofacial abnormalities or Down's syndrome?

K.1.2 Why this is important

OME with associated hearing loss is more common in children with craniofacial abnormalities and children with Down's syndrome and therefore research on the effectiveness of grommets specifically in these groups would be helpful as currently they are preferentially suggested to trial hearing aids so understanding the effectiveness of grommets could change guidance. This could improve the quality of life for children in these groups.

K.1.3 Rationale for research recommendation

Table 32: Research recommendation rationale

Importance to 'patients' or the population	Hearing aids are usually suggested in preference to grommets as interventions for children with OME and craniofacial abnormalities or Down's syndrome in current practice, and therefore understanding the effectiveness of grommets for this population could lead to changes in best practice..
Relevance to NICE guidance	The research is essential to inform future updates of key recommendations in the guidance regarding whether to offer grommets as first-line treatment for children with OME and craniofacial abnormalities or Down's syndrome .
Relevance to the NHS	This research would be beneficial as it might improve patient experience and potentially reduce costs of follow up appointments and maintenance for hearing aids.
National priorities	Core20PLUS5 in paediatrics prioritises reducing health care inequalities. Currently there is variation in practice regarding whether grommet surgery is offered children with craniofacial abnormalities or Down's syndrome because of the lack of evidence for this population, and the potential harms that could be caused by recommending this surgery without an understanding of the potential negative impacts on these children; however, children with craniofacial abnormalities and Down's syndrome thereby cannot regularly access grommet surgery as a treatment option. Research into this could help reduce a potential health care inequality.
Current evidence base	There is no specific high-quality research into this area currently because children with

	craniofacial abnormalities or Down's Syndrome tend to be excluded from research on the effectiveness of interventions for OME.
Equality considerations	This research recommendation would focus on a group who need special consideration (children with craniofacial abnormalities or Down's Syndrome). Children with these conditions can get OME more frequently, and there might be a difference in effectiveness and potential harms of grommet surgery for those who have previously had grommets inserted once or multiple times before. A difference between male and female participants is not expected, although sex disaggregated data may be helpful. There might be differences in effectiveness for children of different ages (for example, children <3 years of age compared to children aged 3-12 years).
Feasibility	Children with craniofacial anomalies or Down's syndrome might be predisposed to a higher risk of complications such as eardrum retraction depending on the shape and width of the ear canal. For ethical reasons, it might be necessary to limit inclusion in studies to children for whom grommet insertion is practical, plus there might be difficulty recruiting children if parents have concerns about randomisation. As a result, the sample size needed to resolve the question might be difficult to achieve. Concerns about recruitment rate and engagement with clinicians mean that a trial with an internal pilot might be necessary. It is likely that any measurements of speech, language and development outcomes will need to be tailored specifically for the population.
Other comments	None

OME: otitis media with effusion

K.1.4 Modified PICO table

Table 33: Research recommendation modified PICO table

Population	Children aged 6 months to 12 years with unilateral or bilateral otitis media with effusion (OME) with a craniofacial abnormality or Down's syndrome.
Intervention	Insertion of grommets performed either unilaterally or bilaterally.
Comparator	• No treatment/watchful waiting; • Hearing aids; • Non-surgical treatment; • Myringotomy
Outcome	Primary outcomes: • Hearing

	○ proportion of children whose hearing has returned to normal; ○ mean final hearing threshold (determined for the child or ear, depending on the unit of analysis); ○ change in hearing threshold from baseline (determined for the child or ear, depending on the unit of analysis). • Disease-specific quality of life measured using a validated instrument, for example: ○ OM8-30; ○ Otitis Media-6. • Adverse events - measured by the number of participants affected: ○ Persistent perforation ○ Tympanic membrane changes, such as: ▪ atrophy; ▪ atelectasis or retraction; ▪ myringosclerosis; ▪ tympanosclerosis ○ Tube-related, such as: ▪ blockage; ▪ extrusion; ▪ granulation tissue formation; ▪ otorrhoea/perforation; ▪ displacement of the ventilation tube into the middle ear space • Cost effectiveness Secondary outcomes: • Presence/persistence of OME • Adverse events - measured by the number of participants affected ○ Patient-related, such as: ▪ vomiting; ▪ diarrhoea; ▪ dry throat; ▪ nasal stinging; ▪ cough; ▪ long-term hearing loss; ▪ postsurgical haemorrhage; ▪ pain • Receptive language skills, measured using a validated scale, for example: ○ Peabody Picture Vocabulary Test – Revised; ○ relevant domains of the Reynell Developmental Language Scales; ○ relevant domains of the Preschool Language Scale (PLS); ○ relevant domains of the Sequenced Inventory of Communication (SCID)

	• Speech development, or expressive language skills, measured using a validated scale, for example: o Schlichting test; o Lexi list; o relevant domains of the Reynell Developmental Language Scales; o relevant domains of the PLS; o relevant domains of the SCID • Cognitive development, measured using a validated scale, for example: o Griffiths Mental Development Scales; o McCarthy General Cognitive Index; o Bayley Scales of Infant and Toddler Development • Psychosocial outcomes, measured using a validated scale, for example: o the Social Skills Scale of the Social Skills Rating System; o Child behaviour Checklist; o Strengths and Difficulties Questionnaire; o Pediatric Symptom Checklist • Listening skills, for example, listening to stories and instructions effectively • Generic health-related quality of life assessed using a validated instrument, for example: o EQ-5D; o TNO AZL Children's QoL (TACQOL); o TNO AZL Pre-school children QoL (TAPQOL); o TNO AZL Infant Quality of Life (TAIQOL); o Infant Toddler Quality of Life Questionnaire (ITQOL); o Child Heath Questionnaire (CHQ) • Parental stress, measured using a validated scale, for example: o Parenting Stress Index • Vestibular function: o balance; o coordination • Number of doctor-diagnosed AOM episodes within a specified time frame
Study design	• RCT
Timeframe	1 week to 3 years
Additional information	None

OME: otitis media with effusion; RCT: randomised controlled trial

K.1.5 Research recommendation 2

What is the clinical and cost-effectiveness of grommets for managing OME with associated hearing loss for children under 12 years?

K.1.6 Why this is important

There is high prevalence of OME in children under 12. The use of grommets is a common practice for managing hearing loss associated with OME. The aim of providing interventions for OME is to minimise impacts on children's development and quality of life. Interventions therefore need to be effective in supporting hearing, suitable and acceptable for children and their carers so that there is good uptake, and cost-effective outcomes.

Interventions need to acknowledge variability in wait times across the UK because wait time influences care givers' decision making.

Cost effectiveness is important to help inform healthcare providers' decision making.

K.1.7 Rationale for research recommendation

Table 34: Research recommendation rationale

Importance to 'patients' or the population	The cost effectiveness of grommets could enhance existing knowledge for healthcare providers and families in the context of other available management options
Relevance to NICE guidance	Updated research on the cost effectiveness of grommets might influence future NICE guidance
Relevance to the NHS	Hearing loss in childhood can have a long-term negative impact on health and well-being as a result of language delay. Difficulty understanding adults and peers often adversely impacts behaviour, resulting in increased risk of mental health disorders. Cost effectiveness will influence local healthcare decision making.
National priorities	Prior to the pandemic, ENT services were struggling to achieve a maximum of 18 weeks from referral to treatment intervals. Access to ENT services was variable across the UK but was showing a declining picture. The pandemic has further impacted access to ENT services at a time when government are trying to reduce variation in ability to access services across the UK. Additionally, one of the national priorities for the government is to improve language and literacy outcomes. Untreated deafness directly impacts on this. The NHS long term plan recommends putting patients (or care givers) at the forefront of decision making for their own needs, and offering value for tax-payers money. Further research on the cost effectiveness of grommet surgery will enable future recommendations to be made that ensure the best, most cost-effective treatments are being offered to children with OME and related hearing loss.
Current evidence base	A systematic review conducted by Cochrane found no evidence on the effectiveness of grommets as compared to hearing aids. Limited

	evidence on the cost-effectiveness of grommets has been conducted.
Equality considerations	A difference between male and female participants is not expected, although sex disaggregated data may be helpful. There might be differences in effectiveness for children of different ages (for example, children <3 years of age compared to children aged 3-12 years).
Feasibility	For outcomes relating to development, such as language and cognitive outcomes, a longer follow-up time period would be necessary. However, studies investigating the effectiveness of grommets at longer follow-up periods there may be problems related to tube extrusion before the full follow-up period has been reached. The sample size needed to resolve the question is likely to be feasible/ achievable.
Other comments	None

ENT: ears, nose and throat; OME: otitis media with effusion; RCT: randomised controlled trial

K.1.8 Modified PICO table

Table 35: Research recommendation modified PICO table

Population	All children under 12 years with hearing loss due to confirmed otitis media with effusion. Stratified sampling to ensure equal numbers across age groups and a sample that represents diversity across deprivation/ affluence, urban/rural, ethnic minorities and additional needs. Studies should stratify according to whether children are >3 or 3-12 years of age.
Intervention	Insertion of grommets performed either unilaterally or bilaterally
Comparator	• Hearing aids

Outcome	Primary outcomes:
	• Hearing
	  ○ proportion of children whose hearing has returned to normal;
	  ○ mean final hearing threshold (determined for the child or ear, depending on the unit of analysis);
	  ○ change in hearing threshold from baseline (determined for the child or ear, depending on the unit of analysis).
	• Disease-specific quality of life measured using a validated instrument, for example:
	  ○ OM8-30;
	  ○ Otitis Media-6.
	• Adverse events: persistent perforation
	• Cost effectiveness

Secondary outcomes:

- Presence/persistence of OME
- Adverse events - measured by the number of participants affected
  - Tympanic membrane changes, such as:
    - atrophy;
    - atelectasis or retraction;
    - myringosclerosis;
    - tympanosclerosis
  - Tube-related, such as:
    - blockage;
    - extrusion;
    - granulation tissue formation;
    - otorrhoea/perforation;
    - displacement of the ventilation tube into the middle ear space
  - Patient-related, such as:
    - vomiting;
    - diarrhoea;
    - dry throat;
    - nasal stinging;
    - cough;
    - long-term hearing loss;
    - postsurgical haemorrhage;
    - pain
- Speech development, or expressive language skills, measured using a validated scale, for example:
  - Schlichting test;
  - Lexi list;
  - relevant domains of the Reynell Developmental Language Scales;
  - relevant domains of the PLS;
  - relevant domains of the SCID
- Cognitive development, measured using a validated scale, for example:
  - Griffiths Mental Development Scales;
  - McCarthy General Cognitive Index;
  - Bayley Scales of Infant and Toddler Development
- Listening skills, for example, listening to stories and instructions effectively
- Receptive language skills, measured using a validated scale, for example:
  - Peabody Picture Vocabulary Test – Revised;
  - relevant domains of the Reynell Developmental Language Scales;
  - relevant domains of the Preschool Language Scale (PLS);
  - relevant domains of the Sequenced Inventory of Communication (SCID)

	• Psychosocial outcomes, measured using a validated scale, for example:
	  ○ the Social Skills Scale of the Social Skills Rating System;
	  ○ Child behaviour Checklist;
	  ○ Strengths and Difficulties Questionnaire;
	  ○ Pediatric Symptom Checklist
	• Generic health-related quality of life assessed using a validated instrument, for example:
	  ○ EQ-5D;
	  ○ TNO AZL Children's QoL (TACQOL);
	  ○ TNO AZL Pre-school children QoL (TAPQOL);
	  ○ TNO AZL Infant Quality of Life (TAIQOL);
	  ○ Infant Toddler Quality of Life Questionnaire (ITQOL);
	  ○ Child Heath Questionnaire (CHQ)
	• Parental stress, measured using a validated scale, for example:
	  ○ Parenting Stress Index
	• Vestibular function:
	  ○ balance;
	  ○ coordination
	• Number of doctor-diagnosed AOM episodes within a specified time frame

Study design	• RCT
Timeframe	1 week to 3 years
Additional information	None

OME: otitis media with effusion; RCT: randomised controlled trial