# The effectiveness of short-term ventilation tube insertion versus surveillance in the management of chronic otitis media with effusion in children with non-syndromic cleft lip and palate

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# TABLE OF CONTENTS

# List of Figures

# Abstract

Chronic otitis media with effusion is a common finding in children with cleft lip and palate. It is thought to be due to associated eustachian tube dysfunction and can lead to impaired hearing, and speech and language development if not appropriately managed. The mainstay treatment is drainage of the effusion with short-term ventilation tubes, but some centres are increasingly choosing to manage cases conservatively with active surveillance following palate repair surgery. Each of these approaches has its advantages but there is currently no consensus on the most appropriate management, therefore a systematic review of effectiveness was conducted using JBI methodology. Firstly, an a priori protocol was developed and published which included a pre-defined search strategy. A systematic search of MEDLINE (PubMed), CINAHL (Ovid), Embase (Ovid) and Scopus (Elsevier) databases was then conducted in July 2021 to find published literature. Grey literature searches were conducted through Central Register of Controlled Trials (CENTRAL), Clinicaltrials.gov and ProQuest (ProQuest Platform) databases. The search was limited to studies published in English. Eligible studies featured children less than 18 years with cleft lip and palate, not associated with a genetic syndrome, who had been diagnosed with chronic otitis media with effusion. Studies that considered the use of short-term ventilation tubes were included with surveillance as the comparator.

Two reviewers screened and conducted critical appraisal of eligible studies, assessed the methodological quality, and extracted the data. Where possible, studies were pooled for analysis with heterogeneity being assessed using the standard Chi-squared and $I^2$ tests. GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) evidence assessment was also reported.

Four studies met the inclusion criteria for the review included in this thesis, three retrospective cohort studies and one prospective. The overall study quality was low with a moderate risk of bias. Only data for hearing thresholds could be pooled for analysis using two studies. Narrative synthesis was used for the remaining outcomes. Lack of data and inconsistent reporting of outcomes significantly limited capacity for pooled analysis. Certainty of evidence for all variables was deemed to be low to very low using GRADE criteria.

No definitive conclusions could be drawn regarding effectiveness of short-term ventilation tubes versus surveillance in the management of chronic otitis media with effusion in children with non-syndromic cleft lip and palate. Short-term ventilation tubes appear to be associated with a higher rate of otological complications, and a conservative approach does not lead to worse hearing outcomes. Due to the methodological limitations of the included studies, a gaps analysis of the collated evidence was performed. It highlighted that incomplete data sets and inadequate reporting standards were common across all the included studies. The findings of this thesis support the need for a well-designed and adequately powered multi-centre randomised controlled trial for further investigation.

# Thesis Declaration

I, Grace Maina, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Grace Maina

9/06/2023

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# CHAPTER 1: INTRODUCTION

## 1.1 Review Question

What is the effectiveness of short-term ventilation tube insertion compared to surveillance on conductive hearing loss in children with chronic otitis media with effusion and non-syndromic cleft lip and palate?

## 1.2 Significance of Review Question

More than eighty percent of children are affected by chronic otitis media with effusion by the age of 4, but this number rises to greater than 96% in children with cleft lip and palate.[1] The chronic inflammatory changes seen in the middle ear are noted as early as 4 months of age and can lead to hearing loss and consequently impaired speech and language development if not managed appropriately.[2, 3] The global prevalence of cleft lip and palate is estimated at 1:700 but this varies between different populations.[3] Around 50% of cases are not associated with any genetic syndrome and are termed non-syndromic.[3, 4] The hearing related complications that occur can have significant impact on long-term educational attainment and psychosocial development in this subset of the paediatric population compared to their peers. However, considerable debate still exists over the best treatment for chronic otitis media with effusion (COME) in children with cleft lip and palate. In 1974 Paradise and Bluestone advocated for the use prophylactic ventilation tube (VT) insertion at the time of palate repair with replacement as necessary. [5] The aim was to reduce-term otological complications and minimize the effects on speech and language development. Whilst this school of thought has considerable support, a more conservative approach involving active surveillance without intervention until necessary has begun to gain more traction. Supporters of

conservative management believe that the morbidity of repeated VT insertion can lead to persistent perforations, scarring of the tympanic membrane and a higher complication rate with no added benefits to hearing, speech and language or behaviour in the long-term.[6]

While some may consider the conservative approach potentially neglectful [6], there is no clear evidence regarding the evolution of COME following successful palate repair and to what extent the insertion of VT is effective at preventing the progression to hearing loss. The insertion of short-term ventilation tubes contributes to added healthcare costs and may increase morbidity due to additional surgery. In addition, prophylactic insertion raises the question of whether to repeat the operation if the VT extrude but the child remains asymptomatic.[6] The objective of this thesis is to assess the effectiveness of these two management options in regards to improvements in conductive hearing loss, speech and language acquisition, and long-term otological complications in children with COME and non-syndromic cleft lip and palate. The amalgamation of the current evidence base will help guide clinicians in making the safest and most efficacious choice for their patients.

## 1.3 Cleft lip and palate

Cleft lip and palate is a broad term used to describe a heterogenous group of congenital orofacial clefts. The term includes clefts of the lip, maxillary alveolus, hard and soft palate in varying combinations. In approximately 50% of cases, cleft lip and palate will occur together.[3, 7] Both genetic and environmental factors have been implicated in the pathophysiology of cleft lip and palate which occurs between the $6^{th}$ and $12^{th}$ week of embryonic development. [3, 8] Non-syndromic cleft lip and palate is the focus of this

thesis because syndromic cases are often associated with other abnormalities of the craniofacial skeleton that predispose patients to multifactorial ear disease as well as combination of conductive and sensorineural hearing loss.[3]

### 1.3.1 Cleft Classification

Several classification systems exist which are based around the embryologic development of the lip and palate. The incisive foramen is an important anatomical landmark that divides the palate into the primary and secondary palate (See Figure 1). The primary palate has the incisive foramen as its posterior border and consists of the premaxilla, lip, nasal tip, and columella. The secondary palate develops after the development of the primary palate and extends from the incisive foramen to the uvula posteriorly. [9] Cleft lip occurs due to impaired development of the primary palate and can be unilateral or bilateral, and its extent can be either complete or incomplete. A complete cleft lip involves the entire vertical thickness of the upper lip and is often associated with an alveolar cleft as they share the same embryologic origin. An incomplete cleft lip involves only a portion of the vertical height of the lip.[3, 9]

**Figure 1: Anatomy of the hard palate**

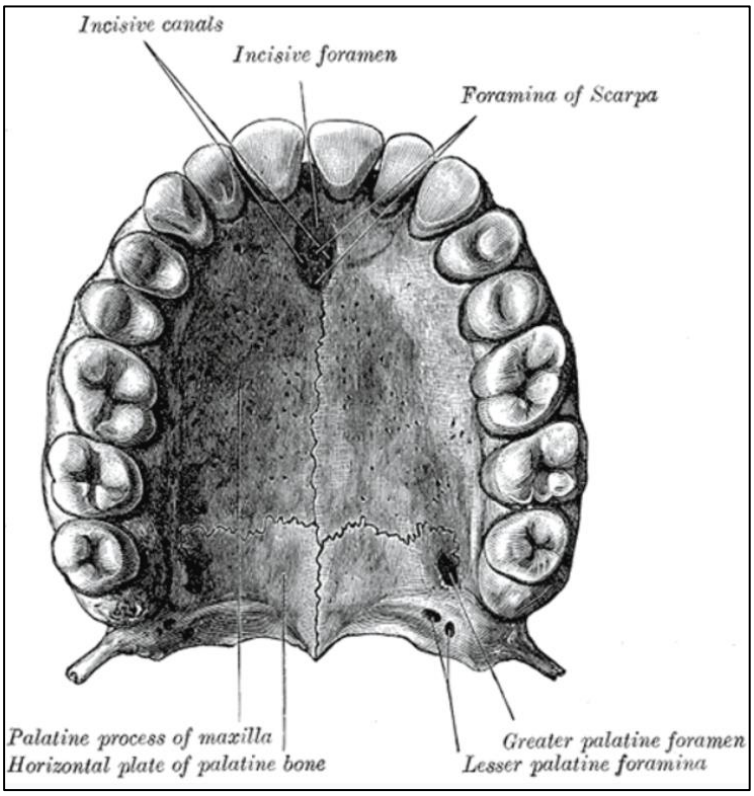



*Image source: Anatomy of the Human Body (1918). Accessed via https://commons.wikimedia.org/wiki/File:Gray160.png, creative commons license.* [10]

Cleft palate is classified similarly to the cleft lip, with the addition of the location of the cleft relative to the incisive foramen.[4] Clefts of the primary palate occur anterior to the incisive foramen and cleft of the secondary palate involve the posterior portion.[3, 7]

A complete cleft involves both the primary and secondary palate and includes one or both sides of the premaxilla/alveolar arch (unilateral or bilateral) and frequently also involves a cleft lip. An isolated cleft palate normally only involves the secondary palate and has varying degrees of severity. The least severe incomplete cleft is the submucous cleft palate (SMCP), in which the underlying palatal musculature is deficient and inappropriately oriented but there is no visible defect.[3]

The two common classification systems seen in the included studies are the Veau and LAHSHAL classification systems. The Veau classification system divides clefts into four groups based on whether the primary and/or secondary palates are affected, and by laterality (see Table 1).[8]

**Table 1: Veau Classification System**

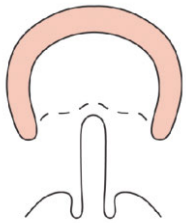
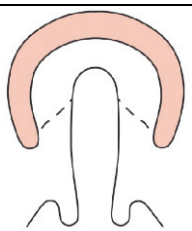
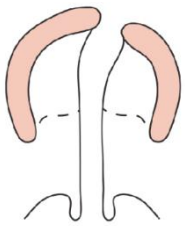
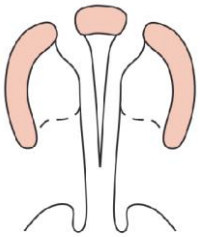
| Classification | Description | Image |
|---|---|---|
| **Group I** | Defect of soft palate only |  |
| **Group II** | Defect involving soft and hard palate |  |
| **Group III** | Defects involving the soft palate to the alveolus, usually involving the lip |  |
| **Group IV** | Complete bilateral clefts |  |

*Image source: Zhang et al. Post-operative outcomes after cleft palate repair in syndromic and non-syndromic children: a systematic review protocol. Syst Rev. 2017;6(1):52, creative common license (CC BY 4.0)*[11]

The LAHSHAL classification system is a palindrome that denotes the anatomic structures that are involved, proceeding from the patient's right to left side (see Figure 2). [12]

**Figure 2: Symbolic representation of LAHSHAL Classification**

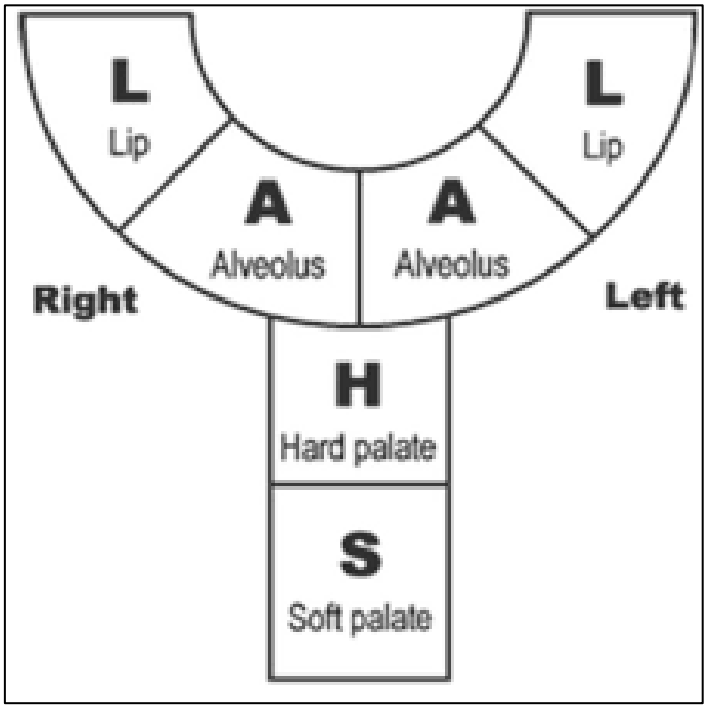



*Image source: Zhang et al. Post-operative outcomes after cleft palate repair in syndromic and non-syndromic children: a systematic review protocol. Syst Rev. 2017;6(1):52. creative common license (CC BY 4.0)*

In the LAHSHAL system, the involvement of an anatomical structure is represented by a capital letter if that structure is completely clefted, a lower-case letter if incompletely clefted, an asterisk (*) if minimally clefted or a period (.) if normally developed. [7] Therefore, a right unilateral incomplete cleft lip, complete alveolus and complete unilateral cleft palate (Veau Group III) would be denoted as lAHS***.

## 1.4 Chronic otitis media with effusion

Otitis media with effusion is characterised by presence of fluid in the middle ear without signs of acute infection. [13] It becomes chronic if it persists for longer than three months and a significant contributing factor is severe and prolonged eustachian tube dysfunction. One of the main functions of the eustachian tube is mucociliary clearance and this is facilitated by the tensor veli palatini muscle which is part of the soft palate and the main dilatory muscle of the eustachian tube. [14] Given the abnormal anatomy and function of soft palate and eustachian tube musculature in children with cleft lip and palate, mucocliliary clearance of effusions is impaired, which leads to development of negative middle ear pressure and an accumulation of mucoid or serous fluid. [3, 15, 16] Early and persistent COME is a common finding regardless of the cleft type.[2]

The effusion in the middle ear impedes the transmission of sound energy into the inner ear by impairing the movement of the eardrum and ossicles. This can result in conductive hearing loss between 25-45 dB, which corresponds to mild to moderate loss.[17, 18] Over time, COME can lead to scarring of the ear drum, perforation, retraction, and cholesteatoma.[3, 19]

Direct visualisation with an otoscope is the primary method of diagnosing COME where the eardrum is characteristically cloudy or opaque. This is coupled with tympanometry, especially if physical examination is inadequate, to provide information about tympanic membrane mobility. The tympanogram is obtained by plotting the acoustic energy of the reflected tone (immittance or compliance) of the middle ear as a function of varying pressure in the external ear canal. Three different tympanogram types can be derived (A, B or C), with type B indicative of a middle ear effusion due its flattened shape with no discernible peak pressure (see Figure 3).[20]

**Figure 3: Tympanogram types**

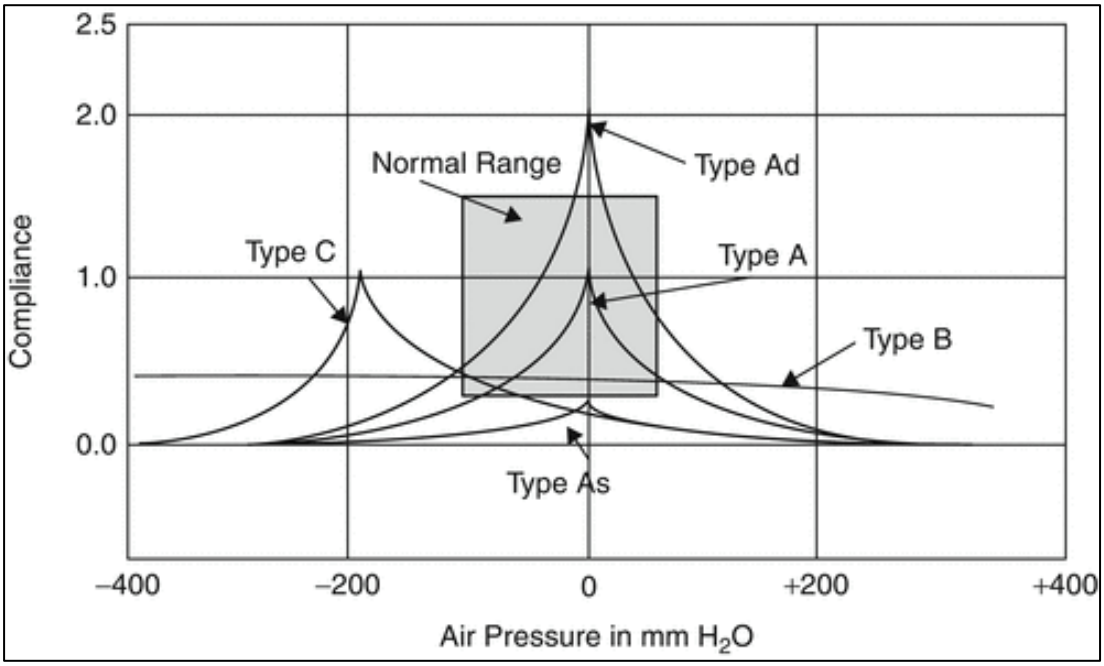



*Image source: Nakayama JR, Ramsey MJ. Tympanometry. In: Kountakis SE, editor. Encyclopedia of Otolaryngology, Head and Neck Surgery. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013. P. 2905-9. Licence number: 5446750140511, License date: 12/12/2022 (Springer Nature)* [21]

Because middle ear effusion is associated with a mild to moderate conductive loss, audiometry is an essential part of the diagnosis and management of COME. For children under the age of 5, behavioural audiometry is used and adapted to the age of the child. Visual reinforcement audiometry is typically used for children between 6 months and 2 years and involves presenting a sound stimulus in the sound field and observing the child's conditioned head-turn response. This reaction is then rewarded with a visual reinforcement such as animated video or toy. For children greater than 2 years but less than 5, conditioned play audiometry is used where the child places toys in a bucket to acknowledge hearing the sound. Hearing thresholds are measured in decibels over several frequencies (0.25, 0.5, 1, 2, 4, and 8 kHz) which correspond to the

frequency range for understanding speech. Thresholds may be ear specific or measured in a sound field depending on the age of the child. Hearing thresholds 20 decibels or less in all frequencies is considered normal hearing (see Figure 4). [20, 22]

**Figure 4: Example audiogram**

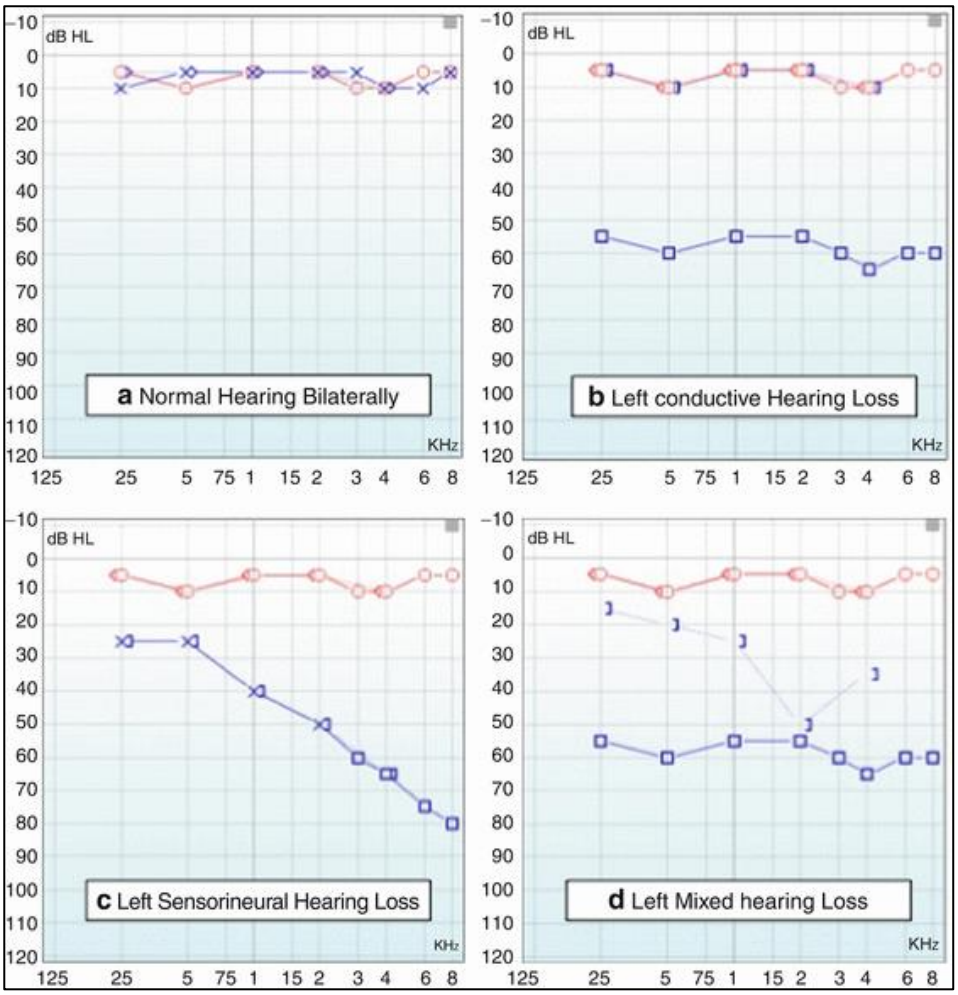



*Image source: Fukuda DK, Ramsey MJ. Audiometry. In: Kountakis SE, editor. Encyclopedia of Otolaryngology, Head and Neck Surgery. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013. p. 199-206. Licence number: 5446760430009, License date: 12/12/2022 (Springer Nature)* [23]

## 1.5 Management

### 1.5.1 Surgical management

Insertion of ventilation tubes (VT) is the standard treatment for COME in patients with cleft lip and palate, but the timing and long-term efficacy remains controversial. [3, 24, 25] They create a pathway for external drainage of the effusion and facilitate middle ear ventilation, acting like a surrogate for the under-functioning eustachian tube (see Figure 5).[20]

**Figure 5: Insertion of ventilation tube**

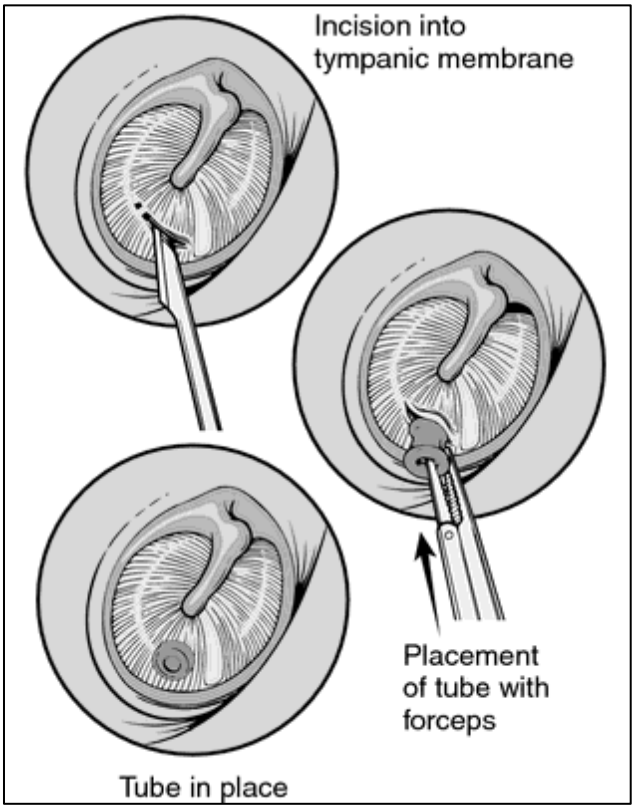



*Image source: Tympanostomy. Accessed via https://passionateinknowledge.com/medical/surgical-procedure-term-auditory-system/, creative commons license.*[26]

For children with cleft lip and palate, VT are commonly inserted opportunistically at the same time as palate repair surgery, but can sometimes be inserted as a separate procedure if there is an ongoing effusion associated with a hearing deficit following repair of the palate. [3] Once inserted, the VT are reviewed at regular intervals visually and with tympanometry and audiometry to assess for presence, patency and hearing thresholds.[15] Spontaneous extrusion normally occurs between 6 and 24 months after insertion depending on type of VT used at which point a hearing assessment is performed to determine if re-insertion is required.[3] It is important to note that the insertion of VT is associated with short-term and long-term complications including persisting otorrhoea (discharge), scarring of the ear drum (tympanosclerosis), persistent perforation and retraction. These complications can worsen hearing outcomes, particularly with repeat VT insertions, without improving hearing in the long-term.[27] This raises an important question regarding the costs and benefits of repeat VT insertion. Currently, it not clear whether numerous sets of VT reflects an increased burden of disease in certain patients, or a vicious iatrogenic cycle related to the procedure itself. [3]

### 1.5.2 Surveillance

The evidence for a more conservative approach comes from several studies including a large Chinese cohort that had unrepaired clefts and no otological treatment but were found to have normal hearing and tympanometry by 7 years of age.[28] Robson *et al.* argued that the presence of middle ear fluid should not be an absolute indication for the insertion of VT as not all effusions are associated with hearing loss.[29] Proponents of close surveillance also cite the long-terms complications associated with insertion of VT as another reason to take a more judicious approach. A study by Sheahan *et al.* published in 2003 that followed 104 children with cleft palate over 7 years found that

those who had undergone a greater number of VT insertions were more likely to have conductive hearing loss and tympanic membrane abnormalities and furthermore, those that did not receive 'prophylactic' VT did not have any significant long-term otological complications.[30] It is important to note however, that a majority of these studies are based on mixed syndromic and non-syndromic cleft populations.

While undergoing active surveillance, children should be reviewed every 3-6 months with otoscopy, tympanometry, and audiometry to ensure that any critical hearing deficits are detected and corrected. [20]

### 1.5.3 Hearing aids

Although many studies have been published looking at management options for COME in children with cleft lip and palate, very few consider the use of hearing aids. Hearing aids are composed of a microphone, amplifier, receiver, battery, and volume control and work by amplifying sound to make speech more audible without being uncomfortable. They can be conventional or implantable, and the studies looking at hearing aid use in cleft palate population mainly considered conventional hearings aids as they are more affordable and less invasive.[31, 32] Similar to the surveillance approach, the use of hearing aids is based on the premise that middle ear effusion will resolve with time following palate repair. Hearing aids are a temporizing measure to facilitate adequate speech and language development if a hearing deficit is present while minimising the complications associated with insertion of VT. A study by Maheshwar *et al*. conducted in 2020 on children with both syndromic and non-syndromic cleft palate found reasonable compliance rates (51.6%) among study participants. This was based on parents' and teachers' perceptions of overall hearing aid use at home and school.[32] Hearing aids were considered as a potential intervention option in the *a priori* protocol.[10] However, no studies were found that explored the use of hearing aids in

purely non-syndromic cleft lip and palate population and thus this intervention was not included in the final review.

## 1.6 Outcomes of interest

When considering the effectiveness of short-term ventilation tubes compared to surveillance, the primary outcome of interest was hearing thresholds. Secondary outcomes included, speech and language development, otological complications, tympanogram type, number of repeat VT insertions and presence of effusion after the completed study period. These outcomes were derived from the MOMENT study (Management of Otitis Media with Effusion in childreN with cleft palaTe) feasibility study which sought to establish a set of core outcome measures for investigating the most effective management of COME in children with cleft lip and palate.[33] The set of 11 outcomes derived from the study were hearing, chronic otitis media, otitis media with effusion, receptive language skills, speech development, psychosocial development, acute otitis media, cholesteatoma, side effects of treatment, listening skills and otalgia.[34] An established and accepted set of core outcome measures facilitates aggregation of data for meta-analyses in key outcome areas [34] as well as improving consistency of reporting to try and overcome the well-known issues of heterogeneity and outcome reporting bias that exist in healthcare research. [35-37]

Another way to minimise the effect of outcome reporting bias that may skew review results is the used of reporting guidelines. One such guideline is the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.[38] When comparing the four included studies to the STROBE checklist, they were found to be deficient in key methodological areas including the reporting potential sources of bias, management of missing data and addressing participants that were lost to follow-up.

This significantly limited the capacity for pooled analysis and is further explored in chapter four of this thesis.

## 1.7 Overview of systematic review methodology and evidence synthesis

There are multiple retrospective and prospective cohort and case-control studies investigating the management of COME in children with cleft lip and palate, most incorporate syndromic and non-syndromic populations, but no randomised controlled trials are available. A preliminary search of *JBI Database of Systematic Reviews and Implementation Reports*, the Cochrane Library, MEDLINE (Ovid), PROSPERO, Embase and CINAHL (Ovid) found no systematic reviews on this topic. One narrative review conducted in 2013 by Kuo *et al.* was identified, but unfortunately this review considered both syndromic and non-syndromic cleft lip and palate populations.[39] Furthermore, critical appraisal of the included studies and evaluation of the quality of evidence was not performed, highlighting the need for a well-conducted systematic review in this area.

When considering the strength of evidence in clinical medicine, the hierarchy of evidence has become the cornerstone of evidence-based health care. [40, 41] This hierarchy is a system of rating the evidence acquired from different types of studies, based on the probability of bias, to determine the best evidence for a particular intervention. It has gone through several iterations since its initial development by Sackett *et al.* [41] in 1989. Due to its methodological rigor and reproducibility, a well conducted systematic review is ranked as the highest level of evidence.[42] For levels of evidence specific to therapeutic studies, systematic reviews of randomised controlled trials (RCTs) are the pinnacle. However, RCTs may not always be possible due to clinical safety concerns, logistical difficulties or in longitudinal research where measurement of outcomes occurs over a long period of time. Despite this, systematic reviews of cohort studies with or

without meta-analyses still offer valuable insights into the efficacy of different treatments when developing clinical practice guidelines.

To minimise the effect of selective outcome reporting and to ensure the transparency and duplicability of the systematic review process, it is best practice to first develop an *a priori* protocol. A study by Allers *et al.* found that while systematic reviews with published protocols take longer to develop and publish, they are far superior in their reporting of methodology and findings.[43] Registration of an ongoing systematic review is another way to minimise bias and allows for public scrutiny of a review's methodology. The Prospective Register of Ongoing Systematic Reviews (PROSPERO) is an international advisory group in collaboration with UK National Institutes of Health Research which allows researchers to freely register their ongoing systematic reviews online. Sideri *et al.* found that systematic reviews that were registered in PROSPERO were of better quality compared to non-registered reviews based on the Assessment of Multiple Systematic Reviews (AMSTAR) tool which assesses the methodological quality of systematic reviews.[44] The protocol developed for the systemic review presented in this thesis has been published in a peer-reviewed journal [45] as well as being registered with PROSPERO (CRD42021255861).

The quality of available evidence also needs to be determined when formulating a systematic review. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group has developed a system for grading the certainty of the evidence and strength of recommendations [46] which is endorsed by many evidence-based healthcare bodies including JBI, The Cochrane Collaboration and the World Health Organisation (WHO). The GRADE approach delineates between quality of evidence and strength of recommendation and has explicit criteria for downgrading or upgrading quality of evidence. It considers the various outcomes that are important to

patients and provides a transparent framework for presenting summaries of evidence for making clinical practice recommendations.

Although most of literature exploring COME in children with non-syndromic cleft lip is in the form of retrospective cohort studies, a well conducted systematic review using the GRADE approach can still provide valid evidence to guide clinical decision-making and inform policy development.[47]

## 1.8 Composition of Thesis

This is a thesis by publication written in five chapters. The included versions of the manuscripts have been accepted for publication and are presented according to University of Adelaide guidelines. The first chapter introduces the topic, key definitions, and current literature regarding the management of COME in non-syndromic cleft lip and palate. Chapter two contains the manuscript of the *a priori* protocol and search strategy that was developed prior to undertaking the systematic review. The systematic review is contained in chapter three, and chapter four contains the manuscript of the gaps analysis that highlights the methodological deficiencies that were identified in the included studies. The final chapter is a broader discussion of the findings and limitations encountered in developing this thesis.

The candidate is the primary author of all manuscripts, has collected and analysed the data and written the first drafts. All other authors have contributed their expertise in research methodology, statistics, and scientific and medical content. They have revised all the manuscripts critically and given final approval of the version to be published.

No work was carried out by the candidate prior to enrolment, and no work has been submitted for other qualifications. No third-party editorial assistance was used for the formatting of this thesis.

# CHAPTER 2: METHODS

## 2.1 Introduction

The development of an *a priori* protocol is an integral part of the systematic review process and is considered best practice.[48] A review process which is rigorous, reproducible, and transparent can minimise selective reporting of outcomes which is a serious issue within clinical research.[42] Selective outcome reporting can affect the direction, magnitude, and precision of pooled effect estimates and ultimately the conclusions that are drawn within a review regarding the risks and benefits of an intervention.[49] The remainder of this chapter is the manuscript of the *a priori* protocol which has been accepted and published in JBI Evidence Synthesis.

# Statement of Authorship

| | |
|---|---|
| Title of Paper | Effectiveness of ventilation tube insertion for conductive hearing loss in children with chronic otitis media with effusion and non-syndromic cleft palate: a systematic review protocol |
| Publication Status | Published |
| Publication Details | Maina G, Pollock D, Lockwood C, Ooi E. Effectiveness of ventilation tube insertion for conductive hearing loss in children with chronic otitis media with effusion and non-syndromic cleft palate: a systematic review protocol. JBI Evid Synth. 2022 Jun 1;20(6):1560-1567. doi: 10.11124/JBIES-21-00217. PMID: 35220383. |

## Principle Author

| | | | |
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| Name of Principal Author (Candidate) | Grace Maina | | |
| Contribution to the Paper | Data collection and analysis, interpretation of data, preparation of manuscript and acted as corresponding author | | |
| Overall percentage (%) | 85% | | |
| Certification: | This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper. | | |
| Signature | | Date | 22/10/2022 |

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

| Name of Co-Author | Danielle Pollock | | |
|---|---|---|---|
| Contribution to the Paper | Supervised development of protocol and manuscript evaluation. | | |
| Signature | | Date | 22/10/2022 |

| Name of Co-Author | Craig Lockwood | | |
|---|---|---|---|
| Contribution to the Paper | Supervised development of protocol and manuscript evaluation. | | |
| Signature | | Date | 22/0/2022 |

| Name of Co-Author | Eng Ooi | | |
|---|---|---|---|
| Contribution to the Paper | Supervised development of protocol and manuscript evaluation. | | |
| Signature | | Date | 22/10/2022 |

## 2.2 Manuscript of *'Effectiveness of ventilation tube insertion for conductive hearing loss in children with chronic otitis media with effusion and non-syndromic cleft palate: a systematic review protocol'*

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**Abstract**

**Objective**: This review aims to investigate the efficacy of ventilation tube insertion versus non-surgical options in the management of chronic otitis media with effusion in children with non-syndromic cleft palate by assessing the degree of conduction hearing change

**Introduction**: Chronic otitis media with effusion is a frequent finding in children with cleft palate due to associated eustachian tube dysfunction. It can lead to impaired hearing, and speech and language development. The main treatment options are drainage of effusion with ventilation tubes, surveillance, or amplification with hearing aids. Each of these approaches has its advantages but there is currently no consensus on the most appropriate management in children with cleft palate.

**Inclusion criteria**: Eligible studies will include children (<18 years) with cleft palate not associated with a genetic syndrome, diagnosed with chronic otitis media with effusion, who have undergone either insertion of ventilation tubes, compared with either surveillance or amplification with hearing aids.

**Methods**: A comprehensive search of MEDLINE (Ovid), CINHAL, Embase and Scopus databases will be conducted to find published literature. Grey literature searches will be conducted through Central Register of Controlled Trials (CENTRAL), Clinicaltrials.gov and ProQuest databases. Two reviewers will screen studies, conduct critical appraisal of eligible studies, assess the methodological quality, and extract the data. Where possible, studies will be pooled in statistical meta-analysis with heterogeneity of data being assessed using the standard Chi-squared and $I^2$ tests.

**PROSPERO**: CRD42021255861

**Keywords**: cleft palate, hearing loss, otitis media with effusion, surveillance, ventilation tubes

## Introduction

Cleft palate is part of a spectrum of congenital orofacial malformations where there is abnormal or displaced soft tissue, muscle, bone and cartilage of the nasal sill, lip, or palate. It occurs to varying degrees and is due to the failure of migration and fusion of the frontonasal, maxillary, and medial and lateral nasal prominences of the lower face. This occurs between the sixth and twelfth weeks of gestation.[1] Cleft lip and palate are common congenital malformations with a strong association with chronic otitis media with effusion (COME) which can lead to hearing loss. OME is characterized by fluid in the middle ear without signs or symptoms of infection[2] and becomes chronic if it persists for longer than 3 months from date of diagnosis. It is diagnosed by visual assessment of the tympanic membrane with an otoscope, coupled with audiometry and tympanometry, which assess the child's hearing and tympanic membrane mobility respectively.[3, 4] The peak incidence of OME in children with cleft lip and palate is earlier than normal, often within the first year of life[5-7], which coincides with the primary developmental period for speech and language acquisition.[8, 9] OME can also affect the vestibular system leading to delayed gross motor skills.[10] This has long term consequences for a child's learning, behavior and psychosocial development. . Furthermore, it carries an increased burden of care for caregivers.[11, 12] The potential impact of OME has been reported to persist into teenage years. It can manifest as decreased reading ability, verbal IQ, and inattention and hyperactive behavior.[13] Effective management of OME in children with cleft palate is vital to ensure their developmental milestones are at par with their peers, to decrease caregiver stress and to minimize any long-term damaging effects on their overall growth and development.

The pathophysiology of cleft lip and palate is still poorly understood but both genetic

and environment factors have been implicated.[14] Orofacial clefts can present as either a cleft lip with or without cleft palate or an isolated cleft palate, but in fifty percent of cases, both occur together.[5] The prevalence of cleft lip and palate is variable in different populations, but globally it occurs in 1:700 cases[15], with a predominance in males. Approximately 50% of children with cleft palate do not have an associated genetic syndrome.[16] Cleft palates can be described as unilateral or bilateral, and their extent can be incomplete or complete. The least severe is the submucous cleft palate where the oral mucosa is intact but there is a defect in the underlying palatal musculature.[5] In complete cleft palate, there is direct communication between the entire length of the nasal passage and the oropharynx.[5, 6] Given the phenotypic variability, it can affect many aspects of growth and development including hearing, speech and language.[5]

Several studies have shown that middle ear effusion is present in greater than 96% of patients with cleft palate, from as early as four months of age, regardless of cleft type.[5, 6] In children with cleft palate, OME is typically more severe and more persistent[17] and this is thought to be primarily due to impaired formation and function of the eustachian tube[18], as well as abnormal insertion of tensor veli palatini and levator veli palatini muscles.[19] These structures normally assist with clearance and drainage of middle ear fluid. In addition, some researchers hypothesize that exposure of the eustachian tube opening to refluxed oropharyngeal materials can lead to inflammation and obstruction.[6] The persistence of fluid in the middle ear leads to impaired conduction of sound waves and can result in conductive hearing loss between 25-45 dB, which corresponds to mild to moderate loss.[8, 10] The long-term sequalae of OME include thickening of the tympanic membrane, perforation and retraction which can further worsen the hearing loss.[20]

The main treatment strategies for OME can be broadly categorized into surgical and non-surgical, and currently, there is no consensus on its management in children with cleft palate.[5, 21] Surgical management involves the insertion of ventilation tubes (VT), sometimes termed grommets which are the current standard of care. [4, 5, 14] They are small cylinders made of plastic or silicone that are inserted into the ear drum, often at the same time as palate repair, and provide a route of drainage for any effusions.[4] This improves the conduction of sound through the middle ear and can normalize hearing. [4, 14] However, they can be associated with persistent ear discharge (otorrhea), sometimes necessitating removal, and often multiple sets are required due to extrusion.[5] In the longer term, VT have been associated with persistent perforation of the tympanic membrane, scarring (tympanosclerosis), retraction and even cholesteatoma, especially with repeat insertions. [4] Cholesteatoma is a collection of keratinized squamous epithelium trapped within the middle ear space that can erode local structures including ossicles. Moreover, some children may still develop chronic OME even with ventilation tubes in situ.[20] Gordon *et al*. [22] showed that VT insertion did not result in better long-term hearing but was strongly associated with tympanosclerosis.

Non-surgical options are surveillance or amplification using hearing aids.[23] Surveillance, is based on evidence that eustachian tube function can improve following repair of cleft palate (palatoplasty) without further intervention. This would probably negate the need for ventilation tubes and their associated complications.[21] Muntz [3] showed that greater than 50% of children with cleft palate naturally recover from OME by three years. The child would be reviewed at regular intervals with audiology and tympanometry to ensure any critical hearing deficits are detected. [4, 21] An alternative approach is the use of hearing aids to minimize associated surgical complications while correcting any hearing impairment. The main limitation is poor compliance. A

retrospective study by Maheshwar et al.[24] in 2002 showed that children with cleft palate and OME could be managed adequately with hearing aids without resulting to VT, unless there were significant compliance issues, or the child developed recurrent suppurative otitis media. Hearing aid use was also associated with minimal complication rates.

The purpose of this systematic review is to evaluate the quantitative effectiveness of ventilation tube insertion versus non-surgical management in the treatment of OME in children with non-syndromic cleft palate. It aims to identify the best treatment option with regards to improvement in hearing, as well as speech and language development, while minimizing complications that may result in permanent hearing loss. VT insertion is considered a mainstay treatment, but an increasing body of evidence shows that it may not offer better hearing in the long-term and can be associated with significant otological complications. Additionally, the gradual resolution of OME with increasing age, supports the need for a more conservative approach. We hope the findings of this review will allow for the formulation of standardized guidelines that allow clinicians to make the most appropriate management choice for their patients based on the current best evidence.

A preliminary search of *the JBI Database of Systematic Reviews and Implementation Reports*, the Cochrane Library, MEDLINE (PubMed), PROSPERO, Embase (Elsevier) and CINAHL (EBSCOhost) revealed one narrative review conducted in 2013 by Kuo *et al.*[21] on the management options of otitis media with effusion in children with cleft lip and palate. A meta-analysis could not be conducted due to lack of adequately powered randomized control trials. Since then, Ji *et al.*[25] have conducted a prospective study of hearing outcomes following palatoplasty without concurrent insertion of VT. The study showed a 30% spontaneous recovery rate at 6 months following palate repair. Azman *et*

*al.*[26] followed up 68 children with cleft palate who had been managed with VT up to 18 years of age. Seventeen percent of children over 4 years of age still developed chronic otitis media despite VT insertion. A history of 3 or more VT insertions which occurred in 20% of study participants, increased the risk of chronic otitis media as well as other sequalae such as persistent perforation or cholesteatoma. Research in this field has progressed since the narrative review in 2013 and given the ongoing lack of consensus, a re-evaluation of the existing evidence base is timely.

**Review question**

In children with non-syndromic cleft palate, what is the effect of VT insertion versus non-surgical management of chronic otitis media with effusion on degree of conductive hearing loss?

**Inclusion criteria**

**Participants**

The review will include children (<18 years)[27] with cleft lip and palate or isolated cleft palate, not associated with a syndrome, diagnosed with chronic otitis media with effusion.

Exclusion criteria includes patients with cleft lip and palate associated with a clinical syndrome as these are often associated with other abnormalities of the craniofacial skeleton that predispose to multifactorial middle ear disease and other causes of deafness.[5] These syndromes include DiGeorge Syndrome, Pierre Robin sequence and CHARGE syndrome.[28, 29]

**Intervention**

This review will consider studies that evaluate the surgical insertion of ventilation tubes as the primary intervention to manage chronic otitis media with effusion, either at the time of palate repair or on subsequent follow-up.

**Comparator(s)**

This review will consider studies that compare the primary intervention to either the surveillance alone or amplification with hearing aids.

**Outcomes**

This review will consider studies that include the following outcomes:

**Primary outcome:**

- Degree of conductive hearing change – as measured in decibels by audiogram[30]

**Secondary outcomes:**

- Speech and language development – measured by clinically validated tools of assessment
- Changes in tympanogram type – as measured by tympanometry [31]
- Number of grommets inserted
- Presence of effusion – by direct visualization on otoscopy
- Otological complications (e.g., tympanosclerosis, retraction, persisting perforation, infection cholesteatoma) of any intervention at any stage

These outcomes will be reported in the GRADE approach.

## Types of studies

This review will consider both experimental and quasi-experimental study designs including randomized controlled trials and non-randomized controlled trials. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies will be considered for inclusion.

## Methods

The proposed systematic review will be conducted in accordance with JBI methodology for systematic reviews of effectiveness.[32] This protocol has been registered in PROSPERO, registration number CRD42021255861.

## Search strategy

The search strategy will aim to locate both published and unpublished studies. An initial limited search of MEDLINE (PubMed) was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE (PubMed) (see Appendix I). The search strategy, including all identified keywords and index terms, will be adapted for each included information source. The reference lists of all studies selected for critical appraisal will be screened for additional studies. No filters will be used in order to capture all available studies.

## Information sources

The databases to be searched include MEDLINE (PubMed), CINAHL (EBSCOhost), Embase (Elsevier) and Scopus (Elsevier). Grey literature will be searched through

Cochrane Central Register of Controlled Trials (CENTRAL), Clinicaltrials.gov and ProQuest Dissertations & Theses Global (ProQuest Platform).

**Study selection**

Following the search, all identified citations will be collated and uploaded into Covidence software (Veritas Health Innovation, Melbourne, Australia) and duplicates removed. A pilot test will be conducted where 10 articles are randomly selected and independently reviewed by two reviewers against the inclusion criteria to ensure a consistent appraisal process. Following a pilot test, titles and abstracts will then be screened. Potentially relevant studies will be retrieved in full for further review. Both the title and abstract screening and the full text screening will be conducted by two reviewers. Any disagreements that arise between the reviewers at each stage of the study selection process will be resolved through discussion or with a third reviewer. Studies selected for critical appraisal and synthesis will then be imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia) for data extraction. [33] Reasons for exclusion of full-text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review as an annexure. The results of the search and study selection and inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[34]

**Assessment of methodological quality**

Eligible studies will be critically appraised by two reviewers independently at the study level for methodological quality. Standardized critical appraisal instruments from JBI will be used for experimental and quasi-experimental, and analytical observational

studies. [32] Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. The results of critical appraisal will be reported in a table with accompanying narrative. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible) to minimize the impact of selection bias.

**Data extraction**

Data will be extracted manually from studies included in the review by two reviewers independently using an adapted version of the JBI data extraction tool in JBI SUMARI[33] supplemented by Microsoft Excel (Redmond, Washington, USA) (see Appendix II). The data extracted will include specific details about the populations, study methods, interventions, and outcomes of significance to the review question and specific objectives. These parameters include age, gender, type of cleft palate, otoscopy findings, timing of VT tube insertion and intervals of repeat insertions, audiology and tympanometry measurements, timing and duration of surveillance period (months), complications, type of hearing aid and duration of use (months). Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

**Data synthesis**

Studies will, where possible, be pooled with statistical meta-analysis based on similar methodological design as well as the study parameters being investigated. An assessment of the studies' suitability for pooled analysis will be made following the data extraction process. This will be completed using JBI SUMARI.[33] Effect sizes will

be expressed as either odds ratios (for dichotomous data) or weighted (or standardized) final post-intervention mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Adjusted estimates will be used preferentially for non-randomized and observational studies. Heterogeneity will be assessed statistically using the standard $\chi^2$ and $I^2$ tests. The choice of model (random or fixed effects) and method for meta-analysis will be based on the guidance by Tufanaru *et al.*[35] Subgroup analyses will be conducted based on methodology of included studies, cleft type, timing and duration of intervention, where there are sufficient data. Sensitivity analyses will be conducted to test decisions made regarding the model analysis and the impact of low compared to high-quality studies. Studies will be deemed as low to high quality following critical appraisal using JBI critical appraisal checklists, as well as assessment of the quality of evidence using the GRADE approach.[35] Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation, where appropriate.

A funnel plot will be generated to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.

**Assessing certainty in the findings**

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed[25] and a Summary of Findings will be created using GRADEpro GDT 2015 (McMaster University, ON, Canada). The Summary of Findings will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias,

directness, heterogeneity, precision, and risk of publication bias of the review results. The outcomes reported in the Summary of Findings will be:

- Degree of conductive hearing change
- Resolution of effusion
- Speech and language development
- Otological complications of any intervention

Any deviation from the protocol will be documented and informed in the final review with appropriate justifications.

**Acknowledgments**

The author acknowledges and thanks Ms. Vikki Langton (Librarian) for her contribution, guidance, and feedback in developing a search strategy.

**Conflicts of interest**

This review is to contribute towards a Master Clinical Science degree for the first author. DP and CL are salaried academic staff members of JBI, Adelaide.

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# CHAPTER 3: RESULTS

## 3.1 Introduction

When considering evidence hierarchies, a well-conducted systematic review with meta-analysis is considered as the highest level of evidence.[42] Given the exponential increase in the medical literature that is available, systematic reviews and meta-analyses that employ methodological rigor provide a valuable summary of the current best evidence to guide clinical decision making.[50] The remainder of this chapter contains a manuscript of the systematic review which has been accepted and published in the American Cleft Palate and Craniofacial Journal.

# Statement of Authorship

| | |
|---|---|
| Title of Paper | Managing chronic otitis media with effusion in children with non-syndromic cleft palate: short-term ventilation tubes versus surveillance |
| Publication Status | Published |
| Publications Details | Maina G, Pollock D, Lockwood C, Cook L, Ooi E. Managing Chronic otitis media with Effusion in Children with non-Syndromic Cleft Palate: Short-Term Ventilation Tubes Versus Surveillance. Cleft Palate Craniofac J. 2023 Jan 4:10556656221148368. doi: 10.1177/10556656221148368. PMID: 36600676. |

## Principle Author

| | | | |
|---|---|---|---|
| Name of Principal Author (Candidate) | Grace Maina | | |
| Contribution to the Paper | Data collection and analysis, interpretation of data, preparation of manuscript and acted as corresponding author | | |
| Overall percentage (%) | 85% | | |
| Certification: | This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper. | | |
| Signature | | Date | 22/10/2022 |

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

| Name of Co-Author | Danielle Pollock | | |
|---|---|---|---|
| Contribution to the Paper | Manuscript evaluation, evaluation of methodology and statistics. | | |
| Signature | | Date | 22/10/2022 |

| Name of Co-Author | Craig Lockwood | | |
|---|---|---|---|
| Contribution to the Paper | Manuscript evaluation, evaluation of methodology and statistics. | | |
| Signature | | Date | 22/20/2022 |

| Name of Co-Author | Lachlan Cook | | |
|---|---|---|---|
| Contribution to the Paper | Second reviewer for study selection, critical appraisal, and data extraction. | | |
| Signature | | Date | 22/10/2022 |

| Name of Co-Author | Eng Ooi | | |
|---|---|---|---|
| Contribution to the Paper | Manuscript evaluation and content expertise. | | |
| Signature | | Date | 22/10/2022 |

## 3.2 Manuscript of *'Managing chronic otitis media with effusion in children with non-syndromic cleft palate: short-term ventilation tubes versus surveillance'*

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**Abstract:**

**Objective:** To compare the effectiveness of short-term ventilation tubes compared to surveillance on conductive hearing loss in children with non-syndromic orofacial clefting involving the muscular palate

**Introduction:** Chronic otitis media with effusion is a common finding in children with cleft palate. The accepted convention is insertion of short-term ventilation tubes at the time of palate repair, but some centres are choosing conservative management. Each approach has its advantages but there is currently no consensus on the most appropriate management in children with non-syndromic cleft palate.

**Inclusion criteria:** Children <18 years with cleft lip and palate, not associated with a genetic syndrome, who have been diagnosed with chronic otitis media with effusion.

**Methods:** A systematic search of MEDLINE, CINAHL, Embase and Scopus databases was conducted. Grey literature searches were conducted through Central Register of Controlled Trials, Clinicaltrials.gov and ProQuest. Two reviewers screened the studies,

conducted critical appraisal, assessed the methodological quality, and extracted the data. Where possible, studies were pooled in statistical meta-analysis with heterogeneity being assessed using the standard Chi-squared and $I^2$ tests.

**Results:** Four studies met the inclusion criteria but were of low quality with a moderate risk of bias. Only data on hearing thresholds could be pooled for meta-analysis and found no statistically significant difference. All other outcomes were presented in narrative form. Certainty of evidence for all outcomes was deemed low to very low using GRADE criteria.

**Conclusions:** No definitive conclusions can be drawn regarding most effective management at improving conductive hearing loss. Missing data and inconsistent reporting of outcomes limited capacity for pooled analysis.

**Keywords:** cleft lip and palate; conductive hearing loss; grommets; otitis media with effusion; surveillance; systematic review

## Introduction

Cleft lip and palate is a broad term used to describe a heterogenous group of congenital orofacial clefts. The term includes clefts of the lip, maxillary alveolus, hard and soft palate in varying combinations, and in 50% of cases, cleft lip and palate will occur together.[1, 2] There is a strong association to chronic otitis media with effusion (COME), which can lead to hearing loss. The prevalence is variable in different populations, but globally it occurs in 1:700 cases, with a predominance in males. [3] Approximately 50% of children with cleft palate do not have an associated genetic syndrome.[4] The focus of this review is children with non-syndromic orofacial clefting, in any combination, affecting the muscular palate. Classification of syndromic versus non-syndromic orofacial clefting is primarily based on the phenotypic appearance of the child, where common cleft-associated syndromes will have characteristic facial morphology. [2] If the cleft lip and palate appears as an isolated defect or if an underlying syndrome cannot be identified, then this is termed non-syndromic.

Several studies have shown that middle ear effusion is present in greater than 96% of patients with cleft involving the muscular palate, from as early as four months of age, regardless of the cleft classification.[2, 5] The condition is characterised by fluid in the middle ear without signs or symptoms of infection[6] and becomes chronic if it persists for longer than three months from date of diagnosis. It is diagnosed by visual examination of the tympanic membrane with an otoscope, coupled with audiometry and tympanometry, which assess the child's hearing and tympanic membrane mobility respectively.[7] In children with cleft palate, COME is typically more severe and more persistent.[8] This is thought to be primarily due to impaired formation and function of the eustachian tube[9], as well as abnormal insertion of tensor veli palatini and levator veli palatini muscles. [10, 11] These structures normally assist with clearance and drainage

of middle ear and the persistence of fluid in the middle ear can result in a conductive hearing loss.[12, 13] The long-term sequalae of untreated COME include thickening of the tympanic membrane, perforation, and retraction.[14]

The peak incidence of COME in children with cleft lip and palate is comparatively earlier than normal, often within the first year of life.[2, 5, 15] This coincides with the primary developmental period for speech and language.[12, 16] COME can also affect the vestibular system leading to delayed gross motor skills.[13] All of this can have consequences for a child's learning, behaviour, and psychosocial development.[17]

Effective management of COME in this population is vital to ensure their developmental milestones are at par with their peers and to minimise any long-term detrimental effects on growth and development. Currently, there is no consensus on management in children with non-syndromic palate.[2, 18] The most common treatment option is surgical insertion of short-term ventilation tubes (VT) at the time of palate repair.[2, 7, 19] They provide a route of drainage for any effusion as well as ventilation of the middle ear.[7] This improves the conduction of sound and can normalise hearing. [7, 19] However, VT can be associated with persistent ear discharge (otorrhoea), sometimes necessitating removal, and often multiple sets are required due to extrusion and recurrence of effusion.[2] In the longer term, VT have been associated with persistent perforation of the tympanic membrane, scarring (tympanosclerosis), retraction and even cholesteatoma[7], especially with repeat insertions. Furthermore, some children may still develop COME even with VT in situ.[14] Gordon *et al.* [20] showed that VT insertion did not result in better long-term hearing but was strongly associated with tympanosclerosis.

Surveillance is a non-surgical option and is based on evidence that eustachian tube

function can improve following palate repair surgery without further intervention. This would negate the need for VT and their associated complications.[18] Muntz [21] showed that greater than 50% of children with cleft palate naturally recover from COME by three years of age. Where watchful waiting is utilised, the child is reviewed at regular intervals with audiology and tympanometry to ensure that any critical hearing deficits are detected.[7,18]

The purpose of this systematic review is to evaluate the effectiveness of VT insertion versus surveillance on degree of conductive hearing loss in children with chronic otitis media with effusion and non-syndromic cleft palate. It aims to identify the best treatment option with regards to improvement in hearing, as well as speech and language development, while minimising complications that may result in permanent hearing loss. VT insertion is considered a mainstay treatment, but an increasing body of evidence shows that it may not offer better hearing in the long-term and can be associated with significant otological complications. Additionally, the gradual resolution of OME with increasing age suggests that a conservative approach holds promise and warrants further investigation. We hope the findings of this review will allow for the formulation of standardised guidelines that allow clinicians to make the most appropriate management choice for their patients based on the current best evidence.

**Review question**

What is the effectiveness of short-term ventilation tube insertion compared to surveillance in the management of chronic otitis media with effusion in children with non-syndromic cleft palate?

## Methods

This systematic review was conducted in accordance with the JBI (formerly Joanna Briggs Institute) methodology for systematic reviews of effectiveness.[22] An *a priori* protocol[23] was developed and registered in PROSPERO (CRD42021255861). The protocol developed also sought to consider hearing aids but unfortunately the studies found considered both syndromic and non-syndromic participants with no distinction made in data analysis, and thus this intervention was not included in the final review. Ethical approval was not sought as this review retrieved and synthesised data from already published studies.

### Inclusion criteria

### Participants

Children less than 18 years with cleft lip and palate, or isolated cleft palate, not associated with a syndrome, diagnosed with chronic otitis media with effusion, who had undergone either insertion of ventilation tubes or conservatively managed with surveillance.

Studies were excluded if participants had syndromic cleft lip and palate as these are often associated with abnormalities of the craniofacial skeleton that predispose to multifactorial middle ear disease and other causes of deafness.[2] Participants with isolated cleft lip were also excluded as there is no association with eustachian tube dysfunction.

### Intervention

Short-term ventilation tubes as the primary intervention to manage chronic otitis media with effusion, either at the time of palate repair or on subsequent follow-up.

**Comparator**

Conservative management through surveillance.

**Outcomes**

- **Primary**
    - Hearing thresholds measured as the pure tone average (PTA) in decibels (dBHL) over 500 - 4000Hz frequencies for both ears
- **Secondary**
    - speech and language development
    - changes in tympanic membrane type, measured by tympanometry[24]
    - number of repeat ventilation tubes inserted
    - presence of effusion, measured by direct visualization on otoscopy and
    - otological complications (e.g., tympanosclerosis, retraction, persisting perforation, infection, cholesteatoma) of any intervention at any stage.

**Types of studies**

Both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies were considered. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies were considered for inclusion.

**Search strategy**

The search strategy aimed to locate both published and unpublished studies. A three-step search strategy was utilized in this review. An initial limited search of MEDLINE (PubMed) was undertaken to identify articles on the topic. The text words contained in

the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE (see Appendix I). Some examples search terms include “children”, “cleft palate, “conductive hearing loss” and “tympanostomy tubes”. The search strategy, including all identified keywords and index terms was then adapted for each included information source. The search strategy was reviewed for accuracy by a University of Adelaide Librarian. The reference lists of all studies selected for critical appraisal were screened for additional studies. The search was varied from the description in the protocol by restricting inclusion to studies published in the English language. This post-hoc change resulted in ten studies being excluded due to a lack of access to translation services. The databases screened were MEDLINE (PubMed), CINAHL (EBSCO), Embase, and Scopus. Gray literature was searched through the Cochrane Central Register of Controlled Trials (CENTRAL), ClinicalTrials.gov, and ProQuest Dissertations and Theses Global (ProQuest Platform) and this was finalised in July 2021.

**Study selection**

All identified citations were collated and uploaded into Covidence software (Veritas Health Innovation, Melbourne, Australia) and duplicates removed. Following a pilot test, titles and abstracts were screened by two independent reviewers (G.M. and L.C.) for assessment against the inclusion criteria for the review. Potentially relevant studies were retrieved in full for further review. Both the title and abstract screening and the full-text screening were conducted by two reviewers. Studies selected for critical appraisal and their citation details were imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (JBI, Adelaide, Australia).[25] Full text studies that did not meet inclusion criteria were excluded and are provided in Appendix III. The results of the search and the study inclusion process are

reported in full and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (see Figure 1).[26]

**Assessment of methodological quality**

Eligible studies were critically appraised by two independent reviewers at the study level for methodological quality using standardized critical appraisal instruments from JBI for cohort studies.[22] The results of critical appraisal are reported in Table 1. All studies underwent data extraction and synthesis, regardless of their methodological quality, to minimise the impact of selection bias.

**Data extraction**

Data was extracted from the included studies by two independent reviewers using an adapted version of the JBI data extraction tool in JBI SUMARI, supplemented by Microsoft Excel (Redmond, Washington, USA) (See Appendix II). Any disagreements during the study selection, critical appraisal and extraction process were resolved with a third senior reviewer. The data extracted included specific details about the population, study method, interventions, as well as the outcomes of significance to the review question. These parameters included age, gender, type of cleft palate and classification system used, otoscopy findings, timing of VT insertion, intervals of repeat insertions, audiogram and tympanometry measurements, timing, and duration of surveillance period (months) and complications. Where data was lacking, the corresponding authors were contacted via email regarding the raw data for the specific outcome that was required, within a time frame of four weeks. If no response was received this was documented in the results section of the review and subsequently excluded.

**Data synthesis**

Only one outcome of interest, hearing thresholds, could be pooled for statistical analysis based on similar methodological design as well as study parameters. This was completed using JBI SUMARI.[25] Effect sizes, expressed as post-intervention mean differences and their standard deviations were calculated for analysis. Statistical analyses were performed using fixed effects model[27] and the inverse-variance statistical method. Heterogeneity was assessed statistically using the standard Chi-squared and $I^2$ tests. Where pooled analysis was not possible, findings were presented in narrative form including figures to aid in data presentation.

**Assessing certainty in the findings**

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach[28] for grading the certainty of evidence was followed and a Summary of Findings (SoF) was created using GRADEpro GDT 2015 (McMaster University, ON, Canada) (see Table 2). The SoF presents information related to risk of bias, consistency, directness, precision and estimates relative and absolute risk to determine the quality of the evidence.

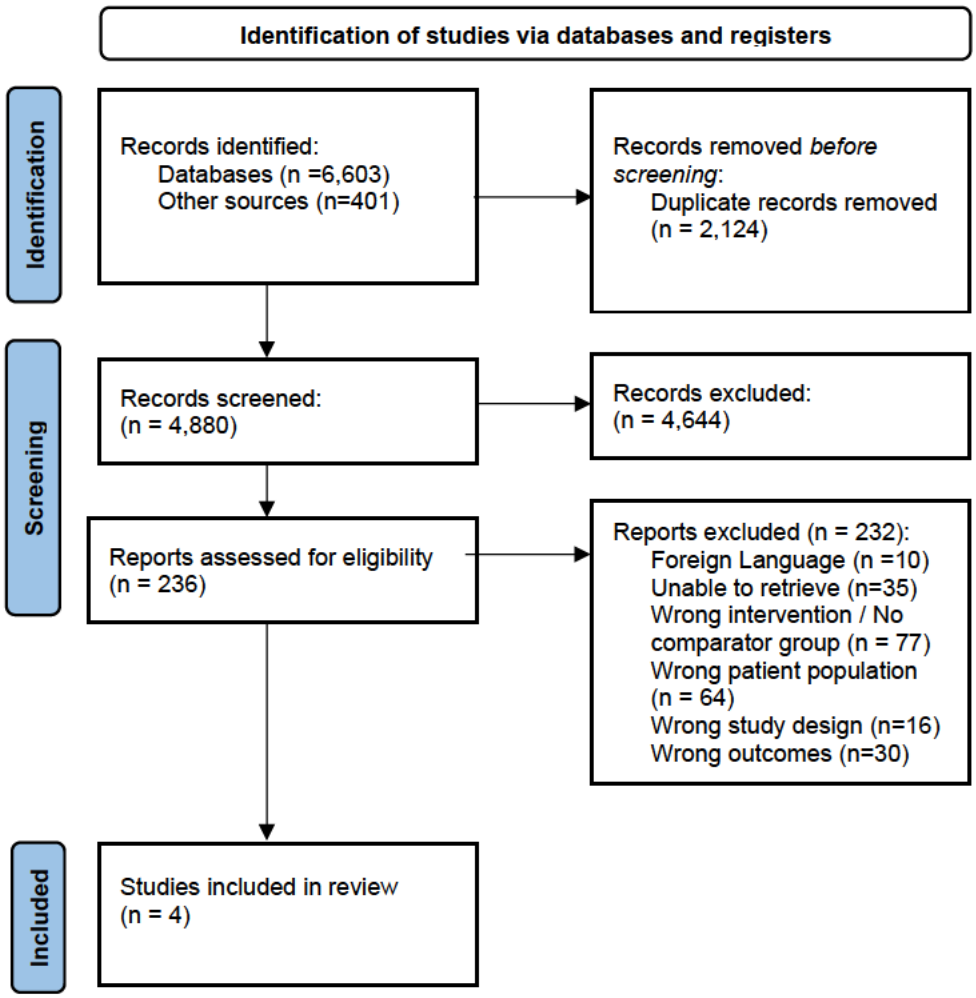
The outcomes reported in the SoF include hearing thresholds, otological complications, speech and language outcomes, tympanogram type, presence of middle ear effusion and repeat tympanostomy rate.

## Results

### Study inclusion

The total number of records identified through database searching and other sources included 2,244 articles from MEDLINE, 3,662 articles from Embase, 229 articles from CINAHL, 468 articles from Scopus and 401 articles from Google Scholar (see Figure 1).[26] After the removal of duplicates 4,880 were screened by title and abstract according to the inclusion criteria, which resulted in the exclusion of a further 4,644 articles. The remaining 236 articles were subjected to full text screening which resulted in exclusion of 232 articles based on requirements established in the protocol.[23] The final four articles were eligible for data extraction.[29-34]

**Figure 1: Search results and study selection and inclusion process[26]**



**Methodological quality**

The four included studies were observational cohort studies. Critical appraisal found that the overall quality of the studies was low (see Table 1). Factors that contributed to the low quality included incomplete data, poor reporting of confounders, poorly defined follow-up periods for intervention and comparators, and variable reporting of outcome measures which would result in a moderate to high risk of bias.

The primary outcome measure for this review was hearing thresholds which is normally measured by an audiometer[35] in decibels (dBHL) over set frequencies. In Australia, a measurement of 21 decibels or greater at any frequency suggests a hearing deficit.[36] There was considerable variability in how audiometric data was reported. Mean hearing thresholds were presented with either a range, confidence interval or standard deviations. The studies that presented their data with ranges required calculations to convert these to standard deviations for pooled analysis and this was done in consultation with a statistician.[37] Only the prospective study by Ŝubarević *et al.* included pre-intervention data on hearing thresholds and thus no comparisons could be made regarding the magnitude of change over time. The post-intervention data for this particular study could not be included in the final pooled analysis as the mean hearing thresholds were presented with only the percentage of participants within a certain threshold range. The authors did not respond when additional data was sought.

An assessment of certainty of evidence using GRADE was performed and detailed in the Summary of Findings table (see Table 2) which revealed very low to low quality of evidence for all the outcome variables measured. [29, 31]

**Table 1: Critical Appraisal of eligible cohort studies**

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Šubarević *et al.* | Y | Y | Y | U | U | N | Y | Y | N | N | Y |
| Shaw *et al.* | Y | Y | N | N | N | U | U | U | N | N | U |
| Robson *et al.* | Y | Y | Y | U | U | Y | Y | Y | U | U | Y |
| Hubbard *et al.* | Y | Y | Y | Y | Y | N | Y | Y | N | N | Y |

Y, yes; U, unclear; N, no; JBI appraisal checklist for cohort studies
Q1 = Were the two groups similar and recruited from the same population?
Q2 = Were the exposures measured similarly to assign people to both exposed and unexposed groups?
Q3 = Was the exposure measured in a valid and reliable way?
Q4 = Were confounding factors identified?
Q5 = Were strategies to deal with confounding factors stated?
Q6 = Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
Q7 = Were the outcomes measured in a valid and reliable way?
Q8 = Was the follow up time reported and sufficient to be long enough for outcomes to occur?
Q9 = Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
Q10 = Were strategies to address incomplete follow up utilized?
Q11 = Was appropriate statistical analysis used?

## Characteristics of included studies

All four included studies were cohort studies[29-32], three of them retrospective and one prospective.[30] A total of 280 participants were included, 127 in the short-term ventilation tube group and 153 in the surveillance group. The total sample size per study ranged from 48 to 90, and all but one study[32] had equal number of participants in each intervention group.

All four studies utilised the same inclusion criteria for participants and ages ranged from 0 to 12 years. Participants were not divided into age groups in any of the included studies. Description of cleft type was limited. Two studies labelled clefts types as either complete or incomplete cleft[29, 31] with equal numbers in both intervention groups. One study did not specify[30], and one study used the LAHSHAL classification system.[32, 38]

In two studies, the maximum follow-up period was stated as five years, but this was not clearly reported in the remaining two studies.[31, 32] All studies considered the use of short-term ventilation tubes to manage chronic otitis media with effusion in the

intervention group, either at the time of palate repair or after subsequent follow-up. This was compared to a similar cohort of children with non-syndromic cleft lip and palate that were managed conservatively with surveillance.

Not all studies compared all the outcomes of interest, with the most commonly reported outcomes being hearing thresholds and otological complications. Each outcome variable was reported differently in each individual study. The characteristics and results of the included studies are shown in Appendix IV.

## Review findings

## Table 2: Summary of systematic review findings

| **Ventilation tubes compared to conservative management for chronic otitis media with effusion** | | | | | |
|---|---|---|---|---|---|
| **Patient or population:** chronic otitis media with effusion<br>**Setting:** children with non-syndromic cleft palate<br>**Intervention:** short-term ventilation tubes<br>**Comparison:** conservative management | | | | | |
| **Outcomes** | **Anticipated absolute effects* (95% CI)** | | **№ of participants (studies)** | **Certainty of the evidence (GRADE)** | **Comments** |
| | **Risk with conservative management** | **Risk with ventilation tubes** | | | |
| **Hearing thresholds assessed with: Audiogram (Decibels) Scale from: 1 to 180 follow-up: mean 5 years** | The mean hearing thresholds ranged from 6.4 - 22 decibels | **MD 1.31 decibels higher** (10.53 lower to 13.14 higher) | 97 (2 observational studies) | ⨁⨁◯◯ Low[a,b,c,d] | The evidence suggests that ventilation tubes may result in little to no difference in hearing thresholds in children with non-syndromic cleft lip/palate. |
| **Otological Complications (Complications) assessed with: Otoscopy (direct visualisation) follow-up: mean 5 years** | • Higher complication rate in children with cleft lip/palate who receive a grommet regardless of timing (early vs. late) | | 208 (3 observational studies) | ⨁⨁◯◯ Low | The evidence suggests ventilation tubes results in an increase in otological complications. |
| **Speech and Language outcomes (Speech and Language) assessed with: Variable follow-up: range 2 years to 5 years** | • Studies show that no significant difference in speech and language outcomes in cleft children when managed with either ventilation tubes or observation. | | 259 (4 observational studies) | ⨁◯◯◯ Very low[a,b,d,f] | The evidence is very uncertain about the effect of ventilation tubes on speech and language outcomes. |
| **Tympanometry (Tympanogram type) assessed with: Tympanogram follow-up: mean 5 years** | • Similar proportions of Type A and B tympanogram after 5 years of observation between children with cleft lip and palate who received ventilation tubes and those who did not<br>• Those who receive early ventilation tubes more likely to have Type A tympanogram at the end of follow-up period | | 138 (2 observational studies) | ⨁⨁◯◯ Low | The evidence suggests ventilation tubes may have little effect on the tympanogram type at the end of the follow-up period. |
| **Presence of middle ear effusion (Persisting effusion) assessed with: Otoscopy (direct visualisation follow-up: mean 5 years** | • Similar rates of effusion in children with cleft lip and palate regardless of ventilation tubes or conservative management<br>• Similar rates of effusion in children with cleft lip and palate regardless of early or late ventilation tube insertion | | 187 (3 observational studies) | ⨁⨁◯◯ Low | The evidence suggests ventilation tubes have little effect on the presence of middle ear effusion at the end of the follow-up period. |
| **Repeat tympanostomy Rate (Number of repeat Ventilation tubes) assessed with: Count follow-up: mean 5 years** | • Slightly higher repeat tympanostomy rate in children who receive ventilation tubes than those who don't | | 86 (1 observational study) | ⨁◯◯◯ Very low[a,b,g] | The evidence suggests that children who receive ventilation tubes have higher rates repeat tympanostomy than those who are managed conservatively. |
| ***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**<br>**CI: confidence interval; MD: mean difference** | | | | | |

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*Explanations*

*a. Incomplete outcome data, retrospective studies*
*b. no documentation of confounders*
*c. follow-up not clearly defined*
*d. non-syndromic cleft lip/palate already a rare condition, difficult to have a large sample size*
*e. Different cut offs for what is considered normal hearing thresholds*
*f. Different tools of assessment used*
*g. Notable heterogeneity between studies*

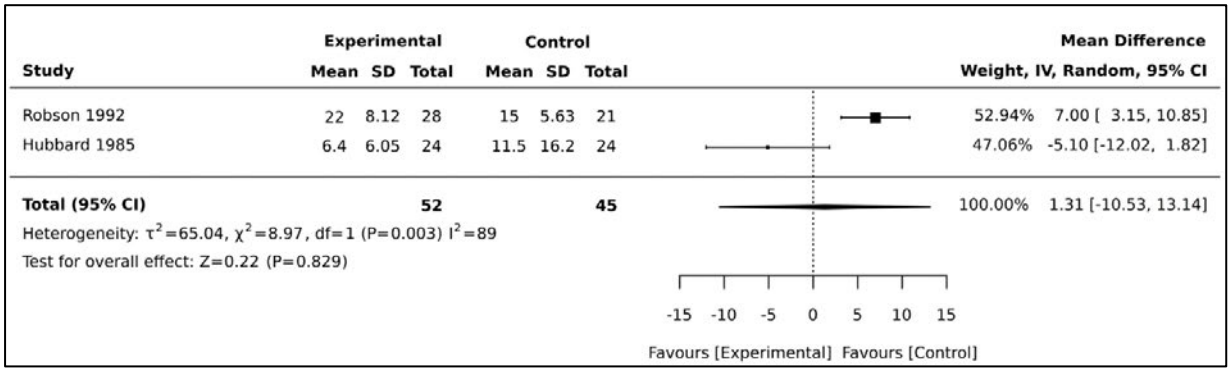
Only data for hearing thresholds could be pooled for statistical analysis. All other outcome data is presented in narrative from using the Synthesis without meta-analysis (SWiM) reporting guideline with additional figures to aid in presentation.[39]

### *Hearing thresholds*

Audiometric data from two of the four included studies was pooled for analysis. Both studies provided the mean hearing thresholds with ranges and the statistical formula developed by Ramirez and Cox[37] was used to calculate the standard deviations with the effect size presented as mean difference. Initially a fixed-effects model was used due to the methodological similarity between the two studies and heterogeneity was explored using $I^2$ statistic.[27] The overall effect size from the fixed-effects model favoured conservative management with a mean difference of 3.83 decibels [1.13, 6.54, p=0.006] however the $I^2$ statistic between the two studies was 93%, which is significant. A random effects model was then trialled which calculated heterogeneity at 89% but the result was inconclusive regarding the most effective management strategy for conductive hearing loss in this population (see Figure 2). Despite this, the average hearing thresholds in both studies for both the short-term ventilation tubes and surveillance groups were within the range of normal hearing (21 decibels or less)[36] after

the 5-year follow-up period. This suggests that insertion of short-term ventilation tubes may result in little to no difference in hearing thresholds in children with non-syndromic cleft lip and palate. However, the paucity of data limits any concrete conclusions.

**Figure 2: Forest plot of hearing thresholds comparing short-term ventilation tubes (experimental) versus surveillance (control)**

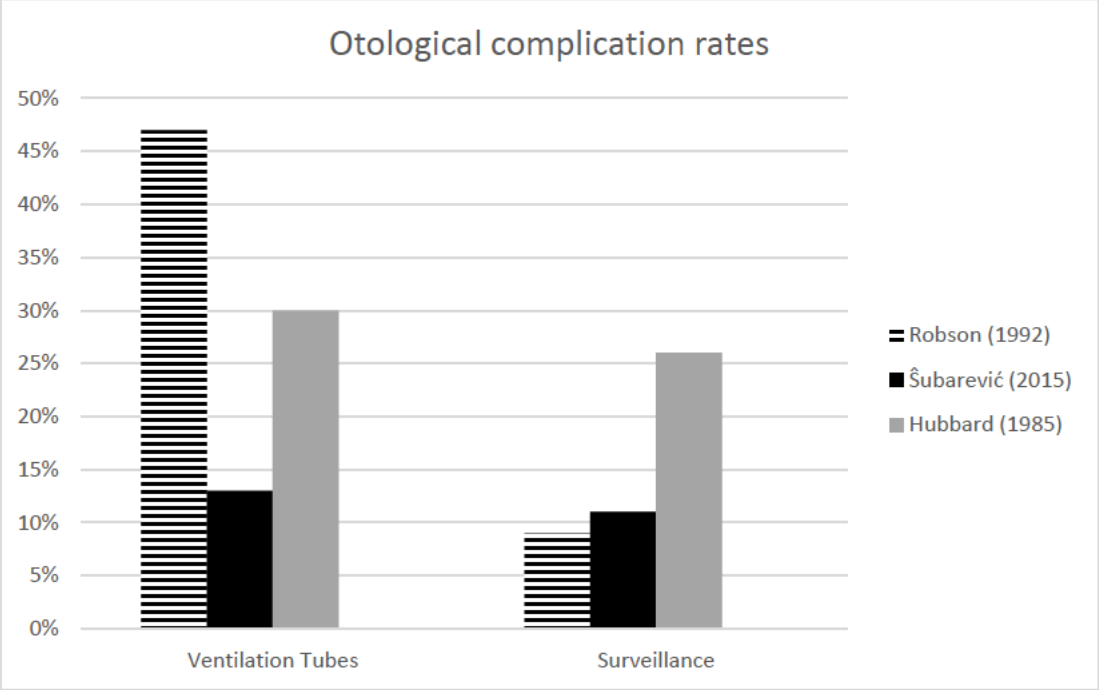



***Otological complications***

Otological complications were reported in three out of four studies. One study reported the proportion of the participants that had any complications but did not specify the types of complications.[30] The remaining two studies gave a breakdown of each complication and the proportion of participants with the complications. Robson *et al.* provided percentages, while Hubbard *et al.* reported the raw figures which were converted into percentages for comparison. There was also no clear documentation about when these complications were noted within the study period. The common complications reported were retraction, perforation, tympanosclerosis (scarring of eardrum), otorrhoea (ear discharge). Figure 3 shows the total complication rates for the three studies when comparing VT to surveillance and the raw data is listed in Appendix

V. Participants who received VT had a higher complication rate than those who did not. Robson *et al.* noted a particularly high rate of 47% compared to only 9% in the group managed conservatively and this was found to be statistically significant in their study. This contrasts with the studies by Ŝubarević *et al.* and Hubbard *et al.* that only found a 2% and 4% difference in the complication rates respectively. The reason for this variation could not be determined but the evidence suggests insertion of ventilation tubes results in a higher rate of otological complications.

**Figure 3: Otological complication rates at 5-year follow-up**




***Speech and Language outcomes***

Speech and language outcomes were reported in all four included studies, but different assessment methods were used in each study. Two studies only noted the proportion of participants that needed speech pathologist input, with no description given regarding how speech and language was assessed.[29, 30] In the study by Robson *et al.* 39 out of 70 participants had data about speech assessment at 2.5 and 5 years of age. Twenty-five

participants (65%) were from the VT group and 14 (44%) from the surveillance group. Of the VT group, 40% required ongoing speech therapy, 4% only a second review appointment and 56% required no formal speech assessment. This is in comparison to 36% who needed ongoing speech therapy, and 64% who required no speech assessment in the surveillance group. There was no documentation of the speech assessment tool used in the study. Ŝubarević *et al.* only documented that each child was monitored by a speech pathologist and no significant differences in the speech development were observed among the study participants. No further details are given in the study.

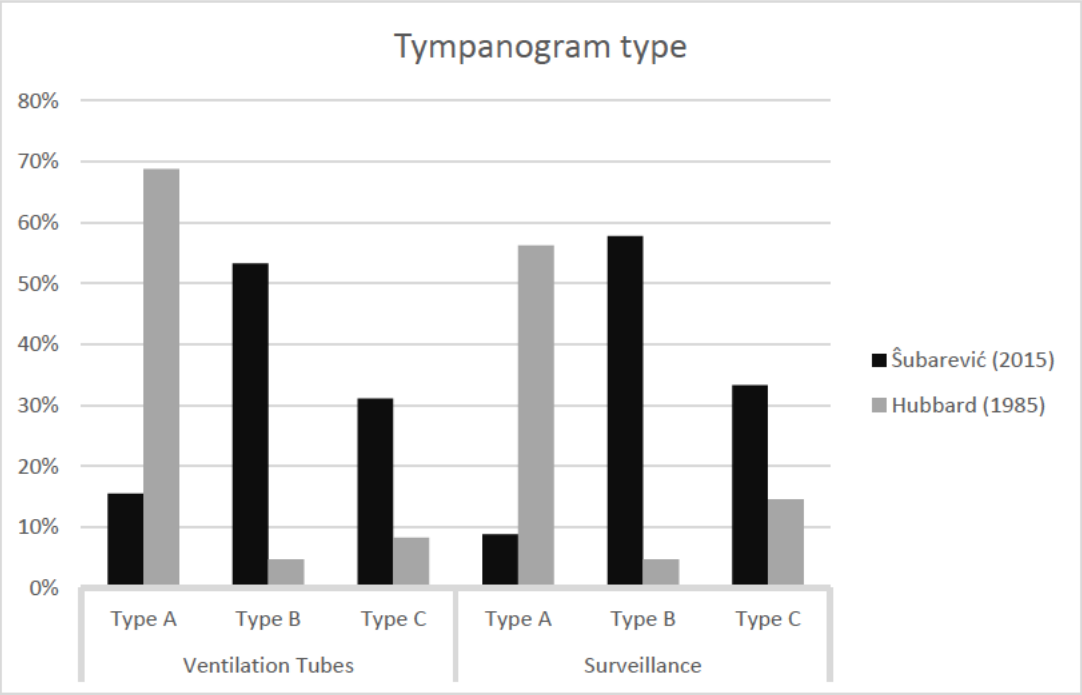
The studies by Hubbard *et al*. and Shaw *et al.* measured nasal resonance and consonant articulation, but each study used a different scale which again limited the capacity for pooled analysis. Hubbard *et al.* found a statistically significant difference in consonant articulation, with those who receive early VT having lower mean error rate of 19.6 (range = 0 - 94) compared to 30.5 (range = 0 - 78), p=0.03 (Wilcoxon signed-rank test) in those who underwent surveillance. The clinical significance of this finding is unclear. Overall, the evidence is uncertain regarding the effect of short-term ventilation tubes on speech and language outcomes.

***Tympanometry***

Tympanometry is a test that provides quantitative information about the presence of fluid in the middle ear through assessment of the mobility of the tympanic membrane, as it can often be difficult to determine if an effusion is present on visual inspection alone. Tympanometry produces tympanogram tracings that are classified as type A (normal), type B (flat) which is indicative if a middle ear pathology such as an effusion or, and type C which indicates a significantly negative pressure in the middle ear which may be associated with eustachian tube dysfunction.[40]

Tympanogram types was only reported in two studies. [30, 31] Ŝubarević *et al.* gave data for the beginning and end of their study period, while Hubbard *et al.* did not detail when the tympanograms were collected. Figure 4 compares the tympanogram types between the two studies for the VT and surveillance groups and considerable variation is evident. The study by Hubbard *et al.* shows that most participants had normal tympanogram types regardless of intervention which contrasted with Ŝubarević *et al.* where the type B tympanogram persists regardless of intervention. In both studies there are slightly higher Type A tympanograms in the ventilation tube group than in the surveillance group. The evidence suggests ventilation tubes may have little effect on the tympanogram type.

**Figure 4: Tympanogram type**



### *Presence of effusion*

The presence of an effusion in the middle ear is diagnosed visually using an otoscope and is the hallmark sign of chronic otitis media.[7] Three of the four included studies[29-31] reported this outcome as a proportion of the participants affected. The study by Robson *et al.* reported a higher rate of effusion in the VT group compared to the surveillance group. This is in contrast with Ŝubarević *et al.* who reported a higher rate in the surveillance group, however this was not found to be statistically significant. Hubbard *et al.* reported equal rates of effusion in both groups and a much lower rate of effusion overall, compared to the other two studies. The evidence suggests that ventilation tubes have little effect on the presence of middle ear effusion at the end of the follow-up period.

### *Repeat tympanostomy rate*

The number of repeat insertions of short-term ventilation tubes or repeat tympanostomy rate was only reported in the study by Robson *et al.* Of the 38 children who received VT, 21 needed more than one set (55.3%) and the average number of ventilation tubes required over the follow-up period was 1.66. The number of repeat ventilation tubes is an important factor to consider as a higher repeat tympanostomy rate has been associated with more significant long-term complications including permanent perforation, tympanosclerosis and cholesteatoma.[7]

## Discussion

The final analysis found inconclusive evidence regarding the most effective management strategy for chronic otitis media with effusion in children with non-syndromic cleft palate. Both fixed-effect and random-effect models were used to analyse hearing threshold data, but substantial heterogeneity was found with both

models and the overall result was unclear. A study by von Hippel *et al.*[41] suggests that the $I^2$ statistic can have substantial bias when the number of studies is small (< 7) and thus the exploration of heterogeneity between the two studies analysed for their hearing threshold data, Robson *et al.* and Hubbard *et al.*, should be interpreted with caution.

It is also important to note that some of these studies are over thirty years old and children may have been falsely categorised as having non-syndromic cleft palate prior to the detection of isolated monogenetic syndromes and it is unclear what impact this has on the aetiology of hearing loss and consequently the efficacy of short-term ventilation tubes. Furthermore, it is assumed that the hearing deficits noted in these children are primarily conductive, but the lack of raw audiometric data limited the investigation of whether mixed or sensorineural hearing loss was contributory.

The included studies were primarily from North America and Europe (USA (n=1), UK(n=2) and Serbia (n=1) which limits the extrapolation of data to other populations. The included studies were also limited to those published in the English language which limited the amalgamation of all the available evidence. The quality of the studies was generally poor due to several factors. They were small with no formal sample size calculations and therefore may have been underpowered to demonstrate any statistically significant effects of intervention. The small sample sizes also limited capacity stratification of age-groups and thus no comment could be made regarding severity in certain age ranges and whether age may be a potential factor in the timing of intervention. The small number of included studies also limited the capacity to assess for risk of publication bias.

The reporting of study outcomes was inconsistent and often missing confidence intervals, making it difficult to estimate the magnitude of effect in studies. Variations in

the measurement of outcomes further contributed to the difficulties encountered with pooled analysis, particularly when considering speech and language outcomes. A validated tool for assessing cleft speech was developed in 2006.[42] which also gives an indication of treatment needs and continuing burden of care from a health economics perspective. The use of a standardised and validated tool to measure speech and language development would not only be useful when assessing outcomes between intervention groups but also between international cohorts, allowing the results to be translatable across various populations.

Classification of palate type was poorly described across all studies children with submucous cleft were commonly excluded[29] despite studies suggesting this condition also carries a significant burden of otological disease despite no overt defect in the palate or lip.[43]

The evidence that guides current practice comes from studies in children without cleft palate with COME which includes randomised controlled trials.[44, 45] However, children with cleft lip and palate have notable higher rates of COME and tend to develop symptoms much earlier than their non-cleft counterparts, thus these findings may not be generalizable for this cohort. Unfortunately, comparison between the non-syndromic cleft palate and non-cleft populations was beyond the scope of this review but it would give useful insights into the long-term outcomes of short-term ventilation tubes versus surveillance when comparing children with and without cleft palate.

**Conclusion**

This systematic review highlights the lack of data available to provide an evidence base for the management COME in children with non-syndromic palate. Given the

inconsistencies in the measurement of outcomes, it is difficult to provide a useful summary for clinicians.

The findings of this review suggests that the use of short-term ventilation tubes is associated with higher otological complications and that a conservative approach does not lead to worse outcomes, provided this cohort is closely monitored for hearing deficits that may lead to impaired speech and language acquisition. Agreement is necessary regarding reporting of mean hearing thresholds, speech and language outcomes and the assessment of otological complications and their severity to facilitate aggregation of data across studies and ultimately, appropriate informed consent when counselling parents and caregivers about these interventions.

It's clear that there is a need for further studies in cleft lip and palate population, in particular, a well conducted, adequately powered multi-centre RCT. Future research in this area should also be extended to investigate impact of cleft type and severity on hearing outcomes.

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# CHAPTER 4: ANALYSIS OF INCLUDED STUDIES

## 4.1 Introduction

Poorly reported research is a significant limiting factor to the synthesis of existing evidence and impedes on the capacity to assess research quality[38]. One of the limiting factors of the included systematic review was the inconsistent reporting of the outcomes of interest, unclear management of missing data, failure to address potential sources of bias within the research methodology and this was explored using a gaps analysis. Reporting guidelines for different study designs [51] are integral to facilitate reproducibility of research methods, critical appraisal, and increased transparency of peer review process. This chapter details the gaps analysis that was undertaken of the four included studies and the limitations identified with reference to the reporting guideline developed for observational studies (STROBE)[38] by the Equator Network. This is an international initiative that aims to improve the quality of health research publications. The manuscript has been accepted and published in the Journal of Research Methods in Medicine & Health Sciences.

# Statement of Authorship

| | |
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| Contribution to the Paper | Data collection and analysis, interpretation of data, preparation of manuscript and acted as corresponding author | | |
| Overall percentage (%) | 85% | | |
| Certification: | This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper. | | |
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By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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| Signature | | Date | 22/20/2022 |

## 4.2 Manuscript of '*Poor reporting quality of observational studies in children with non-syndromic cleft palate makes evidence synthesis difficult'*

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**Abstract**

**Objective:** To assess the reporting quality of observational studies included in a systematic review of the management of chronic otitis media with effusion in children with non-syndromic cleft lip and palate using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

**Methods**: Medline, CINAHL, Scopus and Embase, were searched for studies comparing the use of ventilation tubes to surveillance. Two reviewers screened potential eligible articles, extracted data independently and assessed reporting quality using the STROBE checklist.

**Results**: The median compliance rate with individual STROBE items was low at 25% (range:0 -100%) with 11 of the 22 items not reported in any of the studies. Items reported inconsistently pertained to potential sources of bias, sample size calculations, how loss to follow-up was addressed and management of missing data.

**Conclusion**: The development of this systematic review highlights the inadequate reporting standards in this field. Differences in the way the outcomes are defined, reported, and measured leads to variability in the observed intervention effects and

difficulty in interpreting the true effect size. Future researchers are encouraged to use STROBE guidelines for the design and reporting of observational studies in this field.

## 1. Introduction

Cleft lip and palate are common congenital malformations that result in variable defects of the lip, soft and hard palate.[1] Due to the abnormal insertion of the muscles of the soft palate, there is impaired formation and function of the eustachian tube which normally helps to drain any fluid in the middle ear.[2] Thus, there is a strong association between cleft lip and palate and chronic otitis media with effusion (COME). This chronic inflammation of the middle ear develops within the first year of life which is the primary developmental period for speech and language.[3, 4] COME can persist even after surgical repair of the lip and palate defect, and if not appropriately managed, can eventually lead to deafness. It is important that this condition is managed in a timely manner to ensure that the developmental milestones of these children are at par with their peers, as well as mitigating the associated costs to the public health system.[5]

A recent systematic review conducted to determine the best management for chronic otitis media with effusion in children with non-syndromic cleft palate could not derive concrete conclusions regarding the most effective management. Undertaking the review highlighted the difficulties in evidence synthesis that are brought about by inconsistent and incomplete reporting of outcomes in observational studies, especially when reporting guidelines are not utilised.

Clinicians and policy makers rely on published evidence to help guide decision-making.[6] It is well documented in medical literature that vital information about how outcomes were measured and analysed is often missing or poorly reported. A lack of transparency in reporting study outcomes limits the synthesis and generalisability of results, and overall contributes to reporting biases. This has the potential to bias not only the conclusions of meta-analyses and systematic reviews, but also has far-reaching

impact in the development of inaccurate clinical protocols. To minimise this, various reporting guidelines have been developed for different types of studies to facilitate consistent and reproducible methodology. One such guideline is the STRengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement which was developed and published in 2015.[7] It comprises of a checklist of 22 items which relate to the title, abstract, introduction, methods, results and discussion sections of articles. The STROBE statement provides guidance to authors to facilitate the transparency and completeness of reporting in observational studies.

Medical research is largely observational, and many clinical guidelines are based on evidence gleaned from observation studies[8] especially when randomised controlled trials cannot be conducted due to ethical or logistical considerations. The STROBE checklist is a useful tool to evaluate the reporting quality of the included studies in order to highlight the gaps and to facilitate more robust methodology in this field in the future.

## 2. Methods

The review was conducted in accordance with JBI methodology for systematic reviews of effectiveness[9] and the protocol was registered with PROSPERO (CRD42021255861)[5]. The outcomes of interest in the review were hearing thresholds, speech and language development and otological complications and these were informed by a study that integrated the views of clinical and non-clinical stakeholders in developing core outcomes sets for children with otitis media with effusion and cleft palate.[10]

### 2.1 Quality assessment of included studies

The studies were compared to the 22 item STROBE checklist by two independent reviewers. Each item was assessed with a response option of ‘present’ or ‘absent’ depending on whether the study included that checklist item, and any disagreements were reconciled by re-reading the study. Data processing was completed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA).

## 2 Results

Four articles were identified that fit the review’s inclusion criteria. All four included studies were cohort studies[11-14], three of them retrospective and one prospective. The characteristics of the studies are summarised in Table 1.

**Table 1: Characteristics of included studies**

| Author (year) | Country | Study design | Total participants n, intervention n, control | Age range | Cleft classification | Inter-vention | Follow-up period | Outcomes measures |
|---|---|---|---|---|---|---|---|---|
| **Robson (1992)[14]** | UK | Retros pective cohort | 70 participants<br>38<br>32 | 6 mo – 12 yrs | Complete vs incomplete | Ventilation tubes<br>Observation | 5 years | - Hearing<br>- Speech/ language<br>- Retympanosto my rate<br>- Presence of effusion<br>- Otological complications |
| **Šubarević (2015)[13]** | Serbia | Prospe ctive cohort | 90 participants<br>45<br>45 | 6mo – 5 yrs | Not specified | Ventilation tubes<br>Observation | 5 years | - Hearing<br>- Speech/ language<br>- Tympanogra m type<br>- Presence of effusion<br>- Otological complications |
| **Hubbard (1985)[11]** | USA | Retros pective cohort | 48 participants<br>24<br>24 | 5 – 11 yrs | Complete vs incomplete | Early ventilation tubes<br>Observation/ Delayed ventilation tubes at >36 months | Not specified | - Hearing<br>- Speech/ language<br>- Tympanogra m type<br>- Presence of effusion<br>- Otological complications |
| **Shaw (2003)[12]** | UK | Retros pective audit | 72 participants<br>20<br>52 | Not speci-fied | LAHSHSAL[1] | Ventilation tubes<br>Observation | Not specified | - Speech/ language |

Table 2 shows the proportion of studies that satisfied each check-list item on the STROBE checklist and the inter-observer agreement for each item. The inter-observer agreement (Cohen's kappa) between the two reviewers varied between for 0.5 to 1.0 which suggests moderate to complete agreement.[157] The median compliance rate with individual STROBE items was very low at 25% (range:0-100%). Eleven of the 22 items addressed in STROBE were not reported in any of the studies, which means no study achieved a high reporting quality label (greater than 15 items reported). These items pertained to reporting potential sources of bias, sample size calculations, sensitivity analyses, how loss to follow-up was addressed, management of missing data, discussion regarding external validity and explicit statements regarding sources of

funding. The study by Hubbard *et al.*[11] had the highest score with 12/22 STROBE items reported and Shaw *et al.*[12] had the lowest with 7/22 items reported.

More specifically, reporting in the title and abstract, and introduction section was completed satisfactorily in all studies with rates of 81% on average. Reporting within the methods and results sections was often unclear resulting in an increased risk of bias. The average reporting rate for the study methods section was 38% with minimal documentation on how missing data was addressed, reasons for non-participation or clear definitions of outcomes and potential confounders. Reporting of results was slightly better at 56%, but discussion of study limitations was notably lacking.

The handling of quantitative variables and use of appropriate statistics was only appropriately reported in two studies which significantly affected capacity for pooled analysis for the review, particularly for the three main outcomes of interest: hearing thresholds, speech and language development and otological complications.

## Table 2: Reporting quality of included studies using STROBE checklist (n = 4)

| Item | | Criteria to score as adequately reported | Proportion (%) | Kappa |
|---|---|---|---|---|
| ***TITLE AND ABSTRACT*** | | | | |
| *1(a)* | | Indicate the study's design with a commonly used term in the title or the abstract | 100 | 1.0 |
| *1(b)* | | Provide in the abstract an informative and balanced summary of what was done and what was found | 100 | 1.0 |
| ***INTRODUCTION*** | | | | |
| *2* | ***Background/ rationale*** | Explain the scientific background and rationale for the investigation being reported | 100 | 1.0 |
| *3* | ***Objectives*** | State specific objectives, including any prespecified hypotheses | 25 | 0.5 |
| ***METHODS*** | | | | |
| *4* | ***Study design*** | Present key elements of study design early in the paper | 100 | 1.0 |
| *5* | ***Setting*** | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 50 | 0.9 |
| *6(a)* | ***Participants*** | Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 75 | 0.7 |
| *6(b)* | | Cohort study—For matched studies, give matching criteria and number of exposed and unexposed | 25 | 0.9 |
| *7* | ***Variables*** | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 25 | 0.8 |
| *8** | ***Data sources*** | For each variable of interest, give sources of data and details of methods of assessment (measurement). | 100 | 1.0 |
| *9* | ***Bias*** | Describe any efforts to address potential sources of bias | 0 | 1.0 |
| *10* | ***Study size*** | Explain how the study size was arrived at | 0 | 1.0 |
| *11* | ***Quantitative variables*** | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | 50 | 0.9 |
| *12(a)* | ***Statistical Methods*** | Describe all statistical methods, including those used to control for confounding | 75 | 0.5 |
| *12(b)* | | Describe any methods used to examine subgroups and interactions | 0 | 1.0 |
| *12(c)* | | Explain how missing data were addressed | 25 | |
| *12 (d)* | | Cohort study—If applicable, explain how loss to follow-up was addressed | 0 | 0.9 |
| *12(e)* | | Describe any sensitivity analyses | 0 | 0.9 |
| ***RESULTS*** | | | | |
| *13*(a)* | ***Participants*** | Report the numbers of individuals at each stage of the study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 100 | 0.7 |
| *13*(b)* | | Give reasons for non-participation at each stage | 25 | 1.0 |
| *13*(c)* | | Consider use of a flow diagram | 0 | 1.0 |
| *14*(a)* | ***Descriptive data*** | Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders | 75 | 1.0 |
| *14*(b)* | | Indicate the number of participants with missing data for each variable of interest | 25 | 0.8 |
| *14*(c)* | | Cohort study—Summarise follow-up time (e.g., average and total amount) | 50 | 1.0 |
| *15** | ***Outcome Data*** | Cohort study—Report numbers of outcome events or summary measures over time | 25 | .8 |
| *16(a)* | ***Main results*** | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their | 0 | 1.0 |

| | | | | |
|---|---|---|---|---|
| | | precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included | | |
| *16(b)* | | Report category boundaries when continuous variables were categorized | 0 | 1.0 |
| *16(c)* | | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 0 | 0.8 |
| *17* | ***Other analyses*** | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | 0 | 1.0 |
| ***DISCUSSION*** | | | | |
| *18* | ***Key results*** | Summarise key results with reference to study objectives | 100 | 1.0 |
| *19* | ***Limitations*** | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 25 | 0.7 |
| *20* | ***Interpretation*** | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 100 | .9 |
| *21* | ***Generalisability*** | Discuss the generalisability (external validity) of the study results | 0 | 1.0 |
| ***OTHER INFORMATION*** | | | | |
| *22* | ***Fundings*** | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 0 | 1.0 |

The results of the evaluation against the STROBE checklist are similar to the results of critical appraisal using standardized instruments from JBI for observational studies that was included in the review (see Table 3).[9] Hubbard *et al.* also had the highest score, satisfying 8 out of 11 questions, and Shaw *et al.* had the lowest score at 2 out of 11.

**Table 3: Critical Appraisal of eligible cohort studies**

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Šubarević *et al.* | Y | Y | Y | U | U | N | Y | Y | N | N | Y |
| Shaw R *et al.* | Y | Y | N | N | N | U | U | U | N | N | U |
| Robson *et al.* | Y | Y | Y | U | U | Y | Y | Y | U | U | Y |
| Hubbard *et al.* | Y | Y | Y | Y | Y | N | Y | Y | N | N | Y |

Y, yes; U, unclear; N, no; JBI appraisal checklist for cohort studies
Q1 = Were the two groups similar and recruited from the same population?
Q2 = Were the exposures measured similarly to assign people to both exposed and unexposed groups?
Q3 = Was the exposure measured in a valid and reliable way?
Q4 = Were confounding factors identified?
Q5 = Were strategies to deal with confounding factors stated?
Q6 = Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
Q7 = Were the outcomes measured in a valid and reliable way?
Q8 = Was the follow up time reported and sufficient to be long enough for outcomes to occur?
Q9 = Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
Q10 = Were strategies to address incomplete follow up utilized?
Q11 = Was appropriate statistical analysis used?

## 3. Discussion

Comparison against the STROBE checklist highlights that the reporting quality of the studies included in the review was insufficient in key methodological areas, including reporting potential sources of bias, reporting of outcome data and discussion of limitations. Furthermore, a risk of bias assessment using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) found that the quality of the studies was considered low with a moderate to high risk of bias.[16] This had significant impact on conclusions that can be derived for the three main outcomes of interest. Ultimately, there is a lack of good quality evidence to support the insertion of short-term ventilation tubes as the mainstay treatment or close surveillance as an alternative. Each of outcomes considered had several limitations that hindered evidence synthesis.

### *Hearing thresholds*

Hearing thresholds are normally measured with an audiometer to determine the volume of sound that can be perceived by an individual in decibels over different frequencies.[17] It is commonly accepted that a measurement greater than 21 decibels at any frequency is considered a hearing deficit. However, this ranged from 16-25 decibels in different studies resulting in study participants being considered as having hearing loss in some studies but normal hearing in others.

Furthermore, each study that was included in the systematic review reported their data in various formats. Most studies gave a mean with either a range, confidence interval or standard deviations. The calculations required to transform these values into uniform data for pooled analysis creates opportunities for errors that can be inaccurately interpreted as statistically significant. Unfortunately, none of the authors replied to requests for raw data and this was likely exacerbated by the fact that some of the studies were over 30 years old and the data may no longer be available.[11, 14]As a core outcome measure for this population group, consensus on what is considered hearing loss is vital. In addition, documentation of mean hearing thresholds as unadjusted estimates and with consistent measure of statistical precision i.e., confidence interval needs to be established to allow for accurate aggregation of data for meta-analysis.

### *Speech and language development*

Speech and language development is another core outcome that had significant variability in measurement and reporting between studies. Each of the four included studies measured speech and language development differently. Two studies noted only the proportion of participants that needed speech pathologist input and how many

sessions were required with no descriptions regarding the pathologies that were being assessed.[13, 14] The other two studies considered nasal resonance and consonant articulation but each study used a different scale.[11, 12] The lack of uniformity in the measurement of speech and language outcomes as well as the lack of quantitative data limited the systematic review to descriptive analysis of this outcome.

A validated tool for assessing cleft speech was developed in 2006 for use in inter-centre audit studies. It was noted to have moderate to high intra- and inter-examiner reliability and has been recommend for use in the United Kingdom and Ireland with potential extension to other English-speaking countries.[18] This tool is particularly useful as it also gives an indication of treatment needs and continuing burden of care from a health economics perspective. The use of a standardised and validated tool to measure speech and language development would not only be useful when assessing outcomes between intervention groups but also between international cohorts, allowing the results to be translatable across various populations.

***Otological complications***

Complications arising from each intervention are important considerations for clinicians when recommending any treatment to a patient and were reported in all four included studies. One study reported the proportion of the participants that had any complication between the intervention and comparator groups but did not specify what they considered as complications.[13] The remaining three studies gave a breakdown of each complication and the proportion of participants affected [11, 12, 14] but there was no clear documentation about when these complications were noted within the study period.

This could have significant impact on the results as some of these complications can to self-resolve if given enough time.

Several common complications noted amongst all studies that either contribute to permanent hearing loss, like perforation and cholesteatoma, or can affect a child's quality of life like persisting ear discharge. While it may be difficult to pick which of these complications is the most important or contributes the most significantly, agreement on how these complications are reported would allow for better evaluation of the true complication rate of each intervention and appropriate counselling for parents and caregivers.

Inconsistencies in reporting also extend to reporting requirements by journals. When considering the overall use of reporting guidelines in otolaryngology journals, uptake is less than 50%.

## 4. Conclusion

Although research quality is not directly related to the reporting quality of a study, poor reporting impedes on accurate assessment of the research quality. The development of this systematic review highlights the inadequate reporting standards for studies in this area. The differences in the way the outcomes are defined, reported, and measured between studies could lead to differences in the observed intervention effects, and difficulty in interpreting the true effect size. [7, 19] This impacts on the capacity to aggregate and synthesize these studies and limits their overall generalisability. While the difficulties associated with translating research to clinical practice are multifactorial, poorly reported study outcomes are a significant contributing factor.[7, 19]

Given the constraints that can be associated with conducting randomised trials, observational studies offer useful insights in medical research and the development of

clinical guidelines, but this can only be achieved when studies employ rigorous methodology in their design and are transparent in reporting against standardised criteria for methods and outcomes. One way to achieve this is through the use of reporting guidelines.

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# CHAPTER 5: DISCUSSION

The use of ventilation tubes dates back to as the early 19th century and has remained the mainstay treatment for children with otitis media with effusion,[52] but the procedure is not without complications.[6] Evidence regarding the benefits of short-term ventilation tubes in the general paediatric population is scant and of poor quality and even more so in children with cleft lip and palate as is reflected in the results of the review.[35, 53]

Significant levels of heterogeneity were observed in the included studies. Hearing thresholds were pooled based on estimated data extracted from the published material.[54] Given the small number of studies, their observed clinical and methodological similarities and sample sizes, a fixed-effects model was initially used to statistically analyse the data. Heterogeneity was assessed with the $I^2$ statistic [55]

The overall effect size from the fixed-effects model favoured conservative management, however, the $I^2$ showed significant statistical heterogeneity between the studies (93%). The results from the fixed-effects model suggested unobserved heterogeneity between the two studies and to try and mitigate this, a random-effects model was trialled. This model is generally more appropriate for a larger number of studies (n>5) but the results can be generalised beyond the included studies.[55] While there was a marginal decrease in heterogeneity using the random effects model (89%), neither management option was supported, and the confidence interval was notably wider. It should be acknowledged that each model has its limitations when trying to derive the true estimated effect and caution should be taken when interpreting both models. Both the fixed and random effects models represent a more traditional approach to meta-analysis and have recently been critiqued by statisticians as being flawed. [56] Furthermore, the $I^2$ statistic has been found to be substantially biased when

the number of studies is less than 7, in which case 95% confidence interval should be reported instead.[57] The small number of studies included in the analysis also limited the capacity for the effects of potential publication bias to be investigated. Overall, the difficulty in establishing the true effect size from both models highlights the paucity of well conducted studies in this field.

To facilitate transparent reporting where pooled analysis was not possible, the Synthesis Without Meta-analysis (SWiM) reporting guideline was used.[58] The evidence derived was inconclusive regarding the effect of either management option on speech and language outcomes as each study used a different assessment tool. However, all studies found no significant difference between those treated with VT and those managed conservatively. The data for tympanometry and presence of effusion suggested that VT have little effect on the tympanogram type or resolution of middle ear effusion in the long-term but again, there was notable variability in the results reported by each study. As expected, the cohort treated with VT had a higher repeat tympanostomy rate, but this was only reported in one study.[29] Otological complications were inconsistently reported between studies, but each study reported that participants treated with VT had a higher complication rate than those managed conservatively.

More broadly, despite the rigorous search strategy, only four observational cohort studies were found that fit the inclusion criteria, three retrospective [6, 29, 59] and one prospective. [60] A large number of studies could not be included due the presence of participants with both syndromic and non-syndromic cleft lip and palate. Some studies did make distinctions about number of participants with a particular syndrome,[61-63] but data was analysed as a single cohort. Children with syndromic cleft lip and palate often have other abnormalities of the craniofacial skeleton and cranial nerves that lead to a mixed conductive and sensorineural hearing loss that cannot be rectified with

ventilation tubes alone.[3] A similar issue was noted with lack of inclusion of submucous cleft despite evidence suggesting that these children suffer a similar burden of otological disease despite having no overt cleft.[64]

Racial variation does exist in the prevalence of orofacial clefting globally, with the highest rates reported among Asian populations, however, this was not reflected in the distribution of included studies which were primarily from North America and Europe. Only Hubbard *et al.* gave a description of the race of the participants in their study. It is also important to acknowledge that classification of syndromic versus non-syndromic cleft lip and palate is primarily based on the phenotypic appearance of the child, where common cleft-associated syndromes will have characteristic facial morphology.[3] If the cleft lip and palate appears as an isolated defect or if the syndrome cannot be identified, this is termed non-syndromic. Genetic testing is an evolving field and has only recently been employed in diagnosing the aetiology of clefting. It is therefore likely that some children have been falsely categorised as having non-syndromic cleft lip and palate in the included studies. Given the small number of studies and sample sizes, it is unclear what effect the lack of racial diversity, mixing of cleft populations and exclusion of certain cleft types has had on the generalisability of the results of pooled analysis.[65]

Retrospective studies are easier to conduct because of the immediate availability of data, however, there is limited control over the specific data that can be used. The existing data may be incomplete, inaccurate, or inconsistently measured which contributes to information bias [66], and this was often the case for the included studies. Authors were contacted but did not respond regarding requests for missing or incomplete data sets. Furthermore, despite several attempts through different sources, a significant proportion of studies could not be retrieved for full text analysis (n=35) (See Appendix III) despite meeting inclusion criteria in the title and abstract screening

process.  This had a significant impact on pooled statistical analysis, particularly of the secondary outcomes, and thus narrative synthesis was used. The potential effects of selection bias should also be considered where investigators may preferentially pick participants with complete data sets who may not be a true representative sample of the target population. This could account for the significant statistical heterogeneity seen in the pooled analysis of hearing thresholds. Selection bias, especially when randomisation is not possible, can have varying effects and the magnitude and direction of the effect is often hard to verify. [67]

The poor methodological quality and moderate risk of bias of the included studies was reflected in the critical appraisal using JBI critical appraisal tool for cohort studies (see Appendix I), and the assessment of certainty of evidence using the GRADE approach found low to very low quality of evidence for all outcome variables measured.

Exploration of the methodological quality in chapter 4 highlighted the benefits of using reporting guidelines to clearly outline the methodological approach of observational studies and reporting of outcomes, to decrease the risk of bias that can be inherent to retrospective studies with small sample sizes. The STRengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline[38] is one example that was developed in 2015. Comparison of the four included studies to the STROBE checklist detailed in chapter 4 yielded similar results to the JBI critical appraisal checklist and highlights how poor methodology and outcome reporting impedes on the accurate assessment of research quality.

## 5.1 Conclusion

No concrete conclusions could be drawn regarding the most effective management strategy for COME in children with non-syndromic cleft lip and palate from the available data. However, the evidence suggests that the insertion of VT potentially carries a higher complication rate without offering any additional benefits to long-term hearing. Managing children with non-syndromic cleft palate conservatively following repair of the cleft defect does not significantly impede their speech and language development or result in long-term conductive hearing loss, provided that the children are closely monitored so that any critical hearing deficits can be detected and treated in a timely manner.

A multicentre randomised controlled trial reported in line with the CONSORT criteria would be beneficial in further clarifying this clinical question. This study design when implemented rigorously, reduces the risk of systematic errors such as selection and detection bias, that are intrinsic to observational study designs to maintain internal validity and provide a true estimate of effect. The design of future trials could include separate reporting of outcomes between cleft and non-cleft populations following VT insertion, and the impact of cleft type and severity on otological outcomes could also be considered.

Agreement regarding defined parameters for outcome measurements is necessary in addition to the use of validated tools of assessment. This allows for comparison between different interventions and population groups and minimises the effect of detection bias. Currently, there is a lack of high-quality evidence to confidently inform clinical decision making.

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# APPENDICES

## Appendix I: Search Strategies

### Search strategy – MEDLINE (PubMed)

("child"[MeSH Terms] OR ("preschool child*"[Title/Abstract] OR "preschool child*"[Text Word]) OR ("child, preschool"[MeSH Terms] OR ("child"[All Fields] OR "Preschool"[All Fields]) OR "preschool child"[All Fields] OR "preschooler*"[All Fields] OR "Preschool"[All Fields]) OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields])) OR ("newborn infant"[All Fields] OR "neonatal"[All Fields] OR "neonat*"[All Fields] OR ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields])) OR "infant, newborn"[MeSH Terms] OR "child, preschool"[MeSH Terms] OR ("toddler"[All Fields] OR "toddler s"[All Fields] OR "toddlers"[All Fields]) OR ("adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "teenage*"[All Fields])) AND ((((("cleft palate"[MeSH Terms] OR ("cleft"[All Fields] AND "palate"[All Fields]) OR "cleft palate"[All Fields]) AND ("nonsyndromal"[All Fields] OR "nonsyndromic"[All Fields])) OR ("Orofacial"[All Fields] AND ("cleft"[All Fields] OR "cleft*"[All Fields] OR "Cleft lip and palate"[All Fields] OR ("cleft lip"[MeSH Terms] OR ("cleft"[All Fields] AND "lip"[All Fields]) OR "cleft lip"[All Fields]))) AND ("otitis media with effusion"[MeSH Terms] OR ("otitis media with effusion"[MeSH Terms] OR ("otitis"[All Fields] AND "media"[All Fields] AND "effusion"[All Fields]) OR "otitis media with effusion"[All Fields] OR ("secretory"[All Fields] AND "otitis"[All Fields] AND "media"[All Fields]) OR "secretory otitis media"[All Fields]) OR ("otitis media with effusion"[MeSH Terms] OR ("otitis"[All Fields] AND "media"[All Fields] AND "effusion"[All Fields]) OR "otitis media with effusion"[All Fields] OR ("serous"[All Fields] AND "otitis"[All Fields] AND "media"[All Fields]) OR "serous otitis media"[All Fields]) OR ("otitis media with effusion"[MeSH Terms] OR ("otitis"[All Fields] AND "media"[All Fields] AND "effusion"[All Fields]) OR "otitis media with effusion"[All Fields] OR ("middle"[All Fields] AND "ear"[All Fields] AND "effusion"[All Fields]) OR "middle ear effusion"[All Fields]))) OR ("grommet*"[All Fields] OR (("middle ear ventilation"[MeSH Terms] OR ("middle"[All Fields] AND "ear"[All Fields] AND "ventilation"[All Fields]) OR "middle ear ventilation"[All

Fields] OR "tympanostomies"[All Fields] OR "tympanostomy"[All Fields]) AND "tube*"[All Fields])))

**Search Strategy – Embase**

'tympanostomy tube'/mj OR 'armstrong (tympanostomy tube)' OR 'armstrong v grommets' OR 'goode t-tube' OR 'ear ventilation tube' OR 'grommet' OR 'middle ear tube' OR 'tympanic ventilation tube' OR 'tympanic ventilation tube (physical object)' OR 'tympanostomy tube' OR 'ventilating tube, ear' OR 'ventilation tube (ear)' OR grommet OR (('child'/mj OR 'child' OR 'children' OR 'infant'/exp OR 'infant' OR 'toddler'/exp OR 'toddler' OR 'toddlers' OR 'newborn'/exp OR 'child, newborn' OR 'full term infant' OR 'human neonate' OR 'human newborn' OR 'infant, newborn' OR 'neonate' OR 'neonatus' OR 'newborn' OR 'newborn baby' OR 'newborn child' OR 'newborn infant' OR 'newly born baby' OR 'newly born child' OR 'newly born infant' OR 'adolescent'/exp OR 'adolescent' OR 'teenager') AND ('secretory otitis media'/mj OR 'effusion, middle ear' OR 'exudative otitis media' OR 'middle ear effusion' OR 'otitis media exsudative' OR 'otitis media with effusion' OR 'secretory otitis media') AND ('cleft lip palate'/exp/mj OR 'cleft lip palate'/mj OR 'cleft lip and palate' OR 'cleft lip palate' OR 'cleft palate lip' OR 'labiopalatoschisis' OR 'palatolabioschisis' OR 'cleft lip with or without cleft palate'/exp/mj OR 'nonsyndromic cleft lip with or without cleft palate'/exp/mj))

**Search Strategy – CINAHL**

(MH Child+ OR MH Adolescence+ OR TX (Children OR child OR adolescen* OR teen* OR infant* OR preschool*)) AND (MH "Cleft Palate" OR MH "Cleft Lip" OR TX ("orofacial cleft*" OR "cleft palate*" OR "cleft lip*")) AND (MH "Otitis Media with Effusion" OR MH "Middle Ear Ventilation" OR TX ("serous otitis media" OR “secretory otitis media” OR “middle ear effusion” OR "grommet*" OR "ventilation tube*" OR "tympanostomy tube*" OR "middle ear ventilation" OR "otitis media with effusion"))

**Search Strategy – Scopus**

TITLE-ABS-KEY ((child* OR paediatric OR pediatric OR infant OR toddler OR adolescent* OR teenage*) AND (("cleft palate*") OR "cleft lip and palate*" OR "cleft palate and lip*" OR "non-syndromic cleft palate") AND ("otitis media with Effusion" OR "serous otitis media" OR "secretory otitis media" OR grommet* OR "tympanostomy tube*" OR "armstrong" OR "t-tube*" OR "middle ear ventilation" OR "ventilat* tube"))

## JBI Critical Appraisal list for Cohort Studies

Reviewer_____

Date_____

Author_____Year_____ Record Number_____

| | Yes | No | Unclear | Not applicable |
|---|---|---|---|---|
| 1. Were the two groups similar and recruited from the same population? | □ | □ | □ | □ |
| 2. Were the exposures measured similarly to assign people to both exposed and unexposed groups? | □ | □ | □ | □ |
| 3. Was the exposure measured in a valid and reliable way? | □ | □ | □ | □ |
| 4. Were confounding factors identified? | □ | □ | □ | □ |
| 5. Were strategies to deal with confounding factors stated? | □ | □ | □ | □ |
| 6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? | □ | □ | □ | □ |
| 7. Were the outcomes measured in a valid and reliable way? | □ | □ | □ | □ |
| 8. Was the follow up time reported and sufficient to be long enough for outcomes to occur? | □ | □ | □ | □ |
| 9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored? | □ | □ | □ | □ |
| 10. Were strategies to address incomplete follow up utilized? | □ | □ | □ | □ |
| 11. Was appropriate statistical analysis used? | □ | □ | □ | □ |

Overall appraisal: Include □ Exclude □ Seek further info □

Comments (Including reason for exclusion)

## Appendix II: Data Extraction Tool

| **Study (Title; author; year; location of study; [Study Type] )** | ***A conservative approach to the management of otitis media with effusion in cleft palate children, Robson et al., 1992, UK (Bristol), [retrospective cohort study]*** | ***Importance of early ventilation tubes insertion in chronic otitis media with effusion in children with congenital cleft palate, Subarevic et al., 2018, Serbia [prospective study]*** |
|---|---|---|
| **Intervention-comparator group** | - VT vs. observation | - Early VT at time of palatoplasty (Shepherd)<br>- Surveillance (6 monthly intervals) |
| **Age Range** | - VT → n=38), average age 6.3 (2-13), M:F 22:16<br>- Observation → (n=32), average age 5.2 (6mo-12years), M:F ratio 14:18 | - 6mo -5years (58% male participants) |
| **Number of participants** | n=70 | N=90 (Experiment and control n=45) |
| **Cleft Type** | - complete vs incomplete - similar proportions in both groups with majority being complete cleft | Not specified |
| **Audiogram Results (decibels) – [PRE INTERVENTION]** | Not specified | - No preintervention results as paper states patients not compliant - commenced at 4 years –<br>o experimental →38% (<20dB- normal) ,42% <30dB), 11% <40dB 9% <50dB<br>o control → 31% (<20dB- normal) ,44% <30dB), 9% <40dB 11% <50dB |
| **Audiogram Results (decibels) – [POST INTERVENTION]** | - 28/31 children with VT tested → 22dB<br>- 21/28 children under surveillance→ 15dB | - 60 months<br>o experimental → 36% (<20dB- normal) 38% <30dB) 16% <40dB 11% <50dB<br>o Control → 29% (<20dB- normal) 47% <30dB) 11% <40dB 11% <50dB -- 60 months |
| **Tympanometry Results (Type A, B, C) – [POST INTERVENTION]** | Not specified | - 5 years<br>- experimental → 53.3% type B, 15.5% type A , 31.1% type C<br>- control→ 57.8% type B, 8.8% type A, 33.3% type c |

| | | |
|---|---|---|
| **Number of ventilation tubes inserted and timing of insertion** | - 21 kids had more than 1 set of VT<br>o Average 1.66<br>o mean age of first grommet 2.8 (1-8 years) - only 1 child had grommets at time of palate repair, all others after | - Not specified |
| **Surveillance Intervals (months)** | - seen at 2.5 and 5 years but no indication of intervals of surveillance | - 6 monthly for 5 years - roughly 9 appts (first review age 2) |
| **Speech and language outcomes** | - No formal speech assessment tool documented<br>- Data available for 39 children with speech therapy assessment at 2.5 and 5 years →<br>- 25 = VT<br>o 10 (40%)- regular assessment<br>o 1 (4%) - second review appointment<br>o 14 (56%)- no formal therapy required<br>- 14 = surveillance<br>o 5 (36%) regular assessment<br>o 9 (64%) needed no formal therapy | - Each child was also monitored by a speech pathologist and no significant differences in the speech development among the subjects were observed (no further details given in the study) |
| **Otological Complications** | -<br>- 18 (47%) children with VT have one or more complications compared to 4 (9%) in surveillance group (statistically significant)<br>- complications of children VT<br>o atelectasis (5.3%), retraction (18.4%)<br>o tympanosclerosis (15.7%)<br>o otorrhoea (5.2%)<br>o perforation 2.6%) | - Experimental group →13%<br>- Control group→ 11% in atrophy, retraction, perforation] - not specifically broken down |
| **Presence of effusion and time taken for resolution of effusion (months)** | - Present in 16 (52%) of VT group and 9 (32%) of surveillance at end of study | - Experimental group → 96% effusion at 6 months and 60% at 5 years<br>- Control group → 93% at 6 months and 64% at 5 years - not statistically significant |

| **Study (Title; author; year; location of study; [Study Type] )** | ***Consequences of unremitting middle-ear disease in early life; Hubbard et al.; 1985; USA, [retrospect cohort study]*** | ***Conservative management of otitis media in cleft palate, Shaw et al.,2003, UK, [retrospective audit]*** |
|---|---|---|
| **Intervention-comparator group** | - Early versus delayed VT insertion | - VT insertion versus surveillance |
| **Age Range** | - age matched pairs 5-6 (12.5.%) 7-8 (27%) 9-11 (60%)<br>- 13 boys and 11 girls | No specified |
| **Number of participants** | N=48, 24 in each group → treated at 2 different centres | N= 72 ( VT n=20; Surveillance n-52) |
| **Cleft Type** | - complete vs incomplete - 16 incomplete vs 8 complete (same number in both groups | - "LAHSHSAL" classification - cleft soft palate only 15 (21%), hard and soft palate 21 (29%), unilateral lip, alveolus, and palate, 28 (39%), bilateral lip, alveolus and palate 8 (11%). |
| **Audiogram Results (decibels) – [PRE INTERVENTION]** | Not specified | Not specified |
| **Audiogram Results (decibels) – [POST INTERVENTION]** | - average values given for all participants and at all frequencies (0.5, 1 and 2 kHz)<br>o 6.1 vs 11.7 dB left ear, 5.8 vs 9.4 dB right ear (those with early grommets did better (small magnitude of difference therefore not that clinically important)) | Not specified |
| **Tympanometry Results (Type A, B, C) – [POST INTERVENTION]** | - completed per ear<br>o Early grommets vs observation → 33 vs 27 type A ; 4 vs 7 type C; 2 vs 2 type B - 9 vs 10 perforation or tympanostomy present and 2 not reported | Not specified |
| **Number of ventilation tubes inserted and timing of insertion** | - early grommets → majority at <3 months, 16/24 (66%) and remaining at 4-12 months 8/24 (33%)<br>- observation → at >36 months 13/24 (54%) , 13-36 months 5/24 (21%), 4-12 months 3/24 (12.5%) ,<3 months (4%) 1/24 and 2 who didn't have grommets (8.3%) | Not specified |

| | | |
|---|---|---|
| **Surveillance Intervals (months)** | Not specified | Not specified |
| **Speech and language outcomes** | - speech evaluation done via assessment of nasal resonance - normal 11 vs 15, hyponasal 5 vs 2 and hypernasal 8 vs 7 as well as consonant articulation testing | - "cleft audit protocol for speech - resonance (0-3) and articulation (0-3) - more severe cases of clefting the resonance outcome seemed better for those who received grommets. This benefit in speech, however, was not statistically significant. patients who received grommets seemed to have better speech articulation although these differences did not reach statistical significance." |
| **Otological Complications** | - perforation 6 vs 3/36, retraction 5vs 2/36; atelectasis 2vs 2/36, tympanosclerosis 20vs 22/36 | Not specified |
| **Presence of effusion and time taken for resolution of effusion (months)** | - normal appearance 10 vs 10<br>- active otitis media 2vs 2 (no significant difference in appearance between both groups) | Not specified |

## Appendix III: Excluded studies

### Foreign Language papers

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**Wrong study design**

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## Appendix IV: Characteristics of included studies

| Author (year) | Country | Study design | Total participants n, intervention n, control | Age range | Cleft type classification | Intervention | Follow-up period | Outcomes measures |
|---|---|---|---|---|---|---|---|---|
| **Robson (1992)** | UK | Retrospective cohort | 70 participants<br>38<br>32 | 6 mo – 12 yrs | Complete vs incomplete | Ventilation tubes<br>Observation | 5 years | - Hearing<br>- Speech/language<br>- Repeat tympanostomy rate<br>- Presence of effusion<br>- Otological complications |
| **Ŝubarević (2015)** | Serbia | Prospective cohort | 90 participants<br>45<br>45 | 6mo – 5 yrs | Not specified | Ventilation tubes<br>Observation | 5 years | - Hearing<br>- Speech/language<br>- Tympanogram type<br>- Presence of effusion<br>- Otological complications |
| **Hubbard (1985)** | USA | Retrospective cohort | 48 participants<br>24<br>24 | 5 – 11 yrs | Complete vs incomplete | Early ventilation tubes<br>Observation/ Delayed ventilation tubes at >36 months | Not specified | - Hearing<br>- Speech/language<br>- Tympanogram type<br>- Presence of effusion<br>- Otological complications |
| **Shaw (2003)** | UK | Retrospective audit | 72 participants<br>20<br>52 | Not specified | LAHSHSAL[1] | Ventilation tubes<br>Observation | Not specified | - Speech/language |

[1] A palindrome representing the anatomic structures, proceeding from the patient's right side toward left side. Each letter of the of the acronym confirms involvement of that part of the anatomy as well as the severity of the clefting.

## Appendix V: Raw data for Otological complications

| Study | Intervention group | Controls group | Complications (Intervention vs control) |
|---|---|---|---|
| Robson (1992) | 47% | 9% | - Atelectasis – 5.3%<br>- Retraction 18.4%<br>- Tympanosclerosis – 15.7%<br>- Otorrhoea – 5.2%<br>- Perforation 2.6% |
| Ŝubarević (2018) | 13%<br>- | 11% | Not reported |
| Hubbard (1985 | 30% | 26% | - perforation (16.6%) vs (8.3%)<br>- Retraction/ atelectasis (19.4%) vs (11.1%)<br>- Tympanosclerosis (55.5%) vs (61.1%) |