National Institute for Health and Care Excellence

Final

Otitis media with effusion in under 12s

[A] Evidence reviews for the modifiable risk factors for developing OME in children

NICE guideline number NG233

Evidence reviews underpinning recommendations 1.1.10 and 1.2.3 in the NICE guideline

August 2023

Final

This evidence review was developed by NICE

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Review question

What are the modifiable risk factors for developing OME in children under 12 years?

Introduction

The aim of this review is to identify the modifiable risk factors for developing OME in children under 12 years.

Summary of the protocol

See Table 1 for a summary of the Population, Prognostic factors, Comparison and Outcome characteristics of this review.

Table 1: Summary of the protocol

Population	All children under 12 years with suspected otitis media with effusion (OME)
Prognostic factors	Any risk factors, individually or in combination, including: • Upper respiratory tract infection • Household smoking or passive smoking • Exposure to other children (e.g., attending nursery) • Adenoid hypertrophy • Atopic conditions (e.g., allergic rhinitis) • Gastro-oesophageal reflux • Bottle feeding • Dummy use • Breastfeeding • Swimming • Acute otitis media • Vaccination uptake
Comparison	Absence of risk factor(s)
Outcome	**Critical** • Development of first episode/diagnosis OME • Development of persistent OME • Development of fluctuating OME **Important** None

OME: otitis media with effusion

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

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

Prognostic evidence

Included studies

Seven studies were included for this review, 6 prospective cohort studies (De Felice 2008; Hammaren-Malmi 2005; Hong 2008; Kreiner-Moller 2012; Mackenzie 2009; Paterson 2007), and 1 retrospective cohort study (Ogawa 2022).

The included studies are summarised in Table 2.

One study reported paranasal sinusitis (Hong 2008), and 1 study reported coughs/colds, breathing problems, ear infections, fluid or pus discharge from ears, and bed-sharing (Paterson 2007). One study reported household smoking (mother smokes and father smokes) (Hammaren-Malmi 2005), and 2 studies reported exposure to other children (attending day care, childcare, and church) (Hammaren-Malmi 2005; Paterson 2007). One study reported adenoid hypertrophy (De Felice 2008), and 1 study reported eczema (Kreiner-Moller 2012). One study reported exclusive breastfeeding (Paterson 2007), and 2 studies reported pneumococcal vaccination (Mackenzie 2009; Ogawa 2022).

One study excluded children with cleft palate (Hammaren-Malmi 2005), 1 study excluded children with craniofacial anomalies (Mackenzie 2009), and 5 studies did not report data on whether any participants had Down's syndrome, cleft palate or craniofacial anomalies (De Felice 2008; Hong 2008; Kreiner-Moller 2012; Ogawa 2022; Paterson 2007).

Three studies included children aged less than 2 years (De Felice 2008; Hammaren-Malmi 2005; Mackenzie 2009), 1 study included children aged 2 years (Paterson 2007); 2 studies included children aged 6 years and over (Hong 2008; Kreiner-Moller 2012), and 1 study included children aged up to 8 years (Ogawa 2022).

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

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

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

Table 2: Summary of included studies.

Study	Population	Prognostic factor	Outcomes	Comments
De Felice 2008 Prospective cohort study Italy	N=245 VLBW preterm newborns Age in months, mean (SD): NR Sex (male/female): 127/118	• Adenoid hypertrophy	• Development of fluctuating OME (recurrent OME)	The diagnosis of OME was based on otoscopy examination, type B or C tympanogram, ipsilaterally increased threshold at diagnostic ABR evaluation, and ipsilateral absence of transient evoked otoacoustic emissions responses.

Study	Population	Prognostic factor	Outcomes	Comments
				Adenoid hypertrophy determined by otorhinolaryngologist (based on posterior rhynoscopy, tympanometry, and rhynoscopic fibroscopy findings).
Hammaren-Malmi 2005 Prospective cohort study Finland	N=214 Children aged 1-4 years with RAOM or suspected COME; and no history of adenotonsillar or tympanostomy tubes surgery Age in years, mean (SD): 1.9 (NR) Sex (male/female): 112/102	• Household smoking: Mother smokes • Household smoking: Father smokes • Exposure to other children: Attending day care at age <2 years	• Development of persistent OME (COME)	COME was defined as the presence of mucoid, serous or purulent effusion during tympanostomy tubes surgery, or the presence of atrophic or retracted tympanic membrane with effusion. The study did not specify duration of COME. A questionnaire, completed by parents of the children, was used to assess the prognostic factors.
Hong 2008 Prospective cohort study Republic of Korea	N=520 Children aged 1-14 years who underwent adenotonsillectomy with or without ventilation tube insertion Age in years, mean (SD): 6.95 (2.12) Sex (male/female): 343/177	• Paranasal sinusitis	• Development of OME	OME, defined as presence of retention in the middle ear (amber colour, air-fluid level or air-bubble) and type B or C tympanometry; assessed using otoscopy and tympanometry The study did not specify whether OME was first episode, persistent or fluctuating. Paranasal sinusitis defined as the presence of opaque sinuses, fluid level, and gross mucosal thickening in paranasal sinus series and symptoms of rhinorrhea, postnasal drip and nasal obstruction.

Study	Population	Prognostic factor	Outcomes	Comments
Kreiner-Moller 2012 Prospective cohort study Denmark	N=262 Children aged 6 years from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) 2000 birth cohort Age in years, mean (SD): NR Sex (male/female): NR	• Eczema • Non-allergic rhinitis	• Development of OME	The diagnosis of OME was based on otoscopic and tympanometric findings (e.g., B curve or C2 curve or children with tubes). The study did not specify whether OME was first episode, persistent, or fluctuating. Eczema defined according to Hanifin and Rajka criteria. Non-allergic rhinitis defined as rhinitis without sensitisation or with sensitisation that is not accompanied by symptoms upon exposure.
Mackenzie 2009 Prospective cohort study Australia	N=148 Children from Aboriginal communities with a high burden of sever otitis Age in days at first examination, mean (SD): Pneumococcal vaccination: 41 (NR) No pneumococcal vaccination: 60 (NR) Sex (male/female): Pneumococcal vaccination: 45/52 No pneumococcal vaccination: 30/21	• Pneumococcal vaccination (PCV7 plus PPV23)	• Development of OME	OME assessed with pneumatic otoscopy, tympanometry and clinic records and defined as type B tympanogram with neutral or mild bulging of tympanic membrane. The study did not specify whether OME was first episode, persistent, or fluctuating. Pneumococcal vaccination group received PCV7 at 2, 4 and 6 months of age and PPV23 at 18 months of age (booster).

Study	Population	Prognostic factor	Outcomes	Comments
Ogawa 2022 Retrospective cohort study Japan	N=2758247 Children aged 0-8 years Age in years, mean (SD): NR, but range: 0-8 Sex (male/female): NR	• Pneumococcal vaccination (PCV7 era) • Pneumococcal vaccination (PCV13 era)	• Development of OME (reported as incidence of MTTI)	OME was defined according to ICD-10 criteria. The study reported the incidence of MTTI, rather than rates of OME itself. However, authors reported that about 90% of those with MTTI had OME (based on ICD-10 codes) and10% were suspected to have ROM. The study did not specify whether OME was first episode, persistent, or fluctuating (or whether it was first instance of MTTI).
Paterson 2007 Prospective cohort study New Zealand	N=656 Children were selected from births where at least one parent was a permanent New Zealand resident and of Pacific Islands ethnicity parents Age in months, mean (SD): NR, but median: 24 Sex (male/female): 363/293	• Coughs/colds ≥5 times in past year • Breathing problems ≥5 times in past year • Ear infections in past year • Fluid or pus discharge from ears in past year • Exposure to other children: Attending day care • Exposure to other children: Attending childcare for ≥20 h a week • Exposure to other children: Attending church • Bed-sharing • Exclusive breastfeeding at 6 weeks	• Development of OME	OME was assessed with tympanometry and otoscopy (including pneumatic otoscopy). The study did not specify whether OME was first episode, persistent, or fluctuating.

ABR: auditory brainstem response; COME: chronic otitis media with effusion; ICD-10: the International Classification of Diseases 10th Revision; MTTI: myringotomy with tympanostomy tube insertion; NR: not reported; OME: otitis media with effusion; RAOM: recurrent acute otitis media; ROM: recurrent otitis media; PCV:

pneumococcal conjugate vaccine; PPV23: 23-valent polysaccharide vaccine; SD: standard deviation; VLBW: very low birth weight

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

The evidence was very low quality due to high or moderate risk of bias in some of the domains of the QUIPs checklist and imprecision due to very low number of events.

Prognostic factors for development of OME

Presence of coughs/colds ≥5 times in past year, breathing problems ≥5 times in past year, and ear infections in past year were moderately associated with development of OME. Fluid or pus discharge from ears in the past year and exposure to other children, through attending day care, childcare or church, showed a strong association with development of OME. There was a small association of pneumococcal conjugate vaccine (PCV7 era and PCV13 era) with a reduced risk of developing OME. There was possibly a moderate association between development of OME and paranasal sinusitis (90% confidence interval [CI] 1.04 to 1.88). There was possibly a moderate association between a reduced risk of OME and bed sharing (90% CI 0.50 to 0.99). However, there was no evidence of association between development of OME and eczema, non-allergic rhinitis, exclusive breastfeeding at 6 weeks, or PCV7 plus 23-valent polysaccharide vaccine (PPV23).

Prognostic factors for development of persistent OME (chronic OME)

Household smoking (mother smokes and father smokes) and exposure to other children through attending day care at age <2 years showed no association with development of persistent OME (chronic OME).

Prognostic factors for development of fluctuating OME (recurrent OME)

Presence of adenoid hypertrophy was strongly associated with development of fluctuating OME (recurrent OME).

There were a number of prognostic factors in the protocol that were not reported on by any studies, including gastro-oesophageal reflux, dummy use, swimming, and acute otitis media.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

This review aimed to identify modifiable risk factors for developing OME, and thus development of first episode/diagnosis OME was selected as the critical outcome. The committee were aware that OME may be persistent (chronic) and may recur. Therefore, the committee agreed that it was also important to identify modifiable risk factors associated with the development of persistent OME and fluctuating OME, so these were also chosen as critical outcomes.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The evidence was very low quality due to risk of bias arising from lack of information about recruitment and baseline characteristics, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and presentation summary, and imprecision due to a very low number of events.

No evidence was found for the following prognostic factors: gastro-oesophageal reflux, dummy use, swimming, and acute otitis media.

Benefits and harms

The limited evidence showed that household smoking was not associated with development of persistent OME. However, the evidence was very low quality, and there was no evidence regarding the risk of smoking and development of OME itself. In the committee's experience, household smoking or passive smoking may increase the risk of developing OME Moreover, it is widely accepted that passive smoking has harmful effects and can cause a range of diseases and conditions, including respiratory tract infections that may also increase the risk of OME. Therefore, the committee agreed advising parents and carers to avoid exposing their children to tobacco smoke would be considered good practice and would have wider benefits than potentially reducing risk of OME. For further information about the risks of passive smoking and conditions associated with smoking, the committee agreed to include a cross-reference to the recommendation 1.8.1 in the NICE guideline on tobacco: preventing uptake, promoting quitting and treating dependence (NICE 2021).

There was very low-quality evidence that coughs or colds 5 or more times in the past year, breathing problems 5 or more times in the past year, and ear infections in the past year were moderately associated with an increased risk of developing OME. Similarly, fluid or pus discharge from ears in the past year was strongly associated with an increased risk of developing OME. The committee discussed that, as the evidence was from a population where at least one of the child's parents was Pacific Islander, it could not be generalised to a wider population because Pacific Islanders have been noted to have a high incidence of respiratory infections (Paterson 2007) and have a distinct craniofacial structure, which may increase the risk of OME. Despite the lack of confidence in this evidence, the committee acknowledged that a recommendation raising awareness of the association between these conditions and OME could be important and help increase identification. For example, if general practitioners are aware of the potential link between such conditions and OME and saw a child who had frequent upper respiratory tract infections, they may monitor these children more closely, inform parents and carers that there might be risk of developing OME and to bring the child back if they develop future respiratory symptoms or symptoms of OME, or consider referring the child for further investigations. Therefore, the committee agreed that the possibility of OME should be considered in these children.

There was inconsistency in the evidence regarding the association between pneumococcal vaccination and OME. A study conducted in Japanese children (Ogawa 2022) found that

there was a small association between pneumococcal conjugate vaccine (PCV7 or PCV13) and a reduced risk of developing OME. However, a study in children from Aboriginal communities (Mackenzie 2009) showed no association. The committee discussed that the available evidence was very low quality and might not be generalised because both Japanese and Aboriginal children have distinct craniofacial features that may lead to higher risk of OME, and Mackenzie 2009 reported that there is a high burden of severe otitis in Aboriginal populations. The committee were aware that pneumococcal conjugate vaccine (PCV13) is already recommended for all children in the UK as part of their childhood vaccination programme, via The Green Book (UKHSA 2020, updated 2022); therefore, the committee agreed that a recommendation about pneumococcal vaccination was not needed. The committee acknowledged that not everyone in the UK will respond well to vaccinations and a booster may be needed to improve immunity. However, recommending booster vaccinations was outside the scope of this review.

There was evidence that exposure to other children, for example through attending day care, was strongly associated with an increased risk of developing OME. However, the available evidence was very low quality, and the committee did not think it was appropriate to recommend that children should not attend day care or nursery because they were aware that there are benefits of attending day care or nursery for the child, in terms of socialisation and helping to prepare them for school, and that this may be the only viable childcare option for some families. Therefore, the committee did not make a recommendation about this.

There was a possibility that bed-sharing could be moderately associated with the risk of OME; however, the evidence was very limited and very low quality. Further, the committee were aware that the topic of bed-sharing is quite a complex one and is covered by the NICE guideline on postnatal care (NICE 2021). Therefore, the committee did not think a recommendation about bed-sharing was necessary, or appropriate without full consideration of the risks and benefits.

There was possibly a moderate association between increased risk of OME and paranasal sinusitis. Nevertheless, the evidence was very low quality, and the committee recognised that the method used to measure paranasal sinusitis in Hong 2008 (paranasal sinus series) does not reflect what is routinely done in practice and could not be done in primary care as it involves radiological investigations. The committee, therefore, did not make a recommendation about paranasal sinusitis.

In very low birth weight (VLBW) preterm newborns, very low-quality evidence found a strong association between adenoid hypertrophy and increased risk of fluctuating OME. Nonetheless, the committee were concerned that the evidence from VLBW babies could not be extrapolated to a wider population as these babies might have been given ototoxic drugs (for example, Gentamicin), have eustachian tube dysfunction, or have a hearing impairment. Having considered the quality and generalisability of the evidence, the committee agreed that a recommendation about adenoid hypertrophy should not be made.

Very low-quality evidence showed no association between breastfeeding and the development of OME. The committee were aware of some evidence that showed a protective effect of breastfeeding on the development of acute otitis media (AOM) (Chonmaitree 2016). In the committee's experience, AOM can sometimes lead to OME, and breastfeeding may also have a protective effect on the development of OME. As no association between breastfeeding and development of OME was observed in this review, and no evidence was found regarding an association between AOM and OME, the committee did not make a recommendation about this. However, the committee were aware that there are other beneficial effects of breastfeeding and that information about breastfeeding and supporting women to breastfeed is covered by the NICE guideline on postnatal care (NICE 2021).

Cost effectiveness and resource use

The committee did not consider that their recommendations would lead to a significant change in practice and that advice for parents and carers, to avoid exposing their children to tobacco smoke, was consistent with other NICE guidance. Whilst no formal quantitative assessment of cost effectiveness was made, the committee agreed that providing this advice involved negligible costs to the NHS and had the potential to improve health related quality of life and reduce “downstream” costs where the advice resulted in changes in behaviour and reduced exposure to tobacco smoke.

The committee noted that having a higher index of suspicion for the presence of OME does not in itself have economic implications. However, they considered that their recommendation about having a higher level of suspicion if certain features were present could promote cost-effective management by facilitating early identification and mitigation of harms arising from hearing loss.

Other factors the committee took into account

The committee were aware that the Centers for Disease Control and Prevention (2020) states that there is a link between second-hand smoke in children and having more fluid in their ears and more operations to insert ear tubes for drainage. The committee took into account this to make recommendation 1.1.10.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.10 and 1.2.3. (Only the first bullet point – a history of upper respiratory tract infections). Other evidence supporting these recommendations can be found in the evidence reviews on presenting features associated with OME in children (see evidence review B).

References – included studies

Prognostic

De Felice 2008

De Felice, C., De Capua, B., Costantini, D. et al. (2008). Recurrent otitis media with effusion in preterm infants with histologic chorioamnionitis - a 3 years follow-up study, Early Human Development 84(10), 667-671

Hammaren-Malmi 2005

Hammaren-Malmi, S., Tarkkanen, J., Mattila, P. S. et al. (2005). Analysis of risk factors for childhood persistent middle ear effusion, Acta Oto-Laryngologica 125(10), 1051-1054

Hong 2008

Hong, C. K., Park, D. C., Kim, S. W. et al. (2008). Effect of paranasal sinusitis on the development of otitis media with effusion: influence of eustachian tube function and adenoid immunity, International Journal of Pediatric Otorhinolaryngology 72(11), 1609-1618

Kreiner-Moller 2012

Kreiner-Moller, E., Chawes, B. L. K., Caye-Thomasen, P. et al. (2012). Allergic rhinitis is associated with otitis media with effusion: a birth cohort study, Clinical and Experimental allergy: journal of the British Society for Allergy and Clinical Immunology 42(11), 1615-1620

Mackenzie 2009

Mackenzie, G. A., Carapetis, J. R., Leach, A. J. et al. (2009). Pneumococcal vaccination and otitis media in Australian Aboriginal infants: comparison of two birth cohorts before and after introduction of vaccination, BioMed Central Pediatrics 9, 14

Ogawa 2022

Ogawa, Y., Kunimoto, M., Takeno, S. et al. (2022). Pneumococcal conjugate vaccines reduce myringotomy with tympanostomy tube insertion in young children in Japan, Laryngoscope Investigative Otolaryngology 7(1), 259-265

Paterson 2007

Paterson, J. E., Carter, S., Wallace, J. et al. (2007). Pacific Islands Families Study: risk factors associated with otitis media with effusion among Pacific 2-year-old children, International Journal of Pediatric Otorhinolaryngology 71(7), 1047-1054

Other

Centers for Disease Control and Prevention 2020

Centers for Disease Control and Prevention (2020). Health effects of secondhand smoke. Available at: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/secondhand_smoke/health_effects/index.htm [Accessed 11/07/2022]

Chonmaitree 2016

Chonmaitree, T., Trujillo, R., Jennings, R. et al. (2016). Acute otitis media and other complications of viral respiratory infection, Pediatrics 137(4), e20153555

NICE 2021

National Institute for Health and Care Excellence (2021). Postnatal care. Available at: https://www.nice.org.uk/guidance/ng194 [Accessed 12/07/2022]

NICE 2021

National Institute for Health and Care Excellence (2021). Tobacco: preventing uptake, promoting quitting and treating dependence. Available at: https://www.nice.org.uk/guidance/ng209 [Accessed 07/07/2022]

UKHSA 2020 (updated 2022)

UK Health Security Agency (2020, updated 2022). Pneumococcal: the Green book, chapter 25. Available at: https://www.gov.uk/government/publications/pneumococcal-the-green-book-chapter-25 [Accessed 07/07/2022]

Appendices

Appendix A Review protocols

Review protocol for review question: What are the modifiable risk factors for developing OME in children under 12 years?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42022333912
Review title	The modifiable risk factors for developing OME in children
Review question	What are the modifiable risk factors for developing OME in children under 12 years?
Objective	To determine the modifiable risk factors for developing OME in children under 12 years
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • International Health Technology Assessment (INAHTA) database • MEDLINE & MEDLINE In-Process Searches will be restricted by: • Date limitations: 2000 onwards (see rationale under Section 10) • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews • Citation searches of included studies

Field	Content
	With the agreement of the guideline committee the searches will be re-run between 6-8 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Otitis media with effusion in children under 12 years
Population	Inclusion: All children under 12 years with suspected otitis media with effusion (OME)
Prognostic factor	Any risk factors, individually or in combination, including: • Upper respiratory tract infection • Household smoking or passive smoking • Exposure to other children (e.g. attending to a nursery) • Adenoid hypertrophy • Atopic conditions (e.g. allergic rhinitis) • Gastro-oesophageal reflux • Bottle feeding • Dummy use • Breastfeeding • Swimming • Acute otitis media • Vaccination uptake
Comparator	Absence of risk factor(s) Confounding variables: • Age • Severity of hearing loss • Socio-economic group
Types of study to be included	Include published full-texts: • Systematic reviews of cohort studies • Prospective cohort studies with multivariate analyses with N ≥ 40 per arm/prognostic factor group

Field	Content
	• If insufficient prospective cohort studies: retrospective cohort studies with multivariate analyses with N ≥ 40 per arm/prognostic factor group Studies with univariate analyses will only be included if there are insufficient studies with multivariate analyses. Sufficiency will be judged taking into account factors including number/quality/sample size of multivariate studies, risk factors investigated, outcomes reported and availability of data from subgroups of interest.
Other exclusion criteria	• Country limitations: OECD high-income countries • Date limitations: 2000 as the 2008 OME guideline has changed practice. However, the committee wanted to capture research leading up to the 2008 guideline also, and not just research conducted afterwards. • Language limitations: studies published not in English-language • Conference abstracts will not be considered
Context	This guidance will fully update the following NICE guideline: Otitis media with effusion in under 12s: surgery (2008; CG60)
Primary outcomes (critical outcomes)	• Development of first episode/diagnosis OME • Development of persistent OME • Development of fluctuating OME
Secondary outcomes (important outcomes)	None
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required, if capacity allows it. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and

Field	Content
	dates), participant characteristics, inclusion and exclusion criteria, details of the risk factors, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • PROBAST for risk prediction models • QUIPS checklist for prognostics factor studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the factor and the definitions used and approach to analysis in the primary papers is sufficiently consistent, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds or hazard ratios when required (for example if only available in this form in included studies). Heterogeneity in the effect estimates of the individual studies will be assessed by visual inspection of the forest plots and consideration of the I2 statistic. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled if the random effects model does not adequately address heterogeneity. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences: • Strong association: <0.5 and >2.00 • Moderate association: <0.80 and >1.25

Field	Content	
	• Small association: any statistically significant association • No association: no statistically significant association	

Analysis of sub-groups	Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:
	• Craniofacial anomalies
	  ○ Children with Down's syndrome
	  ○ Children with cleft palate
	  ○ Children with other craniofacial anomalies
	  ○ Children without craniofacial anomalies
	• Age
	  ○ Children <2 years vs ≥2 years
	  ○ Children <4 years vs ≥4 years
	  ○ Children <6 years vs ≥6 years
	
	Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	

Type and method of review	☐	Intervention
	☐	Diagnostic
	☒	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	

Field	Content
Anticipated or actual start date	01/05/2022
Anticipated completion date	23/12/2022
Stage of review at time of this submission	Review stage / Started / Completed Preliminary searches: ☐ / ☑ Piloting of the study selection process: ☐ / ☑ Formal screening of search results against eligibility criteria: ☐ / ☑ Data extraction: ☐ / ☑ Risk of bias (quality) assessment: ☐ / ☑ Data analysis: ☐ / ☑
Named contact	Named contact: National Guideline Alliance Named contact e-mail: otitis@nice.org.uk Organisational affiliation of the review: National Institute for Health and Care Excellence (NICE) and National Guideline Alliance
Review team members	National Guideline Alliance
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or

Field	Content	
	part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10193	
Other registration details	None	
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022333912	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Otitis media with effusion, risk factors, hearing	
Details of existing review of same topic by same authors	None	
Current review status	☐	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; INAHTA: International Health Technology Assessment database; MEDLINE: Medical Literature Analysis and Retrieval System Online; NICE:

National Institute for Health and Care Excellence; PROBAST: Prediction model Risk Of Bias ASsessment Tool; QUIPS: Quality in Prognosis Studies; RCT: randomised controlled trial; ROBIS: risk of bias in systematic reviews

Appendix B Literature search strategies

Literature search strategies for review question: What are the modifiable risk factors for developing OME in children under 12 years?

Clinical search

Database: Medline – OVID interface
Date of last search: 09/11/2022

#	Searches
1	otitis media with effusion/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	risk factors/
5	(risk* adj5 (factor* or interven* or manag* or modif* or monitor* or reduc*)).ti,ab.
6	Respiratory Tract Infections/ or exp Bronchitis/ or Common Cold/ or Influenza, Human/ or Laryngitis/ or exp Pharyngitis/ or Rhinitis/ or exp Sinusitis/ or Tracheitis/
7	((bronchi* or broncho* or laryn* or pharyn* or sinonasal or sinus* or tonsil* or trachea* or upper airway* or upper respirat*) adj3 (disease* or infect* or inflam*)).ti,ab.
8	(bronchit* or bronchiolit* or common cold* or coryza or croup* or epiglott* or flu or grippe or influenza* or laryngit* or laryngotracheobronchit* or laryngotracheit* or nasopharyngit* or parainfluenza* or pharyng?t* or rhinit* or rhinopharyngit* or rhinosinusit* or sinusit* or sore throat* or tonsillit* or tracheiti* or tracheobronchit* or URTI*).ti,ab.
9	exp Smoking/ or Tobacco Smoke Pollution/
10	(smoke* or smoking).ti,ab.
11	exp Child Day Care Centers/ or Child Care/ or Schools/ or Schools, Nursery/
12	exp Child/ or exp Infant/ or Friends/ or Siblings/ or exp Pediatrics/
13	(child* or baby or babies or boy? or girl? or infan* or juvenile? or kid? or kindergar* or p?ediatric* or preschool* or pre school* or schoolchild* or school age? or toddler* or young or youth? or brother* or friend* or sibling* or sister*).ti,ab.
14	(childcare or child care or daycare or day care or kindergarten* or nurser* or preschool* or school*).ti,ab.
15	Adenoids/
16	((adenoid* or adenotonsil* or adeno tonsil* or pharyn*) adj3 (hypertrop* or enlarg* or increas* or infect* or overgrow* or over grow* or swell* or swollen)).ti,ab.
17	exp Allergens/ or Apnea/ or exp Asthma/ or exp Rhinitis, Allergic/ or Cough/ or exp Eczema/ or Tonsillitis/ or exp Conjunctivitis/
18	(allerg* or apn?ea* or asthma* or atopic or atopy or cough* or eczema* or conjunctivitis).ti,ab.
19	exp Gastroesophageal Reflux/
20	(((gastro?esophag* or oesophag* or esophag* or gastric or acid) adj3 (backflow* or leak* or reflux* or regurgitat*)) or GOR or GORD or GER or GERD or LPR).ti,ab.
21	Bottle Feeding/
22	(bottle feed* or bottle fed* or bottlefeed* or bottlefed*).ti,ab.
23	Pacifiers/ or Infant Care/
24	(dumm* or pacifier* or soother* or suck*).ti,ab.
25	Breast Feeding/
26	(breastfeed* or breastfed or breast feed* or breast fed or breastmilk or breast milk).ti,ab.
27	Swimming/
28	swim*.ti,ab.
29	Otitis Media/
30	(otitis media or (middle ear adj3 (infect* or inflam*)) or AOM or OM).ti,ab.
31	exp Immunization/ or exp Vaccines/ or exp Vaccination Refusal/
32	((vaccin* or immuni* or innoculat*) adj (uptake or take up or taking up or refus* or rate* or coverage)).ti,ab.
33	or/4-32
34	3 and 33
35	(animals/ not humans/) or exp animals, laboratory/ or exp animal experimentation/ or exp models, animal/ or exp rodentia/ or (rat or rats or mouse or mice).ti.
36	34 not 35
37	afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or

#	Searches
	exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/
38	"organisation for economic co-operation and development"/
39	australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/
40	european union/
41	developed countries/
42	or/38-41
43	37 not 42
44	36 not 43
45	limit 44 to english language
46	limit 45 to yr="2000 -Current"

Database: Embase – OVID interface
Date of last search: 09/11/2022

#	Searches
1	exp secretory otitis media/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	risk factors/
5	(risk* adj5 (factor* or manag* or modif* or monitor* or reduc* or self manag*)).ti,ab.
6	exp *upper respiratory tract infection/
7	((bronchi* or broncho* or laryn* or pharyn* or sinonasal or sinus* or tonsil* or trachea* or upper airway* or upper respirat*) adj3 (disease* or infect* or inflam*)).ti,ab.
8	(bronchit* or bronchiolit* or common cold* or coryza or croup* or epiglott* or flu or grippe or influenza* or laryngit* or laryngotracheobronchit* or laryngotracheit* or nasopharyngit* or parainfluenza* or pharyng?t* or rhinit* or rhinopharyngit* or rhinosinusit* or sinusit* or sore throat* or tonsillit* or tracheiti* or tracheobronchit* or URTI*).ti,ab.
9	exp smoking/
10	(smoke* or smoking).ti,ab.
11	day care/ or exp child care/ or school/ or kindergarten/ or nursery school/ or primary school/
12	child/ or exp infant/ or preschool child/ or school child/ or toddler/ or friend/ or exp sibling/ or exp pediatrics/
13	(child* or baby or babies or boy? or girl? or infan* or juvenile? or kid? or kindergar* or p?ediatric* or preschool* or pre school* or schoolchild* or school age? or toddler* or young or youth? or brother* or friend* or sibling* or sister*).ti,ab.
14	(childcare or child care or daycare or day care or kindergarten* or nurser* or preschool* or school*).ti,ab.
15	adenoid hypertrophy/
16	((adenoid* or adenotonsil* or adeno tonsil* or pharyn*) adj3 (hypertrop* or enlarg* or increas* or infect* or overgrow* or over grow* or swell* or swollen)).ti,ab.
17	exp allergen/ or exp apnea/ or exp asthma/ or exp allergic rhinitis/ or exp coughing/ or exp eczema/ or exp tonsillitis/ or exp conjunctivitis/
18	(allerg* or apn?ea* or asthma* or atopic or atopy or cough* or eczema* or conjunctivitis).ti,ab.
19	exp gastroesophageal reflux/
20	(((gastro?esophag* or oesophag* or esophag* or gastric or acid) adj3 (backflow* or leak* or reflux* or regurgitat*)) or GOR or GORD or GER or GERD or LPR).ti,ab.
21	bottle feeding/
22	(bottle feed* or bottle fed* or bottlefeed* or bottlefed*).ti,ab.
23	pacifier/
24	(dumm* or pacifier* or soother* or suck*).ti,ab.
25	breast feeding/
26	(breastfeed* or breastfed or breast feed* or breast fed or breastmilk or breast milk).ti,ab.
27	swimming/
28	swim*.ti,ab.
29	exp acute otitis media/
30	(otitis media or (middle ear adj3 (infect* or inflam*)) or AOM or OM).ti,ab.
31	exp immunization/ or exp vaccine/
32	((vaccin* or immuni* or innoculat*) adj (uptake or take up or taking up or refus* or rate* or coverage)).ti,ab.
33	or/4-32
34	3 and 33
35	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.
36	34 not 35

#	Searches
37	afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/
38	exp "organisation for economic co-operation and development"/
39	exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/
40	european union/
41	developed country/
42	or/38-41
43	37 not 42
44	36 not 43
45	limit 44 to english language
46	limit 45 to yr="2000 -Current"

Database: Cochrane Database of Systematic Reviews (CDSR); Cochrane Central Register of Controlled Trials (CENTRAL) – Wiley interface
Date of last search: 09/11/2022

#	Searches
#1	MeSH descriptor: [Otitis Media with Effusion] this term only
#2	(("glue ear" or (("middle ear" or "otitis media") near/2 effusion*) or ome or ((secretory or serous) near/2 "otitis media"))):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Risk Factors] this term only
#5	(risk* near/5 (factor* or interven* or manag* or modif* or monitor* or reduc*)):ti,ab
#6	MeSH descriptor: [Respiratory Tract Infections] this term only
#7	MeSH descriptor: [Bronchitis] explode all trees
#8	MeSH descriptor: [Common Cold] this term only
#9	MeSH descriptor: [Influenza, Human] this term only
#10	MeSH descriptor: [Laryngitis] this term only
#11	MeSH descriptor: [Pharyngitis] this term only
#12	MeSH descriptor: [Rhinitis] this term only
#13	MeSH descriptor: [Sinusitis] this term only
#14	MeSH descriptor: [Tracheitis] this term only
#15	((bronchi* or broncho* or laryn* or pharyn* or sinonasal or sinus* or tonsil* or trachea* or "upper airway*" or "upper respirat*") near/3 (disease* or infect* or inflam*)):ti,ab
#16	(bronchit* or bronchiolit* or "common cold*" or coryza or croup* or epiglott* or flu or grippe or influenza* or laryngit* or laryngotracheobronchit* or laryngotracheit* or nasopharyngit*or parainfluenza* or pharyngit* or pharyngot* or rhinopharyngit* or rhinosinusit* or sinusit* or "sore throat*" or tonsillit* or tracheiti* or tracheobronchit* or URTI*):ti,ab
#17	MeSH descriptor: [Smoke] explode all trees
#18	MeSH descriptor: [Tobacco Smoke Pollution] this term only
#19	(smoke* or smoking):ti,ab
#20	MeSH descriptor: [Child Day Care Centers] explode all trees
#21	MeSH descriptor: [Child Care] this term only
#22	MeSH descriptor: [Schools] this term only
#23	MeSH descriptor: [Schools, Nursery] this term only
#24	MeSH descriptor: [Child] explode all trees
#25	MeSH descriptor: [Infant] explode all trees
#26	MeSH descriptor: [Friends] this term only

#	Searches
#27	MeSH descriptor: [Siblings] this term only
#28	MeSH descriptor: [Pediatrics] explode all trees
#29	(child* or baby or babies or boy? or girl? or infan* or juvenile? or kid? or kindergar* or p?ediatric* or preschool* or "pre school*" or schoolchild* or "school age?" or toddler* or young or youth? or brother* or friend* or sibling* or sister*):ti,ab
#30	(childcare or "child care" or daycare or "day care" or kindergarten* or nurser* or preschool* or school*):ti,ab
#31	MeSH descriptor: [Adenoids] this term only
#32	((adenoid* or adenotonsil* or "adeno tonsil*" or pharyn*) near/3 (hypertrop* or enlarg* or increas* or infect* or overgrow* or "over grow*" or swollen)):ti,ab
#33	MeSH descriptor: [Allergens] explode all trees
#34	MeSH descriptor: [Apnea] explode all trees
#35	MeSH descriptor: [Asthma] explode all trees
#36	MeSH descriptor: [Rhinitis, Allergic] explode all trees
#37	MeSH descriptor: [Cough] this term only
#38	MeSH descriptor: [Eczema] explode all trees
#39	MeSH descriptor: [Tonsillitis] explode all trees
#40	MeSH descriptor: [Conjunctivitis] explode all trees
#41	(allerg* or apnoea* or apnea* or asthma* or atopic or atopy or cough* or eczema* or conjunctivitis):ti,ab
#42	MeSH descriptor: [Gastroesophageal Reflux] explode all trees
#43	(((gastro?esophag* or "gastro oesophag*" or "gastro esophag*" or gastric or acid) adj3 (backflow* or leak* or reflux* or regurgitat*)) or GOR or GORD or GER or GERD or LPR):ti,ab
#44	MeSH descriptor: [Bottle Feeding] this term only
#45	("bottle feed*" or bottlefeed*):ti,ab
#46	MeSH descriptor: [Pacifiers] this term only
#47	(dumm* or pacifier* or soother* or suck*):ti,ab
#48	MeSH descriptor: [Breast Feeding] explode all trees
#49	(breastfeed* or breastfed or "breast feed*" or "breast fed" or breastmilk or "breast milk"):ti,ab
#50	MeSH descriptor: [Swimming] this term only
#51	swim*:ti,ab
#52	MeSH descriptor: [Otitis Media] this term only
#53	("otitis media" or ("middle ear" near/3 (infect* or inflam*)) or AOM or OM):ti,ab
#54	MeSH descriptor: [Immunization] explode all trees
#55	MeSH descriptor: [Vaccines] explode all trees
#56	MeSH descriptor: [Vaccination Refusal] explode all trees
#57	((vaccin* or immuni* or innoculat*) near (uptake or "take up" or "taking up" or refus* or rate* or coverage)):ti,ab
#58	{or #4-#57}
#59	#3 and #58
#60	"conference":pt or (clinicaltrials or trialsearch):so
#61	#59 not #60 with Cochrane Library publication date Between Jan 2000 and Apr 2022

Database: Epistemonikos
Date of last search: 09/11/2022

#	Searches
1	(title:(("glue ear" OR (("middle ear" OR "otitis media") AND effusion*) OR ome OR ((secretory OR serous) AND "otitis media"))) OR abstract:(("glue ear" OR (("middle ear" OR "otitis media") AND effusion*) OR ome OR ((secretory OR serous) AND "otitis media")))
2	(risk* or bronchit* or bronchiolit* or "common cold" or "common colds" or coryza or croup* or epiglott* or flu or grippe or influenza* or laryngit* or laryngotracheobronchit* or laryngotracheit* or nasopharyngit*or parainfluenza* or pharyngit* or pharyngot* or rhinopharyngit* or rhinosinusit* or sinusit* or "sore throat" or "sore throats" or tonsillit* or tracheiti* or tracheobronchit* or "upper airway" or "upper airways" or "upper respiratory" or URTI* or smoke or smoking or adenoid* or adenotonsil* or "adeno tonsil" or "adeno tonsils" or child* or baby or babies or boy* or girl* or infan* or juvenile* or kid* or kindergar* or paediatric* or pediatric* or preschool* or "pre school" or "pre schools" or schoolchild* or "school age" or "school aged" or toddler* or young or youth* or brother* or friend* or sibling* or sister* or allerg* or apnoea* or apnea* or asthma* or atopic or atopy or cough* or eczema* or conjunctivitis or backflow* or leak* or reflux* or regurgitat* or GOR or GORD or GER or GERD or LPR or "bottle feed" or "bottle feeding" or bottlefeed* or dumm* or pacifier* or soother* or suck* or breastfeed* or breastfed or "breast feed" or "breast feeding" or "breast fed" or breastmilk or "breast milk" or swim* or "otitis media" or AOM or vaccin* or immuni* or innoculat*)
3	1 AND 2
4	date limit: 2000-

Database: International Network of Agencies for Health Technology Assessment (INAHTA)
Date of last search: 09/11/2022

#	Searches
1	"Otitis Media with Effusion"[mhe]
2	(("glue ear" or (("middle ear" or " “otitis media") and effusion*) or ome or ((secretory or serous) and "otitis media"))
3	1 OR 2 FROM 2000 TO 2022 AND (English)[Language]

Economic literature search strategy

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

Database: Medline – OVID interface
Date of last search: 09/11/2022

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

Database: Embase – OVID interface
Date of last search: 09/11/2022

#	Searches
1	exp secretory otitis media/
2	(glue ear or ((middle ear or otitis media) adj2 effusion*) or ome or ((secretory or serous) adj2 otitis media)).ti,ab.
3	1 or 2
4	health economics/
5	exp economic evaluation/
6	exp health care cost/
7	exp fee/
8	budget/
9	funding/
10	budget*.ti,ab.
11	cost*.ti.
12	(economic* or pharmaco?economic*).ti.
13	(price* or pricing*).ti,ab.
14	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
15	(financ* or fee or fees).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	or/4-16
18	statistical model/
19	exp economic aspect/

#	Searches
20	18 and 19
21	*theoretical model/
22	*nonbiological model/
23	stochastic model/
24	decision theory/
25	decision tree/
26	monte carlo method/
27	(markov* or monte carlo).ti,ab.
28	econom* model*.ti,ab.
29	(decision* adj2 (tree* or analy* or model*)).ti,ab.
30	or/20-29
31	17 or 30
32	3 and 31
33	(animal/ not human/) or nonhuman/ or exp animal experiment/ or exp experimental animal/ or animal model/ or exp rodent/ or (rat or rats or mouse or mice).ti.
34	32 not 33
35	limit 34 to english language
36	limit 35 to yr="2000 -Current"

Database: Cochrane Central Register of Controlled Trials (CENTRAL) – Wiley interface
Date of last search: 09/11/2022

ID	Search
#1	MeSH descriptor: [Otitis Media with Effusion] this term only
#2	(("glue ear" or (("middle ear" or "otitis media") near/2 effusion*) or ome or ((secretory or serious) near/2 "otitis media"))):ti,ab,kw
#3	#1 or #2
#4	MeSH descriptor: [Economics] this term only
#5	MeSH descriptor: [Value of Life] this term only
#6	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#7	MeSH descriptor: [Economics, Hospital] explode all trees
#8	MeSH descriptor: [Economics, Medical] explode all trees
#9	MeSH descriptor: [Economics, Nursing] this term only
#10	MeSH descriptor: [Economics, Pharmaceutical] this term only
#11	MeSH descriptor: [Fees and Charges] explode all trees
#12	MeSH descriptor: [Budgets] explode all trees
#13	budget*:ti,ab
#14	cost*:ti
#15	(economic* or pharmaco?economic*):ti
#16	(price* or pricing*):ti,ab
#17	(cost* near/2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)):ab
#18	(financ* or fee or fees):ti,ab
#19	(value near/2 (money or monetary)):ti,ab
#20	{or #4-#19}
#21	MeSH descriptor: [Models, Economic] explode all trees
#22	MeSH descriptor: [Models, Theoretical] this term only
#23	MeSH descriptor: [Models, Organizational] this term only
#24	MeSH descriptor: [Markov Chains] this term only
#25	MeSH descriptor: [Monte Carlo Method] this term only
#26	MeSH descriptor: [Decision Theory] explode all trees
#27	(markov* or "monte carlo"):ti,ab
#28	(econom* next model*):ti,ab
#29	(decision* near/2 (tree* or analy* or model*)):ti,ab
#30	{or #21-#29}
#31	#20 or #30
#32	#3 and #31 with Cochrane Library publication date Between Jan 2000 and Apr 2022

Database: NHS Economic Evaluation Database (NHS EED) – CRD interface
Date of last search: 09/11/2022

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

Database: International Network of Agencies for Health Technology Assessment (INAHTA)
Date of last search: 09/11/2022

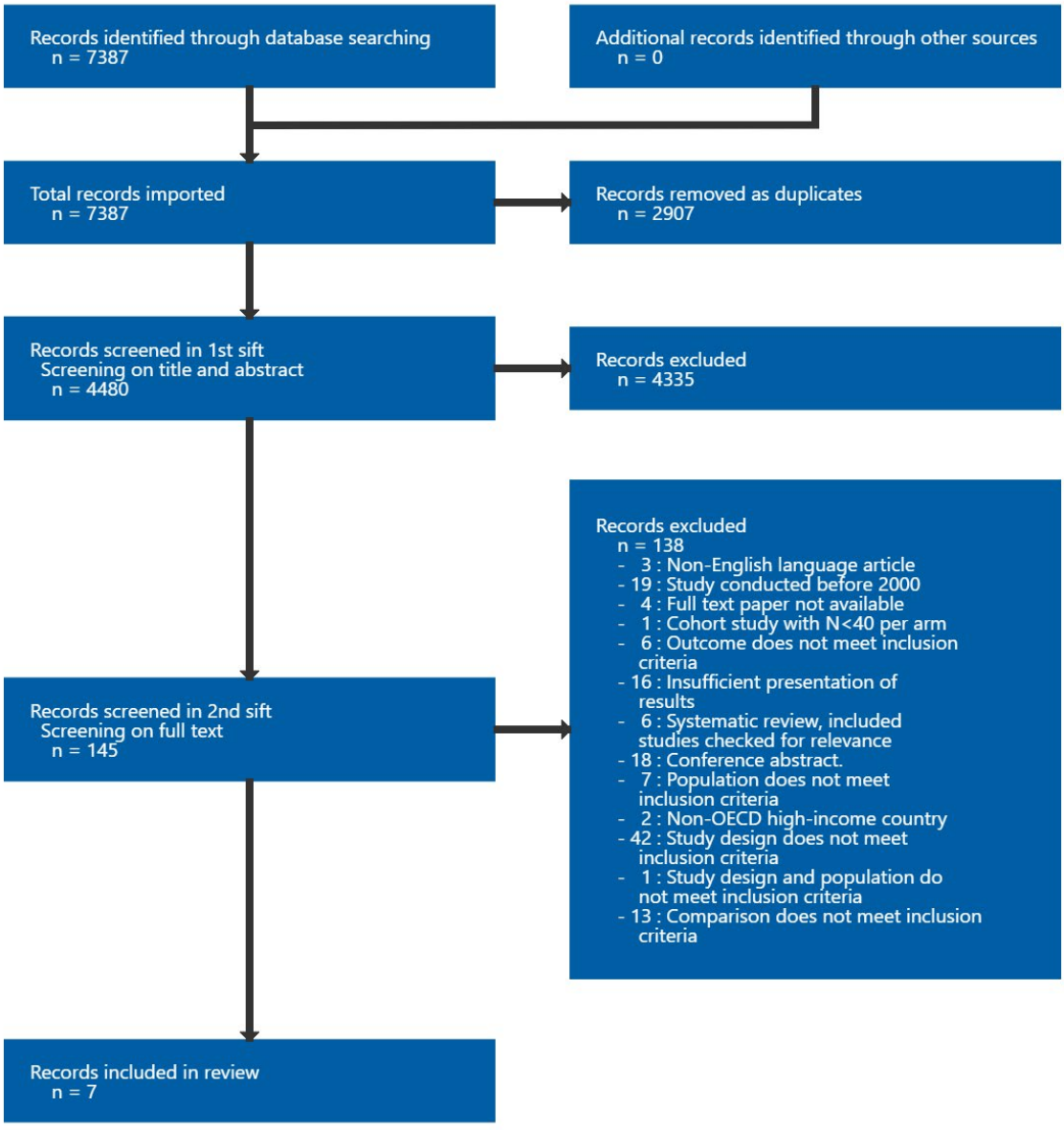
#	Searches
1	((("Otitis Media with Effusion"[mhe]) OR ((("glue ear" or (("middle ear" or "otitis media") and effusion*) or ome or ((secretory or serous) and "otitis media")))
2	1 and FROM 2000 TO 2022 AND (English)[Language]

Appendix C Prognostic evidence study selection

Study selection for: What are the modifiable risk factors for developing OME in children under 12 years?

Clinical search

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What are the modifiable risk factors for developing OME in children under 12 years?

Table 4: Evidence tables

De Felice, 2008

Bibliographic Reference	De Felice, Claudio; De Capua, Bruno; Costantini, Daniele; Martufi, Carla; Toti, Paolo; Tonni, Gabriele; Laurini, Ricardo; Giannuzzi, Annalisa; Latini, Giuseppe; Recurrent otitis media with effusion in preterm infants with histologic chorioamnionitis--a 3 years follow-up study.; Early human development; 2008; vol. 84 (no. 10); 667-71

Study details

Country/ies where study was carried out	Italy
Study type	Prospective cohort study
Study dates	Not reported
Inclusion criteria	Very low birth weight (VLBW) preterm newborns with and without histological chorioamnionitis (HCA)
Exclusion criteria	Infants with craniofacial anomalies, gastroesophageal reflux or any conditions that can cause eustachian tube dysfunction
Patient characteristics	N=245 Sex (male/female): 127/118 Recurrent otitis media with effusion: 88/245
Risk factor(s) of interest	Adenoid hypertrophy

Confounding factor(s) of interest	The matching was not on our comparison of interest, so there is no information on whether there were any differences in age, severity of hearing loss, and socio-economic status based on presence/absence of prognostic factor.
Duration of follow-up	up to 3 years
Setting	Hospital
Sources of funding	Not reported
Other information	The diagnosis of OME was based on otoscopy examination, type B or C tympanogram, ipsilaterally increased threshold at diagnostic auditory brainstem response (ABR) evaluation, and ipsilateral absence of transient evoked otoacoustic emissions responses. All infants were assessed prospectively every 3 months during the first three years of life. The presence of adenoid hypertrophy determined by otorhinolaryngologist and based on posterior rhynoscopy, tympanometry, and rhynoscopic fibroscopy findings.

ABR: auditory brainstem response; HCA: histological chorioamnionitis; OME: otitis media with effusion; VLBW: Very low birth weight

Outcomes

Adenoid hypertrophy versus no adenoid hypertrophy: Development of fluctuating OME (Recurrent OME)

Outcome*	**Presence of prognostic factor vs Absence of prognostic factor, N2 = 76, N1 = 169**
Development of fluctuating OME unadjusted Odds ratio/95% CI	9.96 (5.17 to 19.18)

**Unadjusted OR extracted as raw data not reported*

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Methods used to identify study population not reported, and limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all children)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(Definition of adenoid hypertrophy was not explicitly provided.)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Definition of OME provided, and valid and reliable measurement of outcome used)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for age and other potential confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(The observed baseline differences (e.g., acute otitis media episodes and season at birth) between the groups were not addressed in the analysis. There was no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

OME: otitis media with effusion; QUIPS: quality in prognosis studies

Hammaren-Malmi, 2005

Bibliographic Reference	Hammaren-Malmi, S; Tarkkanen, J; Mattila, P S; Analysis of risk factors for childhood persistent middle ear effusion.; Acta oto-laryngologica; 2005; vol. 125 (no. 10); 1051-4

Study details

Country/ies where study was carried out	Finland
Study type	Prospective cohort study
Study dates	March 2001 - December 2002
Inclusion criteria	Children aged 1-4 years with recurrent acute otitis media (RAOM, defined as ≥3 AOM episodes during the preceding 6 months or ≥5 AOM episodes during the preceding 12 months) or suspected chronic otitis media with effusion (COME); and no history of adenotonsillar surgery or tympanostomy tubes placement surgery
Exclusion criteria	Children with cleft palate, diabetes mellitus or other immune disorder, or children who need prompt removal of adenoids due to obstructive symptoms
Patient characteristics	N=214 Mean age in years: 1.9 Sex (male/female): 112/102
Risk factor(s) of interest	Household smoking (Mother smokes, Father smokes) and exposure to other children (attending day care at age <2 years)
Confounding factor(s) of interest	No confounding factors (for example, age, socioeconomic status and severity of hearing loss) were explicitly identified and controlled for by the authors. The authors only reported a very limited number of baseline characteristics.

Duration of follow-up	Not reported
Setting	Department of Otorhinolaryngology, Hospital
Sources of funding	Part-industry funded
Other information	Suspected COME, for the purpose of study entry criteria, was based on pneumatic otoscopy findings, such as impaired motion of the tympanic membrane. Final diagnosis of COME was defined as the presence of mucoid, serous or purulent effusion in the middle ear during tympanostomy tubes surgery, or the presence of atrophic or retracted tympanic membrane with effusion. Duration of COME was not reported. A questionnaire, completed by parents of the children, was used to assess the prognostic factors (e.g., household smoking).

AOM: acute otitis media; COME: chronic otitis media with effusion; RAOM: recurrent acute otitis media

Outcomes

Household smoking: Mother smokes versus mother does not smoke: Development of persistent OME (COME)

Outcome	**Presence of prognostic factor, N = 68**	**Absence of prognostic factor, N = 140**
Development of persistent OME (COME) No of events	n = 18	n = 37

Household smoking: Father smokes versus father does not smoke: Development of persistent OME (COME)

Outcome	**Presence of prognostic factor, N = 91**	**Absence of prognostic factor, N = 115**
Development of persistent OME (COME)	n = 24	n = 31

Outcome	Presence of prognostic factor, N = 91	Absence of prognostic factor, N = 115
No of events		

Exposure to other children: Attending day care at age <2 years versus not attending day care at age <2 years: Development of persistent OME (COME)

Outcome	Presence of prognostic factor, N = 98	Absence of prognostic factor, N = 110
Development of persistent OME (COME) No of events	n = 25	n = 30

OME: otitis media with effusion; COME: chronic otitis media with effusion

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for almost all participants (97%))*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(The measurement of prognostic factors is subjective (measured by questionnaire), and clear description of prognostic factor not provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of OME provided)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to identify or control for potential confounders)*

Section	Question	Answer
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(Not clear if there were any substantial baseline differences between the groups with and without the prognostic factor as no such data reported. There was no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

QUIPS: quality in prognosis studies

Hong, 2008

Bibliographic Reference	Hong, Chang Kee; Park, Dong Choon; Kim, Sung Wan; Cha, Chang Il; Cha, Sung-Ho; Yeo, Seung Geun; Effect of paranasal sinusitis on the development of otitis media with effusion: influence of eustachian tube function and adenoid immunity.; International journal of pediatric otorhinolaryngology; 2008; vol. 72 (no. 11); 1609-18

Study details

Country/ies where study was carried out	Republic of Korea
Study type	Prospective cohort study
Study dates	August 2004 - July 2007
Inclusion criteria	Children aged 1-14 years who underwent adenotonsillectomy with or without ventilation tube insertion

Exclusion criteria	Children with positive allergic skin tests or multiple allergosorbent chemiluminescent assay (MAST-CLA)
Patient characteristics	N=520 (Paranasal sinusitis: N=319; No paranasal sinusitis: N=201) Mean age in years (SD): 6.95 (2.12) Sex (male/female): 343/177
Risk factor(s) of interest	Paranasal sinusitis
Confounding factor(s) of interest	No confounding factors were explicitly identified and controlled for
Duration of follow-up	2-3 months
Setting	The department of Otorhinolaryngology, KyungHee University Hospital
Sources of funding	Industry funded
Other information	OME, defined as presence of retention in the middle ear (amber colour, air-fluid level or air-bubble) and type B or C tympanometry, was assessed using otoscopy and tympanometry Study did not specify whether OME was first episode, persistent or fluctuating Paranasal sinusitis was defined as the presence of opaque sinuses, fluid level, and gross mucosal thickening in paranasal sinus series and symptoms with rhinorrhea, postnasal drip and nasal obstruction.

OME: otitis media with effusion

Outcomes

Paranasal sinusitis versus no paranasal sinusitis: Development of OME

Outcome	Paranasal sinusitis, N = 319	No paranasal sinusitis, N = 201
Development of OME No of events	n = 80	n = 36

OME: otitis media with effusion

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Methods used to identify study population and recruitment period not reported, and limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(Data presented for all children)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of paranasal sinusitis provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Definition of OME provided, and valid and reliable measurement of outcome used)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to identify or control for potential confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(Not clear if there were any substantial baseline differences between the groups with and without the prognostic factor as no such data reported. There was no evidence of selective reporting of the results)*

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

OME: otitis media with effusion; QUIPS: quality in prognosis studies

Kreiner-Moller, 2012

Bibliographic Reference	Kreiner-Moller, E; Chawes, B L K; Caye-Thomasen, P; Bonnelykke, K; Bisgaard, H; Allergic rhinitis is associated with otitis media with effusion: a birth cohort study.; Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology; 2012; vol. 42 (no. 11); 1615-20

Study details

Country/ies where study was carried out	Denmark
Study type	Prospective cohort study
Study dates	Not reported
Inclusion criteria	Children aged 6 years from the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) 2000 birth cohort
Exclusion criteria	Children with gestational age less than 36 weeks, severe congenital anomalies, history of neonatal mechanical ventilation, and symptoms of lower respiratory tract infection prior to inclusion

Patient characteristics	N=262 OME: 102/262
Risk factor(s) of interest	Eczema, non-allergic rhinitis
Confounding factor(s) of interest	Analyses were adjusted for confounding factors, such as household income, gender, presence of older sibling, paternal atopy, smoking exposure at birth, dog or cat at home, and acute otitis media episodes.
Duration of follow-up	The infants were included in the study at 1 month of age, and they were assessed for OME in their 6th year of life.
Setting	The Copenhagen Prospective Study on Asthma in Childhood (COPSAC) Clinical Research Unit
Sources of funding	Part-industry funded
Other information	The diagnosis of OME was based on otoscopic and tympanometric findings (for example, B curve or C2 curve or children with tubes). The study did not specify how many participants had first episode, persistent or fluctuating OME. Eczema defined according to Hanifin and Rajka criteria. Non-allergic rhinitis defined as rhinitis without sensitisation or with sensitisation that is not accompanied by symptoms upon exposure.

COPSAC: The Copenhagen Prospective Study on Asthma in Childhood; OME: otitis media with effusion

Outcomes

Eczema versus no eczema: Development of OME

Outcome	Presence of prognostic factor vs Absence of prognostic factor, N2 = 121, N1 = 129
Development OME adjusted Odds ratio/95% CI	1.16 (0.68 to 1.98)

Non-allergic rhinitis versus no non-allergic rhinitis: Development of OME

Outcome	Presence of prognostic factor vs Absence of prognostic factor, N2 = 58, N1 = 182
Development of OME adjusted Odds ratio/95% CI	0.8 (0.41 to 1.58)

OME: otitis media with effusion

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Method used to identify study population reported, but limited information regarding inclusion criteria and baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Low risk of bias *(n=12 (4.6%) children and n=22 (8.4%) children are missing from analyses for eczema and non-allergic rhinitis, respectively. No explanation given.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of eczema and non-allergic rhinitis provided.)*

Section	Question	Answer
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Definition of OME provided, and valid and reliable measurement of outcome used)*
Study Confounding	Study Confounding Summary	Moderate risk of bias *(Important potential confounders are accounted for in the analysis, but methods used to measure confounders not provided.)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(Not clear if there were any substantial differences in confounding factors of intertest specified in the review protocol (age, severity of hearing loss, and socio-economic status) between the groups with and without the prognostic factor as no such data reported or controlled for. There was no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

OME: otitis media with effusion; QUIPS: quality in prognosis studies

Mackenzie, 2009

Bibliographic Reference	Mackenzie, Grant Austin; Carapetis, Jonathan Rhys; Leach, Amanda Jane; Morris, Peter Stanley; Pneumococcal vaccination and otitis media in Australian Aboriginal infants: comparison of two birth cohorts before and after introduction of vaccination.; BMC pediatrics; 2009; vol. 9; 14

Study details

Country/ies where study was carried out	Australia
Study type	Prospective cohort study
Study dates	Pneumococcal vaccination group enrolled between 2001 and 2004. No pneumococcal vaccination group enrolled between 1996 and 2001 (prior to vaccination availability).
Inclusion criteria	Children from Aboriginal communities with a high burden of sever otitis
Exclusion criteria	Pneumococcal vaccination group: Children aged >4 months, gestation age <34 weeks and congenital anomalies No pneumococcal vaccination group: Children aged >12 months, gestational age <34 weeks, penicillin allergy, prolonged use of antibiotic, craniofacial anomalies, chronic suppurative otitis media, and immunodeficiency
Patient characteristics	N=148 (Pneumococcal vaccination: N=97; No pneumococcal vaccination: N=51) Mean age in days (at first examination): Pneumococcal vaccination: 41 No pneumococcal vaccination: 60 Sex (male/female): Pneumococcal vaccination: 45/52 No pneumococcal vaccination: 30/21
Risk factor(s) of interest	Pneumococcal vaccine (PCV7 plus PPPV23)
Confounding factor(s) of interest	No confounding factors (for example, socioeconomic status and severity of hearing loss) were explicitly identified and controlled for by the authors. The authors only reported a very limited number of baseline characteristics.
Duration of follow-up	Up to 2 years of age (participants enrolled as soon as possible after birth)

Setting	The Child Health Division, Menzies School of Health Research and clinic
Sources of funding	Part industry funded
Other information	OME was assessed with pneumatic otoscopy, tympanometry and clinic records and defined as type B tympanogram with neutral or mild bulging of tympanic membrane. The study did not specify how many participants had first episode, persistent or fluctuating OME. Participants in pneumococcal vaccination group received PCV7 at 2, 4 and 6 months of age and booster PPV23 at 18 months of age. Participants included in no pneumococcal vaccination group were from a previous study (OM-RCT, 1996-2001).

OME: otitis media with effusion; PCV: pneumococcal conjugate vaccine; PPV23: 23-valent polysaccharide vaccine

Outcomes

Pneumococcal vaccination (PCV7 plus PPV23) versus no pneumococcal vaccination: Development of OME

Outcome	Pneumococcal vaccination, N = 84	No pneumococcal vaccination, N = 41
Development of OME (at 6 months of age) No of events	n = 81	n = 41

OME: otitis media with effusion; PCV: pneumococcal conjugate vaccine; PPV23: 23-valent polysaccharide vaccine

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding inclusion criteria and baseline characteristics of the study population provided)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Moderate risk of bias *(13% of participants (N=13/97) in pneumococcal vaccination group and 19% (N=10/51) are missing from the analysis)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(Description of pneumococcal vaccination provided, but no information about whether appropriate method was used to address missing prognostic factor data)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Definition of OME provided, and valid and reliable measurement of outcome used)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to control for potential confounders in the analysis for the development of OME)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(The observed baseline differences (e.g., lower respiratory illness, and late immunisation) between the groups were not addressed in the analysis for the development of OME. Outcomes were assessed up to 24 months of age, but the development of OME after 6 months of age not reported)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Partially applicable *(Parts of the study conducted before 2000)*

OME: otitis media with effusion; QUIPS: quality in prognosis studies

Ogawa, 2022

Bibliographic Reference	Ogawa, Y.; Kunimoto, M.; Takeno, S.; Sonoyama, T.; Ishino, T.; Hamamoto, T.; Ueda, T.; Pneumococcal conjugate vaccines reduce myringotomy with tympanostomy tube insertion in young children in Japan; Laryngoscope Investigative Otolaryngology; 2022; vol. 7 (no. 1); 259-265

Study details

Country/ies where study was carried out	Japan
Study type	Retrospective cohort study
Study dates	Not reported
Inclusion criteria	Children aged 0-8 years
Exclusion criteria	Not reported
Patient characteristics	N=2758247 (PCV7 era: N=737745; PCV13 era: N=1747807, Pre-PCV era: N=272695) Age (range): 0-8 years
Risk factor(s) of interest	Pneumococcal vaccination (PCV7 era or PCV13 era)
Confounding factor(s) of interest	No confounding factors were explicitly identified and controlled for
Duration of follow-up	Not reported
Setting	The nationwide database obtained from the JMDC Claims Database (https://www.jmdc.co.jp/en/)
Sources of funding	Not reported
Other information	In 2011 and 2012, the Japanese Government Policy on Emergency Vaccination (JGPonEV) encouraged pneumococcal vaccinations of 7 to 60-month-old children. In general, infants were vaccinated four times with PCV7: three doses before 12 months of age and one dose (booster) at 12 to 15 months of age. In November 2013, PCV7 was replaced with PCV13.

	The International Classification of Diseases 10th Revision (ICD-10) was used to define otitis media. Chronic serous otitis media (Code: H65.2), chronic mucoid otitis media (Code: H65.3), other chronic nonsuppurative otitis media (Code: H65.4) and unspecified nonsuppurative otitis media (Code: H65.9) were defined as OME. The study reported the incidence of MTTI, rather than rates of OME itself. However, authors reported that about 90% of those with MTTI had OME (based on ICD-10 codes) and10% were suspected to have ROM. However, the study did not explicitly specify whether OME was first episode, persistent or fluctuating.

ICD: International Classification of Diseases 10th Revision; JGPonEV: Japanese Government Policy on Emergency Vaccination; MTTI: myringotomy with tympanostomy tube insertion; OME: otitis media with effusion; PCV: pneumococcal conjugate vaccine, ROM: recurrent otitis media

Outcomes

Pneumococcal vaccination (PCV7 era) versus pneumococcal vaccination (PCV13 era) versus no pneumococcal vaccination (Pre-PCV era): Development of OME (reported as incidence of MTTI)

Outcome	Pneumococcal vaccination (PCV7 era), N = 737745	Pneumococcal vaccination (PCV13 era), N = 1747807	No pneumococcal vaccination (Pre-PCV era), N = 272695
Development of OME No of events	n = 1961	n = 4433	n = 805

OME: otitis media with effusion; PCV: pneumococcal conjugate vaccine

Critical appraisal – NGA Critical appraisal – QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*

Section	Question	Answer
Study Attrition	Study Attrition Summary	Low risk of bias *(Retrospective data from the nationwide database obtained from the JMDC Claims Database (https://www.jmdc.co.jp/en/))*
Prognostic factor measurement	Prognostic factor Measurement Summary	Low risk of bias *(Valid and reliable description of PCV provided, and retrospective data from the nationwide database used)*
Outcome Measurement	Outcome Measurement Summary	Moderate risk of bias *(Definition of OME provided, but no clear information regarding method and setting of outcome measurement. The study reported the incidence of MTTI, rather than rates of OME itself)*
Study Confounding	Study Confounding Summary	High risk of bias *(No attempts were made to identify or control for potential confounders)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(Not clear if there were any substantial baseline differences between the groups with and without the prognostic factor as no such data reported. There was no evidence of selective reporting of the results.)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Indirectly applicable *(The study reported the incidence of MTTI, rather than rates of OME itself)*

MTTI: myringotomy with tympanostomy tube insertion; OME: otitis media with effusion; PCV: pneumococcal conjugate vaccine; QUIPS: quality in prognosis studies

Paterson, 2007

Bibliographic Reference	Paterson, J E; Carter, S; Wallace, J; Ahmad, Z; Garrett, N; Silva, P A; Pacific Islands Families Study: risk factors associated with otitis media with effusion among Pacific 2-year-old children.; International journal of pediatric otorhinolaryngology; 2007; vol. 71 (no. 7); 1047-54

Study details

Country/ies where study was carried out	New Zealand
Study type	Prospective cohort study
Study dates	Study started in 2000, but no study completion date reported
Inclusion criteria	Children of Pacific Islands ethnicity and New Zealand permanent resident parents were selected from births
Exclusion criteria	Not reported
Patient characteristics	N=656 Age in months (median): 24 Sex (male/female): 363/293
Risk factor(s) of interest	Coughs/colds ≥5 times in past year, breathing problems ≥5 times in past year, ear infections, fluid or pus discharge from ears, exposure to other children (attending day care, attending childcare for ≥20 h a week, attending church), bed-sharing, and exclusive breastfeeding at 6 weeks
Confounding factor(s) of interest	Analyses of coughs/colds, attending childcare, attending church and fluid or pus discharge from ears were adjusted for confounding factors, such as home treatment in past year for breathing symptoms. However, analyses of attending day care, breathing problems, ear infections, bed-sharing, and exclusive breastfeeding were not adjusted for confounding factors. The authors only reported a very limited number of baseline characteristics.
Duration of follow-up	2 years
Setting	Hospital, Pacific Islands Cultural resource Unit, and home visits

Sources of funding	Not reported
Other information	OME was assessed with tympanometry and otoscopy (including pneumatic otoscopy). Study did not explicitly specify whether OME was first episode, persistent or fluctuating.

OME: otitis media with effusion

Outcomes

Coughs/colds ≥5 times in past year versus coughs/colds 0-4 times in past year: Development of OME

Outcome	**Presence of prognostic factor vs Absence of prognostic factor, N2 = 193, N1 = 463**
Development of OME adjusted Odds ratio/95% CI	1.91 (1.22 to 2.99)

Breathing problems ≥5 times in past year versus breathing problems 0-4 times in past year: Development of OME

Outcome	**Presence of prognostic factor, N = 132**	**Absence of prognostic factor, N = 524**
Development of OME No of events	n = 35	n = 78

Ear infections in past year versus no ear infections in past year: Development of OME

Outcome	**Presence of prognostic factor, N = 228**	**Absence of prognostic factor, N = 428**
Development of OME No of events	n = 57	n = 55

Fluid or pus discharge from ears in past year versus no fluid or pus discharge from ears in past year: Development of OME

Outcome	Presence of prognostic factor vs Absence of prognostic factor, N2 = 45, N1 = 611
Development of OME adjusted Odds ratio/95% CI	2.1 (1.01 to 4.35)

Exposure to other children: Attending day care versus not attending day care: Development of OME

Outcome	Presence of prognostic factor, N = 80	Absence of prognostic factor, N = 576
Development of OME No of events	n = 31	n = 80

Exposure to other children: Attending childcare for ≥20 h a week versus not attending childcare for ≥20 h a week: Development of OME

Outcome	Presence of prognostic factor vs Absence of prognostic factor, N2 = 61, N1 = 595
Development of OME adjusted Odds ratio/95% CI	5.21 (2.9 to 9.35)

Exposure to other children: Attending church versus not attending church: Development of OME

Outcome	Presence of prognostic factor vs Absence of prognostic factor, N2 = 591, N1 = 65
Development of OME adjusted Odds ratio/95% CI	2.78 (1.05 to 7.4)

Bed-sharing versus no bed-sharing: Development of OME

Outcome	Presence of prognostic factor, N = 559	Absence of prognostic factor, N = 97
Development of OME No of events	n = 89	n = 22

Exclusive breastfeeding at 6 weeks versus no exclusive breastfeeding at 6 weeks: Development of OME

Outcome	Presence of prognostic factor, N = 312	Absence of prognostic factor, N = 344
Development of OME No of events	n = 46	n = 67

OME: otitis media with effusion

Critical appraisal - NGA Critical appraisal - QUIPS checklist

Section	Question	Answer
Study participation	Summary Study participation	Moderate risk of bias *(Limited information regarding baseline characteristics of the study population provided)*
Study Attrition	Study Attrition Summary	Moderate risk of bias *(36% of participants (N=384/1040) did not complete tympanometry screening and not included in final analyses. There were some differences in characteristics (e.g., sex) between those that completed the study and those that did not.)*
Prognostic factor measurement	Prognostic factor Measurement Summary	Moderate risk of bias *(Clear specification of the method of measurement for prognostic factor not provided)*
Outcome Measurement	Outcome Measurement Summary	Low risk of bias *(Description of the valid and reliable assessment of OME provided.)*

Section	Question	Answer
Study Confounding	Study Confounding Summary	High risk of bias *(Moderate risk for coughs/colds, attending childcare, attending church and fluid or pus discharge from ears: Confounders are accounted for in the analysis, but methods used to measure confounders not explicitly provided. Limited number of baseline characteristics were presented. High risk for attending day care, breathing problems, ear infections, bed-sharing, and exclusive breastfeeding: No attempts were made to control for potential important confounders (e.g., age and severity of hearing loss), and limited number of baseline characteristics were presented)*
Statistical Analysis and Reporting	Statistical Analysis and Presentation Summary	High risk of bias *(Not clear if there were any substantial differences in confounding factors of intertest specified in the review protocol (age, severity of hearing loss and socio-economic status) between the groups with and without the prognostic factor as no such data reported or controlled for. There was no evidence of selective reporting of the results)*
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Directly applicable

OME: otitis media with effusion; QUIPS: quality in prognosis studies

Appendix E Forest plots

Forest plots for review question: What are the modifiable risk factors for developing OME in children under 12 years?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What are the modifiable risk factors for developing OME in children under 12 years?

Table 4: Evidence profile for prognostic factors for development of OME

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of prognostic factor	Absence of prognostic factor	Relative (95% CI)	Absolute		
Prognostic factor: Paranasal sinusitis												
1 (Hong 2008)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	80/319 (25.1%)	36/201 (17.9%)	RR 1.4 (0.99 to 1.99)	72 more per 1000 (from 2 fewer to 177 more)	VERY LOW	CRITICAL
Prognostic factor: Coughs/colds ≥5 times in past year (adjusted)												
1 (Paterson 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24/193 (12.4%)	15/463 (3.2%)	OR 1.91 (1.22 to 2.99)	28 more per 1000 (from 7 more to 59 more)	VERY LOW	CRITICAL
Prognostic factor: Breathing problems ≥5 times in past year												
1 (Paterson 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	35/132 (26.5%)	78/524 (14.9%)	RR 1.78 (1.26 to 2.53)	116 more per 1000 (from 39 more to 228 more)	VERY LOW	CRITICAL
Prognostic factor: Non-allergic rhinitis (adjusted)												
1 (Kreiner-Moller 2012	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	NR	NR	OR 0.80 (0.41 to 1.58)	NC	VERY LOW	CRITICAL
Prognostic factor: Ear infections in past year												
1 (Paterson 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	57/228 (25%)	55/428 (12.9%)	RR 1.95 (1.39 to 2.72)	122 more per 1000 (from 50 more to 221 more)	VERY LOW	CRITICAL
Prognostic factor: Fluid or pus discharge from ears in past year (adjusted)												
1 (Paterson 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/45 (31.1%)	98/611 (16%)	OR 2.1 (1.01 to 4.35)	126 more per 1000 (from 1 more to 293 more)	VERY LOW	CRITICAL
Prognostic factor: Exposure to other children: Attending day care												
1 (Paterson 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	31/80 (38.8%)	80/576 (13.9%)	RR 2.79 (1.98 to 3.93)	249 more per 1000 (from 136 more to 407 more)	VERY LOW	CRITICAL
Prognostic factor: Exposure to other children: Attending childcare for ≥20 h a week (adjusted)												
1 (Paterson 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	28/61 (45.9%)	83/595 (13.9%)	OR 5.21 (2.9 to 9.36)	318 more per 1000 (from 180 more to 463 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of prognostic factor	Absence of prognostic factor	Relative (95% CI)	Absolute		
Prognostic factor: Exposure to other children: Attending church (adjusted)												
1 (Paterson 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	106/591 (17.9%)	6/65 (9.2%)	OR 2.78 (1.05 to 7.4)	128 more per 1000 (from 4 more to 336 more)	VERY LOW	CRITICAL
Prognostic factor: Bed-sharing												
1 (Paterson 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	89/559 (15.9%)	22/97 (22.7%)	RR 0.70 (0.46 to 1.06)	68 fewer per 1000 (from 122 fewer to 14 more)	VERY LOW	CRITICAL
Prognostic factor: Eczema (adjusted)												
1 (Kreiner-Moller 2012	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	NR	NR	OR 1.16 (0.68 to 1.98)	NC	VERY LOW	CRITICAL
Prognostic factor: Exclusive breastfeeding at 6 weeks												
1 (Paterson 2007)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	46/312 (14.7%)	67/344 (19.5%)	RR 0.76 (0.54 to 1.07)	47 fewer per 1000 (from 90 fewer to 14 more)	VERY LOW	CRITICAL
Prognostic factor: Pneumococcal vaccination (PCV7 plus PPV23)												
1 (Mackenzie 2009)	observational studies	very serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	81/84 (96.4%)	41/41 (100%)	RR 0.97 (0.92 to 1.03)	30 fewer per 1000 (from 80 fewer to 30 more)	VERY LOW	CRITICAL
Prognostic factor: Pneumococcal vaccination (PCV7 era)												
1 (Ogawa 2022)	observational studies	very serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	1961/737745 (0.27%)	805/272695 (0.3%)	POR 0.9 (0.83 to 0.98)	0 fewer per 1000 (from 0 fewer to 1 fewer)	VERY LOW	CRITICAL
Prognostic factor: Pneumococcal vaccination (PCV13 era)												
1 (Ogawa 2022)	observational studies	very serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	4433/1747807 (0.25%)	805/272695 (0.3%)	POR 0.85 (0.79 to 0.92)	0 fewer per 1000 (from 0 fewer to 1 fewer)	VERY LOW	CRITICAL

CI: confidence interval; MTTI: myringotomy with tympanostomy tube insertion; NC: not calculable; NR: not reported; OME: otitis media with effusion; OR: odds ratio; PCV: pneumococcal conjugate vaccine; POR: Peto odds ratio; PPV23: 23-valent polysaccharide vaccine; QUIPS: Quality in Prognosis Studies; RR: risk ratio

[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS

[2] <150 events

[3] Parts of study conducted before 2000

[4] The study reported MTTI, rather than rates of OME itself

Table 5: Evidence profile for prognostic factors for development of persistent OME (chronic OME)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of prognostic factor	Absence of prognostic factor	Relative (95% CI)	Absolute		
Prognostic factor: Household smoking: Mother smokes												
1 (Hammaren-Malmi 2005	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/68 (26.5%)	37/140 (26.4%)	RR 1 (0.62 to 1.62)	0 fewer per 1000 (from 100 fewer to 164 more)	VERY LOW	CRITICAL
Prognostic factor: Household smoking: Father smokes												
1 (Hammaren-Malmi 2005)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	24/91 (26.4%)	31/115 (27%)	RR 0.98 (0.62 to 1.54)	5 fewer per 1000 (from 102 fewer to 146 more)	VERY LOW	CRITICAL
Prognostic factor: Exposure to other children: Attending day care at age <2 years												
1 (Hammaren-Malmi 2005)	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	25/98 (25.5%)	30/110 (27.3%)	RR 0.94 (0.59 to 1.48)	16 fewer per 1000 (from 112 fewer to 131 more)	VERY LOW	CRITICAL

CI: confidence interval; OME: otitis media with effusion; QUIPS: Quality in Prognosis Studies; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] <150 events

Table 6: Evidence profile for prognostic factors for development of fluctuating OME (recurrent OME)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Presence of prognostic factor	Absence of prognostic factor	Relative (95% CI)	Absolute		
Prognostic factor: Adenoid hypertrophy (unadjusted)												
1 (De Felice 2008	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	NR	NR	OR 9.96 (5.17 to 19.19)	NC	VERY LOW	CRITICAL

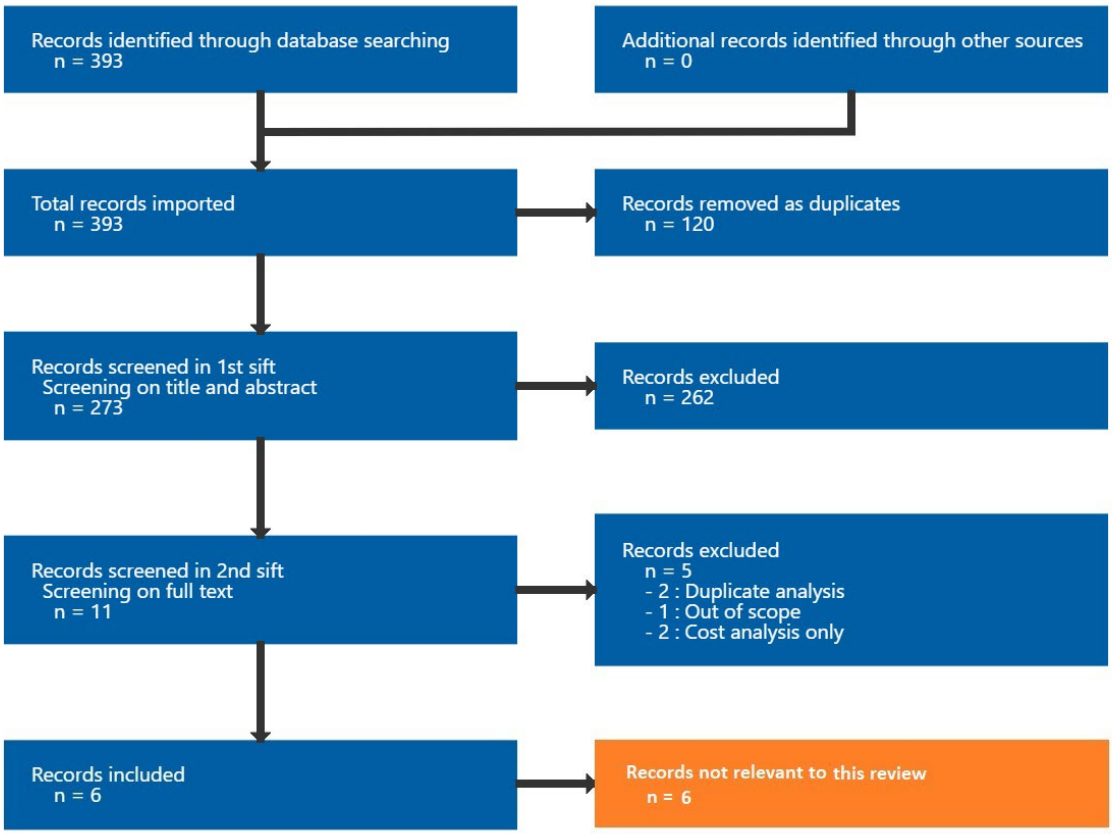
CI: confidence interval; NC: not calculated; NR: not reported; OME: otitis media with effusion; OR: odds ratio; QUIPS: Quality in Prognosis Studies
[1] Very serious risk of bias in the evidence contributing to the outcomes as per QUIPS
[2] <150 events

Appendix G Economic evidence study selection

Study selection for: What are the modifiable risk factors for developing OME in children under 12 years?

A global search was undertaken to cover all the review questions considered in this guideline, but no economic evidence was identified which was applicable to this review question (see Figure 2).

Figure 2: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What are the modifiable risk factors for developing OME in children under 12 years?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What are the modifiable risk factors for developing OME in children under 12 years?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What are the modifiable risk factors for developing OME in children under 12 years?

Excluded prognostic studies

Table 5: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Abrahams, Sheryl W and Labbok, Miriam H (2011) Breastfeeding and otitis media: a review of recent evidence. Current allergy and asthma reports 11(6): 508-12	- Study design does not meet inclusion criteria *Narrative review*
Adamczyk, P., Pucher, B., Prauzinska, M. et al. (2018) Prevalence of allergy in children with adenoid hypertrophy and otitis media with effusion admitted to the department of pediatric otolaryngology in Poznan. Family Medicine and Primary Care Review 20(3): 205-209	- Study design does not meet inclusion criteria *Cross-sectional study*
Al-Saab, Fahad, Manoukian, John J, Al-Sabah, Basel et al. (2008) Linking laryngopharyngeal reflux to otitis media with effusion: pepsinogen study of adenoid tissue and middle ear fluid. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale 37(4): 565-71	- Study design does not meet inclusion criteria *Case-control study*
Alde, Mirko, Di Berardino, Federica, Marchisio, Paola et al. (2021) Effects of COVID-19 Lockdown on Otitis Media With Effusion in Children: Future Therapeutic Implications. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 165(5): 710-715	- Comparison does not meet inclusion criteria *Before COVID-19 vs. Post-/during COVID-19 pandemic (Non modifiable risk factor)*
Alles, R, Parikh, A, Hawk, L et al. (2001) The prevalence of atopic disorders in children with chronic otitis media with effusion. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 12(2): 102-6	- Study conducted before 2000
Alper, C.M., Winther, B., Mandel, E.M. et al. (2009) Rate of concurrent otitis media in upper respiratory tract infections with	- Insufficient presentation of results *Data on rate of OME in those without risk factors not reported*

Study	Code [Reason]
specific viruses. Archives of Otolaryngology - Head and Neck Surgery 135(1): 17-21	
Alshehri, A.M., Alhelali, S.N., Alzahrani, A.A. et al. (2021) Risk factors of otitis media in children, asser region: A case-control study. Bahrain Medical Bulletin 43(3): 576-579	- Study design does not meet inclusion criteria *Cross-sectional study*
Aniansson, Gustaf, Svensson, Henry, Becker, Magnus et al. (2002) Otitis media and feeding with breast milk of children with cleft palate. Scandinavian journal of plastic and reconstructive surgery and hand surgery 36(1): 9-15	- Study conducted before 2000
Anonymous (2002) Selecting persistent glue ear for referral in general practice: a risk factor approach. The British journal of general practice : the journal of the Royal College of General Practitioners 52(480): 549-53	- Study design does not meet inclusion criteria *Nested case control study*
Aydogan, Barlas, Kiroglu, Mete, Altintas, Derya et al. (2004) The role of food allergy in otitis media with effusion. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 130(6): 747-50	- Study conducted before 2000
Balotro, M.V. and Andaya, A.G. (2009) Atopic pediatric patients with otitis media with effusion and its correlation to hearing loss. Annals of Allergy, Asthma and Immunology 103(5suppl3): a52	- Conference abstract.
Ben-Shimol, Shalom, Givon-Lavi, Noga, Leibovitz, Eugene et al. (2019) Studying PCV impact on clinical presentation of otitis media helps to understand its pathogenesis. Vaccine 37(1): 1-6	- Population does not meet inclusion criteria *No information on whether participants had OME*
Benninger, Kristen L, Richard, Celine, Conroy, Sara et al. (2022) One-Year Neurodevelopmental Outcomes After Neonatal Opioid Withdrawal Syndrome: A Prospective Cohort Study. Perspectives of the ASHA special interest groups 7(4): 1019-1032	- Study design does not meet inclusion criteria *The study investigates one-year neurodevelopmental outcomes after neonatal opioid withdrawal syndrome*
Besednjak-Kocijancic, L. et al. (2009) Assessment of the association between	- Conference abstract.

Study	Code [Reason]
Otitis media with effusion, asthma and atopic dermatitis in preschool-children. Allergy: European Journal of Allergy and Clinical Immunology 64(suppl90): 446	
Bhagat, D.R.; Kumar, R.; Chowdhary, A. (2004) Smoking and ear disease: A concern for otologists. Indian Journal of Otology 10(dec): 14-17	- Study design does not meet inclusion criteria *Narrative review*
Bie, X., Sun, X.-Z., Wang, J.-Z. et al. (2010) Relationship between adenoid hypertrophy and secretory otitis media in children. Journal of Dalian Medical University 32(3): 299	- Non-OECD high-income country *China*
Braun, T., Dreher, A., Dirr, F. et al. (2012) Pediatric OSAS and otitis media with effusion. HNO 60(3): 216-219	- Non-English language article
Brown, J.R., Jones, D.J., Siegel, B. et al. (2019) Incidence of otitis media in patients with eosinophilic esophagitis. Otolaryngology - Head and Neck Surgery 161(2supplement): p285	- Conference abstract.
Byeon, Haewon (2019) The association between allergic rhinitis and otitis media: A national representative sample of in South Korean children. Scientific reports 9(1): 1610	- Population does not meet inclusion criteria *No information on how many participants had OME, and results were not presented separately for those with OME*
Carr, M M, Poje, C P, Ehrig, D et al. (2001) Incidence of reflux in young children undergoing adenoidectomy. The Laryngoscope 111(12): 2170-2	- Study conducted before 2000
Casselbrant, Margaretha L; Mandel, Ellen M; Doyle, William J (2016) Information on co-morbidities collected by history is useful for assigning Otitis Media risk to children. International journal of pediatric otorhinolaryngology 85: 136-40	- Study design does not meet inclusion criteria *Case-control study*
Chavanet, Pascal (2008) Viral upper respiratory tract infection and otitis media complication in young children. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 46(6): 824	- Study design does not meet inclusion criteria *Commentary*
Chen, Tiffany, Ashman, Peter E, Bojrab, Dennis I 2nd et al. (2021) Diagnosis and	- Population does not meet inclusion criteria *Adults with eosinophilic otitis media*

Study	Code [Reason]
management of eosinophilic otitis media: a systematic review. Acta oto-laryngologica 141(6): 579-587	
Chonmaitree, Tasnee, Revai, Krystal, Grady, James J et al. (2008) Viral upper respiratory tract infection and otitis media complication in young children. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 46(6): 815-23	- Insufficient presentation of results *Data on rate of OME in those without risk factors not reported*
Chung, Winnie, Leung, Jessica, Lanzieri, Tatiana M et al. (2020) Middle Ear Effusion in Children With Congenital Cytomegalovirus Infection. The Pediatric infectious disease journal 39(4): 273-276	- Comparison does not meet inclusion criteria *Asymptomatic congenital cytomegalovirus infection vs. Symptomatic congenital cytomegalovirus infection. Non-modifiable risk factor.*
Clamp, P J, De-Loyde, K, Maw, A R et al. (2020) Factors associated with the development of paediatric chronic otitis media by age nine: a prospective longitudinal cohort study of 6560 children. The Journal of laryngology and otology: 1-12	- Population does not meet inclusion criteria *Children with chronic otitis media (not OME)*
Clark, C.M.; Benich, S.; Carr, M.M. (2017) Middle ear effusion not linked with tobacco exposure. Otolaryngology - Head and Neck Surgery (United States) 157(1supplement1): p275	- Conference abstract.
Coulson, C J, Drake-Lee, A B, Plant, T et al. (2006) Total serum IgE and IgE antibodies specific to house dust mite found in two aged-matched cohorts of children with and without otitis media with effusion. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 31(2): 130-3	- Study design does not meet inclusion criteria *Case-control study*
Damoiseaux, Roger A M J, Rovers, Maroeska M, Van Balen, Frank A M et al. (2006) Long-term prognosis of acute otitis media in infancy: determinants of recurrent acute otitis media and persistent middle ear effusion. Family practice 23(1): 40-5	- Study conducted before 2000
De Corso, Eugenio, Cantone, Elena, Galli, Jacopo et al. (2021) Otitis media in children: Which phenotypes are most linked to	- Systematic review, included studies checked for relevance

Study	Code [Reason]
allergy? A systematic review. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 32(3): 524-534	*Case-control studies, cross-sectional studies, studies in acute OM or studies from non-OECD high-income countries*
Dewey, C; Midgeley, E; Maw, R (2000) The relationship between otitis media with effusion and contact with other children in a british cohort studied from 8 months to 3 1/2 years. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. International journal of pediatric otorhinolaryngology 55(1): 33-45	- Study conducted before 2000
Doyle, William J; Winther, Birgit; Alper, Cuneyt M (2008) Daily tympanometry for high-resolution measurement of the time between onset of cold-like illness and middle ear effusion. The Laryngoscope 118(6): 1066-71	- Insufficient presentation of results *Data on rate of OME in those without risk factors not reported*
Dreher, A.; Patscheider, M.; Braun, T. (2011) Pediatric obstructive sleep apnea and otitis media with effusion. Otolaryngology - Head and Neck Surgery 145(suppl2): 242	- Conference abstract. *Poster*
Engel, J, Mahler, E, Anteunis, L et al. (2001) Why are NICU infants at risk for chronic otitis media with effusion?. International journal of pediatric otorhinolaryngology 57(2): 137-44	- Study conducted before 2000
Engel, Joost A M; Straetemans, Masja; Zielhuis, Gerhard A (2005) Birth characteristics and recurrent otitis media with effusion in young children. International journal of pediatric otorhinolaryngology 69(4): 533-40	- Cohort study with N<40 per arm
Flasche, Stefan; Givon-Lavi, Noga; Dagan, Ron (2016) Using Pneumococcal Carriage Data to Monitor Postvaccination Changes in the Incidence of Pneumococcal Otitis Media. American journal of epidemiology 184(9): 652-659	- Population does not meet inclusion criteria *No information on how many participants had OME, and results were not presented separately for participants OME*
Galic, Marta Zrinka and Klancnik, Marisa (2022) ADENOID SIZE IN CHILDREN WITH OTITIS MEDIA WITH EFFUSION. Acta clinica Croatica 60(3): 532-539	- Comparison does not meet inclusion criteria *Comparison between different age groups. No comparison between modifiable risk factor and absence of risk factor*

Study	Code [Reason]
Gliddon, M L and Sutton, G J (2001) Prediction of 8-month MEE from neonatal risk factors and test results in SCBU and full-term babies. British journal of audiology 35(1): 77-85	- Study conducted before 2000
Going, J A (2001) Common upper respiratory infections in ambulatory practice: otitis media. Journal of the South Carolina Medical Association (1975) 97(1): 33-6	- Full text paper not available
Gorecka-Tuteja, A., Jastrzebska, I., Sladek, M. et al. (2011) The characteristic of gastroesophageal reflux in children with otitis media with effusion using multichannel impedance (MII) combined with dual PH-metry. Journal of Pediatric Gastroenterology and Nutrition 52(suppl1): e171-e172	- Conference abstract.
Gorecka-Tuteja, Anna, Jastrzebska, Izabela, Skladzien, Jacek et al. (2016) Laryngopharyngeal Reflux in Children with Chronic Otitis Media with Effusion. Journal of neurogastroenterology and motility 22(3): 452-8	- Outcome does not meet inclusion criteria *Study did not report development of first episode/persistent/fluctuating OME*
Haksever, Mehmet, Durgut, Osman, Demirci, Hakan et al. (2022) Relationship between otitis media with effusions and pediatric obesity. International journal of pediatric otorhinolaryngology 161: 111272	- Non-OECD high-income country *Turkey*
Heo, Kyung Wook; Kim, Min Jae; Lee, Jun Ho (2018) Impact of nasal conditions on chronic otitis media: a cross-sectional study in Koreans. Acta oto-laryngologica 138(2): 116-121	- Population does not meet inclusion criteria *Participants with suppurative chronic otitis media*
Huang, Y., Holley, A., Suarez, D. et al. (2022) Sensorineural Hearing Loss in Infants With Failed Newborn Hearing Screen and Otitis Media With Effusion. Otolaryngology - Head and Neck Surgery 167(1supplement): p130	- Conference abstract.
Hullegie, Saskia, Schilder, Anne G M, Marchisio, Paola et al. (2021) A Strong Decline in the Incidence of Childhood Otitis Media During the COVID-19 Pandemic in the Netherlands. Frontiers in cellular and infection microbiology 11: 768377	- Comparison does not meet inclusion criteria *Before COVID-19 vs. Post-/during COVID-19 pandemic (Non modifiable risk factor)*

Study	Code [Reason]
Humaid, Al-Humaid I, Ashraf, Abou-Halawa S, Masood, Khan A et al. (2014) Prevalence and risk factors of Otitis Media with effusion in school children in Qassim Region of Saudi Arabia. International journal of health sciences 8(4): 325-34	- Study design does not meet inclusion criteria *Cross-sectional study*
Hurst, David S (2008) Efficacy of allergy immunotherapy as a treatment for patients with chronic otitis media with effusion. International journal of pediatric otorhinolaryngology 72(8): 1215-23	- Outcome does not meet inclusion criteria *Study did not report development of first episode/persistent/fluctuating OME*
Iannella, Giannicola, Magliulo, Giuseppe, Lechien, Jerome R et al. (2022) Impact of COVID-19 pandemic on the incidence of otitis media with effusion in adults and children: a multicenter study. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 279(5): 2383-2389	- Comparison does not meet inclusion criteria *Comparison between before and during COVID-19 pandemic (Non modifiable risk factor)*
Igde, M., Erkilet, E., Koyuncu, M. et al. (2010) The role of allergic rhinitis in the development of otitis media with effusion. Allergy: European Journal of Allergy and Clinical Immunology 65(suppl92): 298	- Conference abstract.
Inoue, Maki, Yamamoto, Kouji, Hirama, Mariko et al. (2021) Prognostic factors of early-onset otitis media with effusion in children treated using tympanostomy. Acta oto-laryngologica 141(8): 742-748	- Outcome does not meet inclusion criteria *Study did not report development of first episode/persistent/fluctuating OME*
Jang, Chul Ho and Jung, Jae Kwon (2003) Expression of mast cell tryptase in pediatric otitis media with effusion. International journal of pediatric otorhinolaryngology 67(11): 1185-8	- Outcome does not meet inclusion criteria *Study did not report development of first episode/persistent/fluctuating OME*
Jastrzebska, I., Gorecka-Tuteja, A., Sladek, M. et al. (2012) Characteristics of laryngopharyngeal reflux as well as of gastroesophageal reflux in children with otitis media with effusion. Pediatria Wspolczesna 14(2): 69-73	- Non-English language article
Johnston, Brittany N A, Preciado, Diego A, Ondrey, Frank G et al. (2008) Presence of otitis media with effusion and its risk factors	- Study design does not meet inclusion criteria *Case-control study*

Study	Code [Reason]
affect serum cytokine profile in children. International journal of pediatric otorhinolaryngology 72(2): 209-14	
Johnston, James, McLaren, Holly, Mahadevan, Murali et al. (2019) Clinical characteristics of obstructive sleep apnea versus infectious adenotonsillar hyperplasia in children. International journal of pediatric otorhinolaryngology 116: 177-180	- Insufficient presentation of results *Data on rate of OME in those without risk factors not reported*
Kalcioglu, M Tayyar, Sallavaci, Suela, Hrncic, Nermin et al. (2021) Prevalence of and factors affecting otitis media with effusion in children in the region from Balkans to Caspian basin; A multicentric cross-sectional study. International journal of pediatric otorhinolaryngology 143: 110647	- Study design does not meet inclusion criteria *Cross-sectional study*
Kang, Noeul, Shin, Joongbo, Cho, Yang-Sun et al. (2022) Intractable middle ear effusion in EGPA patients might cause permanent hearing loss: a case-control study. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 18(1): 68	- Population does not meet inclusion criteria *Participants aged ≥40 years were included*
Karawani, H., Matanis, W., Na'ara, S. et al. (2022) Middle ear effusion and newborn hearing screening. European Archives of Oto-Rhino-Laryngology	- Study design does not meet inclusion criteria *Non-comparative study*
Kim, S.K., Park, I.-S., Hong, S.J. et al. (2022) Association Between Pneumonia and Chronic Otitis Media: A Nested Case-Control Study Using a National Health Screening Cohort. International Journal of Infectious Diseases 118: 54-61	- Study design does not meet inclusion criteria *Case-control study*
Kim, So Young, Son, Bu-Soon, Park, Hee-Jin et al. (2017) Impact of environmental volatile organic compounds on otitis media in children: Correlation between exposure and urinary metabolites. International journal of pediatric otorhinolaryngology 93: 157-162	- Study design does not meet inclusion criteria *Cross-sectional study*
Klopp-Dutote, Nathalie, Kolski, Catherine, Strunski, Vladimir et al. (2018) Tympanostomy tubes for serous otitis media and risk of recurrences. International	- Insufficient presentation of results *Data on rate of OME in each group not reported*

Study	Code [Reason]
journal of pediatric otorhinolaryngology 106: 105-109	
Kourelis, Konstantinos; Avgeri, Aikaterini; Kourelis, Theodoros (2021) Rising Resonance Frequency Is the Sole Sign of Early Middle Ear Disease in Children With Adenoid Hypertrophy. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 42(6): e724-e729	- Study design does not meet inclusion criteria *The observations are not independent as the unit of analysis is 'ears' not 'people', and the observations within participants could be more similar than those between participants*
Kouwen, H B and DeJonckere, P H (2007) Prevalence of OME is reduced in young children using chewing gum. Ear and hearing 28(4): 451-5	- Study design does not meet inclusion criteria *Cross-sectional study*
Kubba, Haytham (2007) Re: Umapathy et al. A community based questionnaire study on the association between symptoms suggestive of otitis media with effusion, rhinitis and asthma in primary school children Int. J. Pediatr. Otorhinolaryngol. 2007;71:705-12. International journal of pediatric otorhinolaryngology 71(11): 1813-1814	- Study design does not meet inclusion criteria *Letter to the editor*
Kwon, Chul, Lee, Ho Yun, Kim, Myung Gu et al. (2013) Allergic diseases in children with otitis media with effusion. International journal of pediatric otorhinolaryngology 77(2): 158-61	- Study design does not meet inclusion criteria *Case-control study*
Landry, E.C., Behzadpour, H.K., Afsar, N. et al. (2022) Impact of Upper Airway Management in Robin Sequence on Rates of Serous Otitis Media: A Prospective Cohort Analysis. Otolaryngology - Head and Neck Surgery 167(1supplement): p119-p120	- Conference abstract.
Leach, Amanda J, Wigger, Christine, Beissbarth, Jemima et al. (2016) General health, otitis media, nasopharyngeal carriage and middle ear microbiology in Northern Territory Aboriginal children vaccinated during consecutive periods of 10-valent or 13-valent pneumococcal conjugate vaccines. International journal of pediatric otorhinolaryngology 86: 224-32	- Insufficient presentation of results *Data on rate of OME in those without risk factors not reported*

Study	Code [Reason]
Lechien, Jerome R, Hans, Stephane, Simon, Francois et al. (2021) Association Between Laryngopharyngeal Reflux and Media Otitis: A Systematic Review. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 42(7): e801-e814	- Systematic review, included studies checked for relevance *Case-control studies, non-comparative studies, and studies from non-OECD high-income countries were included*
Lopez Perez, G.; Ruiz Hernandez, F.; Mora Magana, I. (2011) What is the frequency between otitis and allergic rhinitis?. Allergy: European Journal of Allergy and Clinical Immunology 66(suppl94): 692	- Conference abstract.
Lovett, A.; Walters, B.; Kumar Bhimrao, S. (2022) Outcomes for Paediatric Patients Awaiting Bilateral Myringotomy and Ventilation Tube Insertion for Otitis Media with Effusion Listed Prior to the COVID-19 Pandemic. British Journal of Surgery 109(supplement6): vi38	- Conference abstract.
Luong, Amber and Roland, Peter S (2008) The link between allergic rhinitis and chronic otitis media with effusion in atopic patients. Otolaryngologic clinics of North America 41(2): 311-vi	- Study design does not meet inclusion criteria *Narrative review*
Manole, F. (2012) Allergic rhinitis and related diseases in children. Allergy: European Journal of Allergy and Clinical Immunology 67(suppl96): 186	- Conference abstract.
Manole, F. (2011) Clinical correlation of allergic rhinitis and middle ear diseases. Allergy: European Journal of Allergy and Clinical Immunology 66(suppl94): 354	- Conference abstract.
Marseglia, Gian Luigi, Pagella, Fabio, Caimmi, Davide et al. (2008) Increased risk of otitis media with effusion in allergic children presenting with adenoiditis. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 138(5): 572-5	- Study design does not meet inclusion criteria *Cross-sectional study*
Martines, F, Bentivegna, D, Maira, E et al. (2011) Risk factors for otitis media with effusion: case-control study in Sicilian	- Study design does not meet inclusion criteria *Case-control study*

Study	Code [Reason]
schoolchildren. International journal of pediatric otorhinolaryngology 75(6): 754-9	
Martines, F, Martinciglio, G, Martines, E et al. (2010) The role of atopy in otitis media with effusion among primary school children: audiological investigation. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 267(11): 1673-8	- Comparison does not meet inclusion criteria *Atopy (non-modifiable risk factor) vs. No atopy*
Martines, Francesco, Bentivegna, Daniela, Di Piazza, Fabiola et al. (2010) The point prevalence of otitis media with effusion among primary school children in Western Sicily. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 267(5): 709-14	- Comparison does not meet inclusion criteria *Atopy (non-modifiable risk factor) vs. No atopy*
Martines, Francesco, Martines, Enrico, Sciacca, Vincenzo et al. (2011) Otitis media with effusion with or without atopy: audiological findings on primary schoolchildren. American journal of otolaryngology 32(6): 601-6	- Comparison does not meet inclusion criteria *Atopy (non-modifiable risk factor) vs. No atopy*
McKenna Benoit, Margo, Henry, Kenneth S, Orlando, Mark et al. (2022) Tone in Noise Detection in Children with a History of Temporary Conductive Hearing Loss. Journal of the Association for Research in Otolaryngology : JARO	- Study design does not meet inclusion criteria *The study investigates the effect of early conductive hearing loss on tone in noise detection in healthy children*
Midgley, E J, Dewey, C, Pryce, K et al. (2000) The frequency of otitis media with effusion in British pre-school children: a guide for treatment. ALSPAC Study Team. Clinical otolaryngology and allied sciences 25(6): 485-91	- Study conducted before 2000
Minto, H. and Hogan, A.D. (2013) Allergic rhinitis is associated with otitis media with effusion: A birth cohort study. Pediatrics 132(suppl1): 29-s30	- Study design does not meet inclusion criteria *Commentary*
Miura, Mauricio Schreiner; Mascaro, Miguel; Rosenfeld, Richard M (2012)	- Systematic review, included studies checked for relevance

Study	Code [Reason]
Association between otitis media and gastroesophageal reflux: a systematic review. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 146(3): 345-52	*Prospective cohort study in acute OM, Cross-sectional studies and randomised controlled trials were included*
MRC Multi-centre Otitis Media Study, Group (2001) Risk factors for persistence of bilateral otitis media with effusion. Clinical otolaryngology and allied sciences 26(2): 147-56	- Insufficient presentation of results *Insufficient data to calculate rate of OME in each group*
Ngo, Chinh C, Massa, Helen M, McMonagle, Brent A et al. (2022) Predominant Bacterial and Viral Otopathogens Identified Within the Respiratory Tract and Middle Ear of Urban Australian Children Experiencing Otitis Media Are Diversely Distributed. Frontiers in cellular and infection microbiology 12: 775535	- Study design does not meet inclusion criteria *Case-control study, and data on rate of OME in those without risk factors not reported*
Nguyen, Dang-Khoa, Jueng, Jeremy, Maul, Timothy M et al. (2021) Middle ear effusion prevalence at time of tympanostomy before and during COVID-19 pandemic. International journal of pediatric otorhinolaryngology 147: 110785	- Comparison does not meet inclusion criteria *Pre-COVID-19 vs. During COVID-19 (Non modifiable risk factor)*
Novikova, V.P., Savenko, I.V., Garbaruk, E.S. et al. (2021) Otitis media with effusion in extremely premature children. Archives of Disease in Childhood 106(suppl2): a14-a15	- Conference abstract.
Oliveira, Karen Amanda Soares de, Esper, Marina Tomaz, Oliveira, Morgana Livia de et al. (2021) Correlation between cow's milk protein allergy and otitis media: a systematic review. Brazilian journal of otorhinolaryngology	- Systematic review, included studies checked for relevance *Cross-sectional studies and study conducted before 2000 were included*
Padia, Reema, Alt, Jeremiah A, Curtin, Karen et al. (2017) Environmental contributions to otitis media requiring tympanostomy tubes. International journal of pediatric otorhinolaryngology 101: 97-101	- Study design does not meet inclusion criteria *Case-control study*
Parietti-Winkler, Cecile, Baumann, Cedric, Gallet, Patrice et al. (2009) Otitis media with effusion as a marker of the inflammatory process associated to nasal polyposis. Rhinology 47(4): 396-9	- Study design does not meet inclusion criteria *Case-control study*

Study	Code [Reason]
Passali, D., Damiani, V., Passali, G.C. et al. (2005) The impact of persistent allergic rhinitis on the middle ear - Data from the observation of 100 children. Allergy and Clinical Immunology International 17(3): 114-116	- Full text paper not available
Passali, Desiderio, Passali, Giulio C, Lauriello, Maria et al. (2014) Nasal Allergy and Otitis Media: A real correlation?. Sultan Qaboos University medical journal 14(1): e59-64	- Insufficient presentation of results *Data on rate of OME in those without risk factors not reported*
Patel, S; Wooles, N; Martin, T (2020) A systematic review of the impact of cigarettes and electronic cigarettes in otology. The Journal of laryngology and otology: 1-6	- Systematic review, included studies checked for relevance *Non-comparative studies, case-control studies and studies from non-OECD high-income countries were included*
Pau, B.C. and Ng, D.K. (2016) Prevalence of otitis media with effusion in children with allergic rhinitis, a cross sectional study. International Journal of Pediatric Otorhinolaryngology 84: 156-160	- Study design does not meet inclusion criteria *Cross-sectional study*
Pelikan, Z; Pelikan-Filipek, M; Miessen, WMA (2002) The possible role of the nasal allergy in some patients with chronic secretory otitis media (SOM) and the protective effects of intranasal cromolyn (DSCG). XXI congress of the european academy of allergology and clinical immunology (EAACI), 1-5 june 2002, naples, italy allergy 57(s73): 247-8, Abstract No. 794	- Conference abstract.
Pereira, Nicola M, Maresh, Alison M, Modi, Vikash K et al. (2022) Tympanostomy tubes in the age of quarantine. International journal of pediatric otorhinolaryngology 154: 111047	- Comparison does not meet inclusion criteria
Plasschaert, Astrid I O, Rovers, Maroeska M, Schilder, Anne G M et al. (2006) Trends in doctor consultations, antibiotic prescription, and specialist referrals for otitis media in children: 1995-2003. Pediatrics 117(6): 1879-86	- Comparison does not meet inclusion criteria *Comparison between boys and girls, but no comparison between those with modifiable risk factor and those without modifiable risk factor*
Poehling, Katherine A, Szilagyi, Peter G, Grijalva, Carlos G et al. (2007) Reduction of frequent otitis media and pressure-equalizing tube insertions in children after	- Insufficient presentation of results *No information on how many participants had OME, and results were not presented separately for participants with OME*

Study	Code [Reason]
introduction of pneumococcal conjugate vaccine. Pediatrics 119(4): 707-15	
Quaranta, Nicola, Milella, Claudia, Iannuzzi, Lucia et al. (2013) A study of the role of different forms of chronic rhinitis in the development of otitis media with effusion in children affected by adenoid hypertrophy. International journal of pediatric otorhinolaryngology 77(12): 1980-3	- Study design does not meet inclusion criteria *Cross-sectional study*
Ralli, Giovanni, Ruoppolo, Giovanni, Mora, Renzo et al. (2011) Deleterious sucking habits and atypical swallowing in children with otitis media with effusion. International journal of pediatric otorhinolaryngology 75(10): 1260-4	- Study design does not meet inclusion criteria *Case-control study*
Rezes, Szilard, Kesmarki, Katalin, Sipka, Sandor et al. (2007) Characterization of otitis media with effusion based on the ratio of albumin and immunoglobulin G concentrations in the effusion. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 28(5): 663-7	- Outcome does not meet inclusion criteria *Study did not report development of first episode/persistent/fluctuating OME, and no risk factor of interest*
Rihkanen, Heikki, Carpen, Olli, Roivainen, Merja et al. (2004) Rhinovirus in adenoid tissue. International journal of pediatric otorhinolaryngology 68(7): 903-8	- Study design does not meet inclusion criteria *Cross-sectional study*
Roditi, Rachel E; Veling, Maria; Shin, Jennifer J (2016) Age: An effect modifier of the association between allergic rhinitis and Otitis media with effusion. The Laryngoscope 126(7): 1687-92	- Study design does not meet inclusion criteria *Cross-sectional study*
Rovers, M.M., Zielhuis, G.A., Roberts, J.E. et al. (2004) Otitis media meta-analysis [2] (multiple letters). Pediatrics 114(2i): 508-509	- Study design does not meet inclusion criteria *Letters to the editor*
Rozmanic, Vojko, Velepic, Mitja, Ahel, Vladimir et al. (2002) Prolonged esophageal pH monitoring in the evaluation of gastroesophageal reflux in children with chronic tubotympanal disorders. Journal of pediatric gastroenterology and nutrition 34(3): 278-80	- Insufficient presentation of results *Data on rate of OME in those without risk factors not reported*

Study	Code [Reason]
Sade, Jacob, Russo, Eyal, Fuchs, Camil et al. (2003) Is secretory otitis media a single disease entity?. The Annals of otology, rhinology, and laryngology 112(4): 342-7	- Study conducted before 2000
Schloss, M.D.; Sobol, S.E.; Hamid, Q.A. (2003) The role of allergies in the pathogenesis of otitis media with effusion. Today's Therapeutic Trends 21(1): 15-26	- Study design does not meet inclusion criteria *Narrative review*
Scholz, F., Kohn, A., Rissmann, A. et al. (2013) Otitis media with effusion: Frequency, diagnosis, and therapy in early childhood. HNO 61(10): 859-865	- Non-English language article
Shaffer, A., Ford, M., Tobey, A. et al. (2021) Impact of breast milk feeding on early otologic outcomes in children with cleft palate. Cleft Palate-Craniofacial Journal 58(4suppl): 27	- Conference abstract.
Shaffer, A., Tobey, A., Ford, M. et al. (2019) Survey of barriers to breast milk feeding in children with cleft palate. Cleft Palate-Craniofacial Journal 56(1supplement): 66-67	- Conference abstract.
Shafiei Esfidvajani, A. and Bemanian, M. (2017) Role of allergy in the management of patients subjected to adenoid hypertrophy and otitis media with effusion. Allergy: European Journal of Allergy and Clinical Immunology 72(supplement103): 788-789	- Conference abstract.
Sheahan, P, Blayney, A W, Sheahan, J N et al. (2002) Sequelae of otitis media with effusion among children with cleft lip and/or cleft palate. Clinical otolaryngology and allied sciences 27(6): 494-500	- Study conducted before 2000
Shinogami, Masanobu and Ishibashi, Toshio (2004) Presence of human herpesviruses in young children with acute otitis media. International journal of pediatric otorhinolaryngology 68(2): 205-10	- Study conducted before 2000
Slack-Smith, Linda M; Read, Anne W; Stanley, Fiona J (2002) Experience of respiratory and allergic illness in children attending childcare. Child: care, health and development 28(2): 171-7	- Study conducted before 2000

Study	Code [Reason]
Smith, Clyde G, Paradise, Jack L, Sabo, Diane L et al. (2006) Tympanometric findings and the probability of middle-ear effusion in 3686 infants and young children. Pediatrics 118(1): 1-13	- Study conducted before 2000
Smith-Vaughan, Heidi, Byun, Roy, Nadkarni, Mangala et al. (2006) Measuring nasal bacterial load and its association with otitis media. BMC ear, nose, and throat disorders 6: 10	- Insufficient presentation of results *Data on rate of OME in those without risk factors not reported*
Souter, Melanie Anne, Mills, Nicola Anne, Mahadevan, Murali et al. (2009) The prevalence of atopic symptoms in children with otitis media with effusion. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 141(1): 104-7	- Study design does not meet inclusion criteria *Cross-sectional study*
Stol, Kim, Verhaegh, Suzanne J C, Graamans, Kees et al. (2013) Microbial profiling does not differentiate between childhood recurrent acute otitis media and chronic otitis media with effusion. International journal of pediatric otorhinolaryngology 77(4): 488-93	- Study design does not meet inclusion criteria *Case-control study*
Sudhoff, H, Rajagopal, S, Baguley, D M et al. (2008) A critical evaluation of the evidence on a causal relationship between Helicobacter pylori and otitis media with effusion. The Journal of laryngology and otology 122(9): 905-11	- Insufficient presentation of results *Data on rate of OME in those without risk factor not reported*
Sun, Wenxing, Jacoby, Peter, Riley, Thomas V et al. (2012) Association between early bacterial carriage and otitis media in Aboriginal and non-Aboriginal children in a semi-arid area of Western Australia: a cohort study. BMC infectious diseases 12: 366	- Insufficient presentation of results *No information on how many participants had OME, and results were not presented separately for participants with OME*
Szczepanik, Agnieszka, Koziol-Montewka, Maria, Tuszkiewicz-Misztal, Ewa et al. (2004) Evaluation of the association between atypical bacteria infections and respiratory tract diseases with emphasis on bronchial asthma exacerbations in children. Annales Universitatis Mariae Curie-Sklodowska. Sectio D: Medicina 59(1): 105-11	- Full text paper not available

Study	Code [Reason]
Szydlowski, J.; Pucher, B.; Walkowiak, J. (2010) The identification of adenoviruses, parvoviruses, Chlamydia pneumoniae and human papillomaviruses DNA sequence in otitis media with effusion. Family Medicine and Primary Care Review 12(3): 846-848	- Full text paper not available
Taha, Ahmed, Pitaro, Jacob, Lazarovitch, Tsilia et al. (2022) The association between Helicobacter pylori and chronic otitis media with effusion. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery	- Study design does not meet inclusion criteria *Case-control study*
Takata, Glenn S, Chan, Linda S, Morphew, Tricia et al. (2003) Evidence assessment of the accuracy of methods of diagnosing middle ear effusion in children with otitis media with effusion. Pediatrics 112(6pt1): 1379-87	- Study conducted before 2000 *Included studies conducted before 2000*
Talathi, Saurabh, Gupta, Neha, Sethuram, Swathi et al. (2017) Otitis Media in Fully Vaccinated Preschool Children in the Pneumococcal Conjugate Vaccine Era. Global pediatric health 4: 2333794x17749668	- Insufficient presentation of results *Data on rate of OME in those without risk factors not reported*
Tapia, Mario and Schmidt, Thomas (2021) Prevalence of middle ear disease in Chilean natives and the impact of development over 14 years. Brazilian journal of otorhinolaryngology 87(3): 283-289	- Insufficient presentation of results *Data on rate of OME in those with/without risk factors not reported*
Tong, M.C.F., Yue, V., Ku, P.K.M. et al. (2006) Risk factors for otitis media with effusion in Chinese schoolchildren: A nested case-control study and review of the literature. International Journal of Pediatric Otorhinolaryngology 70(2): 213-219	- Study design does not meet inclusion criteria *Nested case-control study*
Torretta, Sara, Pignataro, Lorenzo, Carioli, Daniela et al. (2018) Phenotype Profiling and Allergy in Otitis-Prone Children. Frontiers in pediatrics 6: 383	- Insufficient presentation of results *Results were not presented separately for participants with OME*
Umapathy, Dolores; Alles, Roshini; Scadding, Glenis K (2007) A community based questionnaire study on the	- Study conducted before 2000

Study	Code [Reason]
association between symptoms suggestive of otitis media with effusion, rhinitis and asthma in primary school children. International journal of pediatric otorhinolaryngology 71(5): 705-12	
van Balen, F A and de Melker, R A (2000) Persistent otitis media with effusion: can it be predicted? A family practice follow-up study in children aged 6 months to 6 years. The Journal of family practice 49(7): 605-11	- Study conducted before 2000
Velepic, Marko M, Velepic, Mitja S, Starcevic, Radan et al. (2004) Gastroesophageal reflux and sequelae of chronic tubotympanal disorders in children. Acta oto-laryngologica 124(8): 914-7	- Outcome does not meet inclusion criteria *Sequelae (e.g., retraction of eardrum and atelectasis) of chronic tubotympanal disorders*
Wu, Zeng-Hong, Tang, Yun, Niu, Xun et al. (2021) The Relationship Between Otitis Media With Effusion and Gastroesophageal Reflux Disease: A Meta-analysis. Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology 42(3): e245-e253	- Systematic review, included studies checked for relevance *Cross-sectional studies, case-control studies and randomised controlled trials were included*
Xenellis, John, Paschalidis, John, Georgalas, Christos et al. (2005) Factors influencing the presence of otitis media with effusion 16 months after initial diagnosis in a cohort of school-age children in rural Greece: a prospective study. International journal of pediatric otorhinolaryngology 69(12): 1641-7	- Study conducted before 2000
Yang, Betty and Brook, Christopher D (2017) The Role of Allergy in Otologic Disease. Otolaryngologic clinics of North America 50(6): 1091-1101	- Study design does not meet inclusion criteria *Narrative review*
Yeo, Seung Geun, Park, Dong Choon, Eun, Young Gyu et al. (2007) The role of allergic rhinitis in the development of otitis media with effusion: effect on eustachian tube function. American journal of otolaryngology 28(3): 148-52	- Study design does not meet inclusion criteria *Case-control study*
Yoo, Myung Hoon, Cho, Yang-Sun, Choi, June et al. (2022) Factors affecting extrusion rate and complications after ventilation tube insertion: Multicenter	- Comparison does not meet inclusion criteria *Comparison between no modifiable risk factors of interest*

Study	Code [Reason]
registry study on the effectiveness of ventilation tube insertion in pediatric patients with chronic otitis media with effusion-Part II. Clinical and experimental otorhinolaryngology	
Yoshida, Saeko, Seki, Saori, Sugiyama, Tomonori et al. (2022) Clinical characteristics of atelectatic eardrums and adhesive otitis media in children. International journal of pediatric otorhinolaryngology 159: 111188	- Study design and population do not meet inclusion criteria *Case-control study, and participants with adhesive otitis media included*
Yoshitomi, A., Baba, S., Tamada, I. et al. (2022) Relationship between cleft palate width and otitis media. Laryngoscope Investigative Otolaryngology	- Comparison does not meet inclusion criteria *Comparison between cleft palate types (non-modifiable risk factor)*
Zeisel, Susan A, Roberts, Joanne E, Burchinal, Margaret et al. (2002) A longitudinal study of risk factors for otitis media in African American children. Maternal and child health journal 6(3): 189-93	- Study conducted before 2000
Zielnik-Jurkiewicz, Beata and Stankiewicz-Szymczak, Wanda (2016) Pro-inflammatory interleukins in middle ear effusions from atopic and non-atopic children with chronic otitis media with effusion. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 273(6): 1369-78	- Study design does not meet inclusion criteria *Case-control study*

COVID-19: coronavirus disease 2019; OECD: The Organization for Economic Cooperation and Development; OM: otitis media; OME: otitis media with effusion

Excluded economic studies

No economic evidence was identified for this review.

Appendix K Research recommendations – full details

Research recommendations for review question: What are the modifiable risk factors for developing OME in children under 12 years?

No research recommendations were made for this review question.