Effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections

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Thesis with a summary in Dutch.
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Effectiviteit van adenotomie bij kinderen met recidiverende bovenste luchtweg infecties
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op vrijdag 20 december 2013 des middags te 2.30 uur

door

Maria Theodora Agnes van den Aardweg
geboren op 20 juni 1980, te Leiden

Promotores Prof. dr. A.G.M. Schilder
Prof. dr. M.M. Rovers

Content

Chapter 1

General introduction

In 1870 Wilhelm Meyer first used the term 'adenoid' to describe the 'nasopharyngeal vegetations'. He proposed that adenoid vegetations were responsible for nasal symptoms and impaired hearing, and presented a series of 48 adenoidectomies.[1,2] After this, adenoidectomy became more popular. In 1911 in the textbook 'Diseases of the ear, nose and throat' Waterhouse wrote that in his expert opinion: "it is beyond question that 99 of every 100 children from whom the adenoid vegetations have been removed improve markedly in every way within a few weeks of the operation."[2] Although no studies had been performed to ascertain the true effect of adenoidectomy, it became a frequently performed surgical procedure in children in Western countries and it has remained so to this day.

In 2009 21 451 adenoidectomies were performed in Dutch children up to the age of 18 years as a single procedure or in combination with myringotomy or insertion of tympanostomy tubes.[3] This makes it the third most common operation in children in the Netherlands. Remarkably, the Dutch adenoidectomy rate is considerably higher than that in most other Western countries: for example, in 2009 in the Netherlands 15 179 children (16.3 per 1000) aged 0-4 years and 5573 children (5.5 per 1000) aged 5-9 years underwent adenoidectomy.[4,5] In 2011-2012 in the UK 5677 children (9 per 1000) aged under 15 years underwent adenoidectomy and in 2006 in the United States 129 540 children (1.76 per 1000) up to the age of 18.[6,7] In 2002 in Finland and Norway the adenoidectomy rates were 9.5 and 3.9 per 1000 children aged 0-16 years, respectively.[8,9] In 2000 in Italy the adenoidectomy rate was 5.6 per 1000 children aged up to the age of 18.[10]

Indications for adenoidectomy include recurrent upper respiratory tract infections, otitis media (recurrent acute otitis media and persistent otitis media with effusion) and upper airway obstruction.[2,11-19] In the Netherlands the main indication is recurrent upper respiratory tract infections i.e. common colds or episodes of rhinosinusitis. It is the most common infectious disease in young children and the most common pediatric diagnosis in primary care.[20-22] Every year the diagnosis is made in one in every two children aged 0-4 years and in one in ten of those aged 5-9 years.[23] The true incidence of the condition in the community is much higher as usually parents to not consult their doctor when their child develops an upper respiratory tract infection. Children experience, on average, 4 to 6 upper respiratory tract infections per year.[24,25]

The term upper respiratory tract infection encompasses both viral infections leading to the common cold as well as bacterial infections such as acute bacterial rhinosinusitis. Viruses associated with upper respiratory tract infections are RSV, rhinovirus, coxsackieviruses, echoviruses, adenoviruses and coronaviruses.[26] The most common potential pathogenic bacteria associated with upper respiratory tract infections are *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*. The signs and symptoms of viral and bacterial upper respiratory tract infections are very similar and in daily medical practice the distinction is seldom made. In general, these infections are self-limiting and do not require treatment. With increasing age the natural course in children becomes more favorable: while the child's immune system develops and the anatomy of the upper airway changes, the frequency and severity of these infections decrease. However, an estimated 20% of children experience persistent or recurrent upper respiratory tract infections. While in most countries they are treated with antibiotics, in Dutch clinical practice many of these children are referred to the ENT surgeon for a surgical intervention.[8,9,27-29]

Upper respiratory tract infections not only affect the children's health, but given the frequency of the condition accounts for a large proportion of annual health care expenditure.[30-32]
We estimated the annual costs of adenoidectomy as a day-case procedure, with or without myringotomy, in the Netherlands in 2002 at a total of 5 million Euros. Additional costs such as those related to complications or parents' work loss were not included in these estimates. Although our study will not reduce the number of upper respiratory tract infections, if surgical intervention proves not be superior to a watchful waiting strategy in these children then implementation of the study results could lead to a considerable reduction in the number of adenoidectomies. In the light of the adenoidectomy rates in other countries a reduction with 30% to 50% seems feasible with a cost reduction of 2 to 3 million Euros per year.

The frequencies of adenoidectomy rates and indications vary strongly across Western countries. How can these differences be explained? Cultural differences, such as the preference of doctors and patients for antibiotic (UK and US) or surgical (the Netherlands) management of recurrent upper respiratory tract infections surely play a role. However, not only across, but also within these countries similar children suffering from the same disease are treated differently.[8,33-36] These differences can be explained by the fact that scientific evidence for the effectiveness of this common procedure in children with recurrent upper respiratory tract infections is scarce and (inter-)nationally accepted guidelines are lacking.[36,37] Practice is experience-based rather than evidence-based. Both in general practice and ENT practice there is an urgent call for evidence-based guidelines: e.g. the Dutch College of General Practitioners and the ENT guideline on diseases of the adenoid and tonsils have listed 'effectiveness of adenoidectomy' as one of the gaps in medical knowledge.[37,38]
Trials performed so far have mostly focused on the effects of adenoidectomy as an adjuvant procedure next to myringotomy or the insertion of tympanostomy tubes in children suffering from otitis media.[39-51] Despite the frequency with which adenoidectomy is performed for upper respiratory tract infections, no trials have been performed in this field. Internationally, no studies assessing the effects of adenoidectomy alone and focusing mainly on outcomes other than otitis media are available or underway.

Aim and outline of this thesis

The overall aim of this thesis is to study the clinical and cost effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections.

First, we performed an audit of current indications for adenoidectomy used by Dutch ENT surgeons, which is presented in **chapter 2**. We present an overview of the literature, in **chapters 3 and 4** as two systematic reviews for the Cochrane library on the effectiveness of adenoidectomy: one in children with recurrent or chronic nasal symptoms and the other in children with otitis media. This is followed by a systematic review of the literature on the effects of adenoidectomy on the nasopharyngeal flora in **chapter 5**.
After this literature overview the next chapters focus on our open, multi-center randomised controlled trial on the effectiveness of adenoidectomy in children aged 1-6 years with recurrent upper respiratory tract infections. In **chapter 6** we present the clinical results of our RCT, the main outcomes being episodes and prevalence of upper respiratory tract infections, along with otitis media and quality of life.
Chapter 7 shows the results of our microbiological studies that ran in parallel to our RCT showing the effects of adenoidectomy on the nasopharyngeal flora and its relation to recurrence of upper respiratory tract infections. **Chapter 8** focuses on the cost effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections.
The implications of the results of our trial for clinical practice and recommendations for future research are discussed in **chapter 9**.
The thesis is completed with a summary in English and Dutch.

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Chapter 2

Current indications for adenoidectomy in a sample of children in the Netherlands

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B-ENT. 2010;6(1):15-8

Abstract

Objective: To study current indications for adenoidectomy in Dutch children.

Methods: During 6 months, ENT surgeons in 1 academic and 7 general hospitals in the Netherlands filled out a questionnaire for all children aged below 15 years that were selected for adenoidectomy either as a single procedure or combined with myringotomy or tympanostomy tube placement. This questionnaire collected data on patient characteristics, ENT history and indication(s) for the procedure.

Results: Questionnaires were returned on 159 children. The study population was comparable to the general population of children undergoing adenoidectomy in the Dutch Health Care Services database concerning age and sex.
Adenoidectomy alone was performed in 38%, adenoidectomy and myringotomy in 15%, and adenoidectomy tympanostomy tube placement in 47%.
In children selected for adenoidectomy alone, indications were recurrent upper respiratory tract infections or chronic rhinosinusitis in 60%, persistent otitis media with effusion or recurrent acute otitis media in 33% and obstructive symptoms in 42%.
In children selected for adenoidectomy and myringotomy, and those selected for adenoidectomy and tympanostomy tube placement, indications were persistent otitis media with effusion or recurrent acute otitis media in 96% and 99%, recurrent upper respiratory tract infections or chronic rhinosinusitis in 88% and 59%, and obstructive symptoms in 33% and 24%, respectively.

Conclusion: In Dutch ENT practice, almost two-thirds of adenoidectomies are combined with myringotomy or tympanostomy tube placement. The most common indication for adenoidectomy in combination with myringotomy or tympanostomy tubes is middle ear disease. For adenoidectomy alone, recurrent upper respiratory tract infections is the most common indication.

Introduction

Adenoidectomy is one of the most common surgical procedures in children. It is performed either as a single procedure or in combination with myringotomy or tympanostomy tube placement. Adenoidectomy rates vary from 24 per 10 000 children in the United States and 39 per 10 000 children in the United Kingdom[1] to 74 per 10 000 children in the Netherlands.[2] These large differences across Western countries suggest that there is not a general consensus as to which children benefit from the operation. Current indications for adenoidectomy include recurrent upper respiratory tract infections (URTI), middle ear disease and upper airway obstruction.[3,4] These indications are practice based rather than evidence based since randomized controlled trials of adenoidectomy in children have focused on middle ear disease, whereas the effects of adenoidectomy in upper respiratory tract infections and obstructive symptoms have not been studied systematically. This was emphasized recently in the ZATT guideline[5], the Dutch national guideline on diseases of tonsils and adenoid, in which the performance of a randomized controlled trial on the effectiveness of adenoidectomy in children with recurrent URTI was advised.
The aim of this study was to determine the indications used by Dutch ENT surgeons to determine which children are treated with adenoidectomy.

Material and methods

Data collection

From July until December 2004, ENT surgeons from 7 general hospitals and 1 academic hospital, collaborating in our multi-center studies on upper respiratory disease[6,7] in the Netherlands, filled out a questionnaire in all children younger than 15 years of age whom they selected for adenoidectomy. In addition to age, sex, and ENT history of the child, the questionnaire covered the selected procedure: adenoidectomy as a single procedure, adenoidectomy combined with myringotomy, or adenoidectomy combined with placement of tympanostomy tubes. Four potential indications were listed: (1) persistent otitis media with effusion (pOME) or recurrent acute otitis media (rAOM); (2) recurrent URTI or chronic rhinosinusitis; (3) obstructive symptoms; and (4) other. ENT surgeons were asked to provide a ranking order if more than one indication was applicable in a single child. Children that were selected for adenotonsillectomy were excluded since we studied the indications and effectiveness of this procedure earlier.[6,8]

Statistical analysis

We calculated: 1) percentages of children selected for adenoidectomy as a single procedure, adenoidectomy in combination with myringotomy, and adenoidectomy in combination with tympanostomy tube placement; 2) the distribution of the indications over the three procedures; and 3) the combinations of indications reported. We also compared the characteristics of the children included this study with those having undergone adenoidectomy included in the Dutch Health Care Services database. This national database includes information on medical procedures, age and sex as provided by all Dutch hospitals. It does not include information on medical diagnoses related to these procedures.

Results

Population characteristics

In total 159 questionnaires were completed by the collaborating ENT surgeons. Of the 159 children, 93 were boys (59%) and the median age was 3.0 years (range 0-15 years). Children selected for adenoidectomy because of rURTI were slightly younger (mean age 2.0 years, range 0-7 years) and those selected for adenoidectomy because of obstructive symptoms were slightly older (mean age 4.0 years, range 1-6). The age and sex distribution is comparable to the general population of children undergoing adenoidectomy included in the Dutch Health Care Services database.[2]

Thirty-three (21%) patients had previously undergone an ENT operation: 21 (13%) adenoidectomy, 18 (11%) tonsillectomy, 10 (6%) placement of tympanostomy tubes and 9 (6%) myringotomy. Thirty-eight percent of children were selected for adenoidectomy alone, 15% for adenoidectomy in combination with myringotomy and 47% for adenoidectomy and tympanostomy tube placement.

Table 1. Frequency of indications for adenoidectomy in Dutch children.

	Adenoidectomy alone (n=60)	**Adenoidectomy and myringotomy (n= 24)**	**Adenoidectomy and tympanostomy tubes (n=75)**
Indication	**N (%)**	**N (%)**	**N (%)**
pOME or rAOM	20 (33%)	23 (96%)	74 (99%)
Recurrent URTI or chronic rhinosinusitis	36 (60%)	21 (88%)	44 (59%)
obstructive symptoms	25 (42%)	8 (33%)	18 (24%)
other*	4 (7%)	0 (0%)	3 (4%)
Total **	85	52	139

pOME= persistent otitis media with effusion; rAOM= recurrent acute otitis media; rURTI= recurrent upper respiratory tract infections.

** Other indications listed were: speech or language delay (n=3), fever(n=3) and failure to thrive (n=1)*

*** Total percentages exceed 100% because ENT surgeons could give more than one indication*

Indications

In children selected for adenoidectomy alone, indications were rURTI or chronic rhinosinusitis in 60%, pOME or rAOM in 33% and obstructive symptoms in 42%. In children selected for adenoidectomy in combination with myringotomy, indications were rURTI or chronic rhinosinusitis in 88%, pOME of rAOM in 96% and obstructive symptoms in 33%. In children selected for adenoidectomy in combination with tympanostomy tube placement, indications were rURTI or chronic rhinosinusitis in 59%, pOME or rAOM in 99% and obstructive symptoms in 24% (Table 1).

A total of 118 of the 159 children had more than one indication for adenoidectomy (Table 2), with the most frequent combination being pOME / rAOM and rURTI / chronic rhinosinusitis (38%). The indications for adenoidectomy in the single academic center were similar to those of the general hospitals.

Table 2. Frequency and combinations of indications for adenoidectomy in Dutch children.

Combination of indications	N (%)
pOME/rAOM alone*	29 (18%)
Recurrent URTI / chronic rhinosinusitis alone*	19 (12%)
obstructive symptoms alone*	13 (8%)
pOME/rAOM and recurrent URTI/ chronic rhinosinusitis	60 (38%)
pOME/rAOM and obstructive symptoms	16 (10%)
recurrentURTI/chronic rhinosinusitis and obstructive symptoms	10 (6%)
pOME/rAOM and recurrent URTI/ chronic rhinosinusitis and obstructive symptoms	12 (8%)

** Children with only one indication for adenoidectomy*

Discussion

Our results show that next to middle ear disease, recurrent upper respiratory tract infections is a very common indication for adenoidectomy in Dutch ENT practice.
Although we have shown that the children selected for adenoidectomy included in this study are representative of those included in the Dutch Health Care Services database[2], the question can be raised whether the results of this study can be generalized to other countries. It is known that adenoidectomy rates are higher in The Netherlands than in most other Western countries.[1,2] The literature suggests that in most countries middle ear disease and upper airway obstruction are the most frequent indications for adenoidectomy, rather than rURTI.[9-12] As far as we know, this is the first prospective inventory of indications for adenoidectomy in children in daily ENT practice.
Modern indications as listed in textbooks[3,4] lack solid scientific basis. We found the most frequent indication for adenoidectomy to be middle ear disease. Some evidence is indeed available regarding a small beneficial effect of adenoidectomy in children with recurrent acute otitis media and chronic otitis media with effusion.[12,13] The second most frequent indication for adenoidectomy in our population was rURTI. Evidence to support this indication however, is scarce.[11,14] The need for randomized controlled trials evaluating the role of adenoidectomy in this population was underlined recently in national guidelines issued in Italy and the Netherlands.[5,15] Similarly, the effects of adenoidectomy alone rather than adenotonsillectomy in children with symptoms of upper airway obstruction deserve further study.[14] With these trials, we hope to update current guidelines as has recently been done with the Allergic Rhinitis and its impact on asthma (ARIA) guideline.[16]

Conclusion

In conclusion, this prospective study shows that two-thirds of adenoidectomies carried out in children in the Netherlands are combined with myringotomy or tympanostomy tube placement. The most common indication for adenoidectomy combined with myringotomy or tympanostomy tubes is middle ear disease, whereas recurrent upper respiratory tract infections is the most common indication for adenoidectomy alone.

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Chapter 3

Adenoidectomy for recurrent or chronic nasal symptoms in children

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Plain language summary

Infections of the upper respiratory tract, presenting as recurrent nasal symptoms (nasal discharge with or without nasal obstruction) are very common in children. Removal of the adenoids (adenoidectomy) is a surgical procedure that is frequently performed in these children. It is thought that adenoidectomy prevents recurrence of nasal symptoms.
Our review, which includes two studies (256 children), shows that it is uncertain whether adenoidectomy is effective in children with recurrent or chronic nasal symptoms. Further high quality trials are needed.

Abstract

Background: Adenoidectomy, surgical removal of the adenoids, is a common ENT operation worldwide in children with recurrent or chronic nasal symptoms. A systematic review on the effectiveness of adenoidectomy in this specific group has not previously been performed.

Objectives: To assess the effectiveness of adenoidectomy versus non-surgical management in children with recurrent or chronic nasal symptoms.

Search methods: We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT and additional sources for published and unpublished trials. The date of the most recent search was 30 March 2009.

Selection criteria: Randomised controlled trials comparing adenoidectomy, with or without tympanostomy tubes, versus non-surgical management or tympanostomy tubes alone in children with recurrent or chronic nasal symptoms. The primary outcome studied was the number of episodes, days per episode and per year with nasal symptoms and the proportion of children with recurrent episodes of nasal symptoms. Secondary outcomes were mean number of episodes, mean number of days per episode and per year, and proportion of children with nasal obstruction alone.

Data collection and analysis: Two authors assessed trial quality and extracted data independently.

Results: Only one study included children scheduled for adenoidectomy because of recurrent or chronic nasal symptoms or middle ear disease. In this study no beneficial effect of adenoidectomy was found. The numbers in this study were, however, small (n = 76) and the quality of the study was moderate. The outcome was improvement in episodes of common colds. The risk differences were non-significant, being 2% (95% CI -18% to 22%) and -11% (95% CI -28% to 7%) after 12 and 24 months, respectively.
A second study included children with recurrent acute otitis media (n = 180). As otitis media is known to be associated with nasal symptoms, the number of days with rhinitis was studied as a secondary outcome measure. The risk difference was non-significant, being -4 days (95% CI -13 to 7 days).

Conclusion: Current evidence regarding the effect of adenoidectomy on recurrent or chronic nasal symptoms or nasal obstruction alone is sparse, inconclusive and has a significant risk of bias.
High quality trials assessing the effectiveness of adenoidectomy in children with recurrent or chronic nasal symptoms should be initiated.

Background

Incidence

Adenoidectomy is one of the most frequently performed surgical procedures in children in Western countries. Annual adenoidectomy rates, however, differ between countries, from 127/10 000 children per year in Belgium, 101/10 000 children per year in the Netherlands and 39/10 000 children per year in England to 24/10 000 and 17/10 000 children per year in the United States and Canada, respectively (Schilder (2004)).

Adenoidectomy

Indications for adenoidectomy include recurrent or chronic nasal discharge, recurrent episodes of acute otitis media (AOM), persistent otitis media with effusion (OME) and symptoms of upper airway obstruction. In most cases children are operated on for a combination of nasal and middle ear symptoms. The operation involves removing the adenoids - a nasopharyngeal reservoir of potential respiratory pathogens and a potential cause of obstruction of the nasal airway. As such, nasal breathing is thought to improve and recurrence of nasal discharge is thought to decrease.

Evidence for adenoidectomy

At present the effectiveness of adenoidectomy in children with recurrent or chronic nasal symptoms remains uncertain and practice is experience-based rather than evidence-based. Some surgeons prefer to perform adenoidectomy in these children, whereas others do not. In previous systematic reviews for The Cochrane Library the effectiveness of 1) grommets (ventilation tubes) for recurrent acute otitis media in children (McDonald (2008)), 2) grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children (Lous (2005)) and 3) tonsillectomy or adeno-tonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis (Burton (2009)) have all been assessed. For adenoidectomy in children with nasal symptoms no such review is available. This study therefore provides a comprehensive systematic review and meta-analysis of randomised controlled trials evaluating the effectiveness of adenoidectomy in children with recurrent or chronic nasal symptoms.

Objectives

To assess the effectiveness of adenoidectomy with or without tympanostomy tubes compared with non-surgical management or tympanostomy tubes alone in children up to 18 years of age with recurrent or chronic nasal symptoms.

Methods

Criteria for considering studies for this review

Types of studies

We considered all identified randomised controlled trials of adenoidectomy for recurrent or chronic nasal symptoms compared with non-surgical treatment or tympanostomy tubes alone for inclusion in this review. We included trials in which the method of randomisation was not specified in detail, but we excluded quasi-randomised trials (e.g. allocation by date of birth or record number).

Studies had to have a follow up of at least six months. Studies with a follow up of six to 12 months were reported separately from those with a follow up of 12 months or more.

Desirable time points of outcome assessment were six months, 12 months, 24 months and 36 months.

Types of participants

Children up to 18 years of age diagnosed with recurrent or chronic nasal symptoms.

Types of interventions

To evaluate the effects of adenoidectomy we compared the following interventions:

1. adenoidectomy (with or without myringotomy) versus non-surgical treatment or myringotomy only;
2. adenoidectomy with unilateral tympanostomy tube versus unilateral tympanostomy tube only (in studies of this type the ear without the tympanostomy tube is evaluated to study the effect of adenoidectomy);
3. adenoidectomy with bilateral tympanostomy tubes versus bilateral tympanostomy tubes only.

Non-surgical management included watchful waiting and medical treatment including antibiotics (intermittent and long-term), steroids, antihistamines and analgesics.

Types of outcome measures

Primary outcomes

The primary outcome measure was the number of episodes, days per episode and per year with nasal symptoms, and the proportion of children with recurrent episodes of nasal symptoms. Nasal symptoms are defined as nasal discharge with or without obstruction as observed by the parents or physician.

Secondary outcomes

Secondary outcomes are as follows:

- Nasal obstruction alone.
  - Number of episodes per year.
  - Number of days with symptoms per episode and per year.
  - Proportion of children with recurrent episodes.

'Recurrent' was defined as the patient having three or more episodes of nasal symptoms in a period of six months, or four or more episodes in a period of 12 months (Rosenfeld (2000)).

Search methods for identification of studies

We conducted systematic searches for randomised controlled trials on the effectiveness of adenoidectomy in children up to 18 years of age with recurrent or chronic nasal symptoms and middle ear disease. After finalising the first draft of the review in which we combined recurrent or chronic nasal symptoms and middle ear disease, there was a general consensus that the review would benefit from being split into two separate reviews; one looking at the effects of adenoidectomy on nasal symptoms (this review) and the other at the effect of otitis media (van den Aardweg (2010)). There were no language, publication year or publication status restrictions. We contacted original authors for clarification and further data if trial reports were unclear and arranged translations of papers where necessary. The date of the last search was 30 March 2009.

Electronic searches

We searched the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue 1, 2009); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; mRCT (Current Controlled Trials); ClinicalTrials.gov; ICTRP (International Clinical Trials Registry Platform); ClinicalStudyResults.org and Google.

All other search strategies were modelled on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1, Box 6.4.b. (Handbook (2008)). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources

We checked the reference lists of identified publications for additional trials. We searched PubMed; TRIPdatabase; NHS Evidence - ENT and Audiology; and Google to retrieve existing systematic reviews possibly relevant to this systematic review, in order to search their reference lists for additional trials. We scanned abstracts of conference proceedings via the Cochrane Ear, Nose and Throat Disorders Group Trials Register and CENTRAL.

Data collection and analysis

We conducted the review according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions 5.0.1 (Handbook (2008)).

Selection of studies

Two review authors (MvdA, EH) scanned the abstracts to identify relevant randomised controlled trials. The same two authors obtained and reviewed the full texts of these articles. We assessed eligibility of the trials independently and resolved any differences in opinion by discussion between the two authors. Reasons for exclusion of potentially relevant studies are given in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (MvdA, EH) also performed data extraction independently, followed by a consensus conference to resolve differences. We extracted the following data from each study: total number of children in each trial, description of participants (mean age, country of origin, inclusion and exclusion criteria, allergy status, adenoid size), follow-up time in months, description of intervention and control therapy, number of patients per intervention group, primary and secondary outcomes, and the authors conclusion.

Assessment of risk of bias in included studies

Two authors (MvdA, CB) assessed the quality of all included trials independently using the Cochrane Collaboration's tool for assessing risk of bias ('Risk of bias' table, Cochrane Handbook for Systematic Reviews of Interventions, chapter 5 (Handbook (2008)). Six specific domains were addressed, i.e. sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other biases. By answering pre-specified questions we reported the execution of the study and judged the risk of bias for each domain. The outcome for each domain was either 1) yes, a high risk, 2) no, a low risk or 3) an unknown or unclear risk of bias. We resolved disagreement by discussion (MvdA, CB, MR). We planned to assess publication bias with a scatter plot (funnel plot) of the log rate ratios (x-axis) versus precision defined as 1/standard error (y-axis) (Handbook (2008)).

Data synthesis

We planned to use RevMan version 5.0 (RevMan (2008)) to carry out the meta-analyses for comparable trials and outcomes.

For continuous outcomes (i.e. number of episodes, number of days per episode and number of days per year) we calculated standard mean differences (SMD) and their corresponding 95% confidence intervals (CI).

For dichotomous outcomes, we measured the estimates of effect as risk differences (RD) with their corresponding 95% confidence intervals. Risk differences were calculated using: (proportion of children with outcome present in adenoidectomy group) - (proportion of children with outcome present in control group).

If heterogeneity was low ($I^2 < 25\%$) we planned to calculate the summary weighted risk differences and 95% confidence intervals (random-effects model) by the Mantel-Haenszel method, which weighs studies by the number of events in the control group, using the Cochrane statistical package in RevMan (version 5.0).

Furthermore, we also planned to perform sensitivity analyses excluding the studies with the lowest methodological quality, according to the Cochrane Collaboration's risk of bias assessment, to establish whether this factor influences the final outcome. We also intended to perform subgroup analyses for age groups and adenoid size.

Ultimately it was not possible to either pool the data in a meta-analysis nor to perform sensitivity and subgroup analysis. Data allowing, we hope to pool the data in a meta-analysis and include sensitivity and subgroup analyses in future updates of this review.

Results

Results of the search

Our search of CENTRAL, PubMed, EMBASE and other databases retrieved a total of 204 articles. We first sifted the articles by title/abstract and this left us 31 articles to read in full text. We excluded 28 publications from the review: 12 did not specifically include nasal symptoms as an outcome measure. A further 11 were duplicate or follow-up reports of studies already excluded. One study by Sagnelli et al (Sagnelli (1990)) could not be retrieved. Full details of the reasons for excluding studies can be found in the 'Characteristics of excluded studies' table.

No additional trials were identified by checking the bibliographies of the selected trials and reviews, nor by contacting the first or corresponding author of the eligible trials.

Two studies (n = 256 children) that looked at the effect of adenoidectomy on nasal symptoms were included in this review (Rynnel-Dagöo (1978); Koivunen (2004)).

Included studies

1) Adenoidectomy (with or without myringotomy) versus non-surgical treatment or myringotomy only.
   - Rynnel-Dagöo (1978)
   - Koivunen (2004)

2) Adenoidectomy with unilateral tympanostomy tube versus unilateral tympanostomy tube only; non-operated ear examined for comparison.
   - No studies found.

3) Adenoidectomy with bilateral tympanostomy tubes versus bilateral tympanostomy tubes only.
   - No studies found.

Adenoidectomy (with or without myringotomy) versus non-surgical treatment or myringotomy only

Rynnel-Dagöo (1978) reported on 105 children aged less than 12 years with recurrent serous and purulent otitis media, frequent upper airway infections and nasal obstruction. After randomisation 29 children were excluded for various reasons, i.e. 76 children remained for analysis; 37 in the adenoidectomy group and 39 in the control group. Outcomes were change (better, deteriorated or unchanged) in frequency of common colds, purulent or serous otitis media and nasal obstruction. The follow up was two years.

Koivunen (2004) reported on 180 children aged 10 months to two years with at least three episodes of acute otitis media during the previous six months, which is known to be associated with nasal symptoms. They were randomly allocated to 1) adenoidectomy (n = 60), 2) chemoprophylaxis (n = 60) or 3) placebo (n = 60). One of the secondary outcomes was days with rhinitis. The primary outcome was intervention failure in the first six months, which was defined as two or more episodes of acute otitis media in two months or at least three in six months, or middle ear effusion for at least two months. Other secondary outcomes were mean number of 1) episodes of acute otitis media, 2) visits to a doctor, 3) antibiotic prescriptions and 4) days with earache or fever. Follow up was two years.

In summary, both studies differed regarding inclusion criteria and the outcomes measured. Only one study (Rynnel-Dagöo (1978)) included children for whom the primary indication for adenoidectomy was nasal symptoms.

Risk of bias in included studies

Figure 1 and Figure 2 show the results of the quality assessment according to the Cochrane Collaboration's tool for assessing risk of bias. Figure 1 shows the judgements about each methodological quality item presented as percentages across included studies, whereas Figure 2 shows the judgements of both included studies separately.

Sequence generation and allocation concealment: Both studies had a low risk of bias for sequence generation and allocation concealment.

Blinding: Both studies had a high risk of bias for blinding.

Incomplete outcome data: One study had a high risk of bias for incomplete outcome data (Rynnel-Dagöo (1978)) and in the other study the risk of bias for this reason was unclear (Koivunen (2004)).

Selective outcome reporting: The risk of selective outcome reporting was unclear in one study (Koivunen (2004)) and low in the other study (Rynnel-Dagöo (1978)).

Other sources of bias: The risk of other sources of bias was unclear in one study (Rynnel-Dagöo (1978)) and low in the other study (Koivunen (2004)).

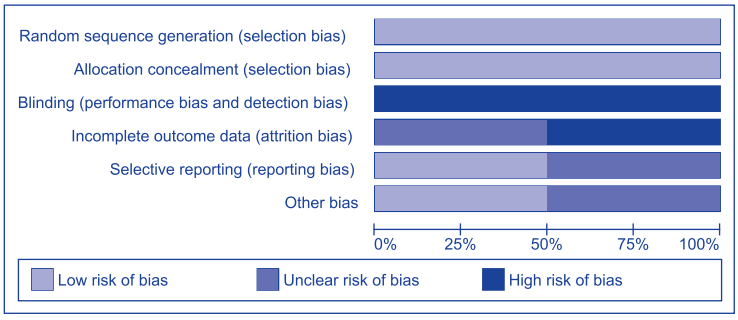

Figure 1. risk of bias methodological quality graph: review authors judgements about each methodological quality item presented as percentages across all included studies.

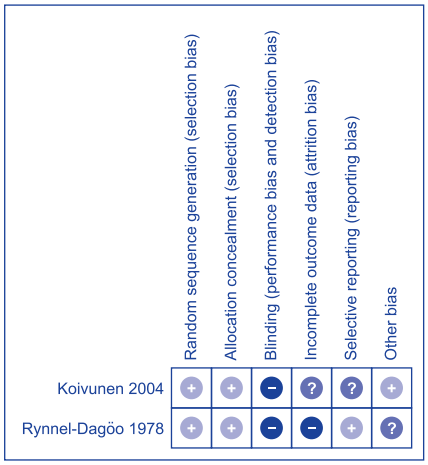

Figure 2. risk of bias methodological quality summary: review authors judgements about each methodological quality item for each included study.

Effects of interventions

Adenoidectomy (with or without myringotomy) versus non-surgical treatment
Rynnel-Dagöo (1978) found an overall improvement in the frequency of common colds and otitis media in both the adenoidectomy and control group, but no difference was found between intervention groups.
Improvement in episodes of common colds, defined as a reduction in number of more than two periods of snottiness, were found in 75% versus 73% after 12 months, and in 77% versus 88% after 24 months in the adenoidectomy and control group, respectively. The risk differences were non-significant, being 2% (95% CI -18% to 22%) and -11% (95% CI -28% to 7%).
Improvement in frequency of nasal obstruction, meaning a change from frequent to infrequent (not quantified in absolute numbers), was found in 61% versus 41% after 12 months, and in 63% versus 55% after 24 months in the adenoidectomy and control group, respectively. The risk differences were non-significant, being 20% (95% CI -2% to 43%) and 8% (95% CI -15% to 32%).

Koivunen (2004) showed that at six months the mean number of days with rhinitis in children who underwent adenoidectomy was 26 (SD 23) as compared to 23 (25) days in the control group. The difference was non-significant, being -4 days (95% CI -13 to 7 days).

The trials were too heterogeneous to pool in a meta-analysis.

Discussion

Summary of main results

Current evidence regarding the effect of adenoidectomy on recurrent or chronic nasal symptoms and nasal obstruction alone is sparse, inconclusive and has a significant risk of bias.

Potential biases in the review process

During the review process potential biases were identified both in the individual trials and in the review process itself. Only Koivunen (2004) provided a power analysis and included adequate numbers. Rynnel-Dagöo (1978) included relatively fewpatients, therefore the power of the study may have been too low, leading to either a type I or type II error.

Loss to follow up was significant in both studies (up to 28%). This can be associated with either good or poor outcome. In one trial children were excluded after randomisation, which may have led to residual confounding (Rynnel-Dagöo (1978)).

One study was analysed per protocol and no data were available to perform intention to treat analyses (Rynnel-Dagöo (1978)). Per protocol analyses in which children who change groups are excluded may underestimate the treatment effect. In surgical trials only children in the watchful waiting group with severe complaints can change treatment group, whereas children in the surgical group who may experience similarly severe complaints cannot change treatment group. Analysing children on the basis of time spent in a treatment arm may over or underestimate the treatment effect.

Information bias may be considerable since trials on adenoidectomy, like most surgical trials, cannot be performed in a true double-blind fashion. Such bias will overestimate the effect of the intervention.

Generalisability of the trials can be questioned since only a very small proportion of children undergoing adenoidectomy were included in the trials.

Due to the lack of data on factors that may modify the effect of adenoidectomy, such as age, adenoid size or allergic rhinitis, it was not possible to perform subgroup analyses and identify children that may benefit more or less from the operation.

The authors of this review were not blinded to authorship and origin of the included studies, since they knew most of the literature before embarking on this review.

Conclusion

Implications for practice

Current evidence regarding the effectiveness of adenoidectomy for nasal symptoms is sparse, inconclusive and has a significant risk of bias. It therefore remains uncertain whether adenoidectomy has an effect on recurrent or chronic nasal symptoms and nasal obstruction alone.

Implications for research

High quality trials assessing the effectiveness of adenoidectomy on recurrent or chronic nasal symptoms or nasal obstruction alone should be initiated. These trials should be sufficiently powered for analysis of potential effect modifiers, so that subgroups benefiting most from adenoidectomy can be identified. Further, a broader spectrum of outcomes should be included, such as quality of life and cost-effectiveness.

Acknowledgements

We acknowledge the work of Mohammed Attrach in the early stages of the protocol

Table 1. Characteristics of included studies including risk of bias table per author.

Rynell-Dagöo (1978)

Methods	Prospective controlled study
Participants	105 children aged less than 12 years with recurrent acute otitis media/otitis media with effusion, frequent upper respiratory airway infections and nasal obstruction.
Interventions	Adenoidectomy (n=37), control group (n=39)
Outcomes	Measured at 12 and 24 months: · Change in frequency of commons colds, purulent otitis media, serous otitis media and nasal obstruction
Notes	11% of the children were lost to follow-up (8% in the adenoidectomy group and 13% in the control group) after 24 months follow-up. 35% of the children in the adenoidectomy group and 56% of the children in the control group had insertion of tympanostomy tubes. When those children still had tubes at the end of the trial they were excluded from analysis (8% in the adenoidectomy group and 3% in the control group). No intention to treat method was used for analysis. No complications were reported by surgeons.

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote:'All children (...) received a number between 0-105 randomly acquired by casting of lots. Children with even numbers came to belong to the adenoidectomy group and those with odd numbers to the control group.'
Allocation concealment?	Yes	Quote:'All children (...) received a number between 0-105 randomly acquired by casting of lots. Children with even numbers came to belong to the adenoidectomy group and those with odd numbers to the control group.'
Blinding?	No	Quote:'(...) we were naturally aware of whether the children belonged to the A- or C-group.'
Incomplete outcome data addressed?	No	Quote:'Twenty-nine children were omitted for reasons shown in table 1, leaving 76 children to participate in the investigation.' Comment: these children were excluded after randomisation. The most common reasons were severe nasal obstruction and administrative mishaps. It is unclear whether the 29 omitted children were otherwise clinically similar to the 76 children included in the study.
Free of selective reporting?	Yes	Comment: all outcomes are reported on (nasopharyngeal flora, improvement, unchanged or deterioration in episodes of common colds, purulent otitis media, serous otitis media, and nasal obstruction)
Free of other bias?	Unclear	Quote:'(...) data concerning frequency of illnesses were obtained retrospectively by interviews with the parents.'

Koivunen (2004)

Methods	**RCT**
Participants	180 children aged 10 months to 2 years with recurrent acute otitis media
Interventions	Adenoidectomy (n=60), chemoprophylaxis (n=60), placebo (n=60)
Outcomes	Primary outcome measured at 12 and 24 months: · Intervention failure Secondary outcomes measured until intervention failure, drop-out, or 6 months of follow-up, whichever came first: · Mean number of episodes of acute otitis media · Sick child visits · Antimicrobial prescriptions · Day with rhinitis · Days with earache · Days with fever
Notes	Duration of an episode is not described. Follow-up 24 months; 34 children (28%) were lost to follow-up in the non-adenoidectomy groups and 2 children (3%) were lost to follow-up in the adenoidectomy group after 24 months follow-up. At the beginning of the study 12 children in the adenoidectomy group concurrently received tympanostomy tubes. During follow-up 23 children (13%) (6 adenoidectomy, 6 chemoprofylaxis, 11 placebo) received tympanostomy tubes because of persistent middle ear fluid. Intention to treat method was used for analysis. No complications in the adenoidectomy procedures were reported by the surgeons.

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote:'We randomly assigned children to receive (...). We performed block randomisation with a block size of six using numbered containers so that allocation was concealed from the investigator.'
Allocation concealment?	Yes	Quote:'We performed block randomisation with a block size of six using numbered containers so that allocation was concealed from the investigator.'
Blinding?	No	Quote:'The sulfafurazole and placebo suspensions were given in a double blind fashion.' Comment: blinding for adenoidectomy versus placebo was not possible. Outcome measures are subjective.
Incomplete outcome data addressed?	Unclear	Quote:'Children in the sulfafurazole and placebo groups discontinued intervention and received another profylaxis more often than children in the adenoidectomy group (fig.1).' Comment: 1 child was lost to follow-up in the adenoidectomy group whereas 15 and 14 children were lost to follow-up in the sulfafurozole and placebo group respectively. However, intention to treat analysis with all 180 randomised children was performed.
Free of selective reporting?	Unclear	Comment: all outcome measures are presented. The primary outcome in table 2 and the secondary outcome measures in table 3.
Free of other bias?	Yes	Quote 1:'However, as the children in the placebo group and sulfafurazole groups discontinued the allocated intervention mor often than the children in the adenoidectomy group (...), as these children may have had more severe otitis media, this could have caused some bias by weakening the true effect of adenoidectomy.' Quote 2:'There are two other important sources of bias that may have diminished the true effects of the treatments: firstly, the use of symptom diaries to collect the outcome, and, secondly, the possibility of misdiagnosis.' Comment: 12 children in the adenoidectomy group also received tympanostomy tubes.

Table 2. Inclusion and exclusion criteria of studies included in this review.

Author	Inclusion criteria	Exclusion criteria
Koivunen (2004)	Three or more episodes of acute otitis media in the last 6 months	Previously performed adenoidectomy or tympanostomy tubes, cranio anomalies, documented immunological disorders and ongoing antimicrobial profylaxis
Rynnel-Dagöo (1978)	Recurrent serous/purulent otitis media, frequent upper airway infections and nasal obstruction	Cases of severe nasal obstruction, previous operation performed, refused operation by parents, cases of recurring adenoids, diabetes or administrative mishaps

Table 3. Characteristics of excluded studies; reasons for exclusion.

Author	Reason for exclusion
Black (1990)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Bulman (1984)	Allocation: not concealed Participants: selection of patients not restricted by clear boundaries; not all had bilateral OME and bilateral similar deafness. Preoperative middle ear effusion only measured for 6 weeks. Outcome measures: 'Adenoidectomy only' versus 'Control' are the only two groups that can be compared; 15 versus 14 patients were allocated to those groups. Overall, results of the different intervention groups are impossible to differentiate.
Casselbrant (2009)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Dempster (1993)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Fiellau-Nikolajsen (1980)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Fiellau-Nikolajsen (1982)	Same study as Fiellau-Nikolajsen 1980
Gates (1987)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Gates (1988)	Same study as Gates 1987
Gates (1989)	Same study as Gates 1987; Outcome measures: results are specified in adenoid size (in our study this is not an outcome measure).
Hammarén-Malmi (2005)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Marshak (1980)	Allocation: non-randomised controlled study
Mattila (2003)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Maw (1983)	Same study as Maw 1986
Maw (1985)a	Same study as Maw 1986
Maw (1985)b	Same study as Maw 1986
Maw (1986)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Maw (1987)	Same study as Maw 1986
Maw (1988)	Same study as Maw 1986
Maw (1993)	This study was excluded because data from the adenoidectomy group could not be analysed separately from those undergoing adenotonsillectomy. The authors combined the adenoidectomy group and the adenotonsillectomy group because in the study Maw 1986 adenotonsillectomy appeared to have no additional benefit compared to adenoidectomy alone.
Maw (1994)a	Same study as Maw 1993, long-term effect
Maw (1994)b	Same study as Maw 1986
Nguyen (2004)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Paradise (1990)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Paradise (1999)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Roydhouse (1980)	Did not specifically include nasal symptoms as an inclusion criteria or outcome measure
Widemar (1982)	Allocation: randomisation process (used date of birth to randomise). Same study as Widemar 1985. The first year follow-up of 44 children is presented.
Widemar (1985)	Allocation: randomisation process (used date of birth to randomise). Participants: only data from 59 children were used for analysis because 19 children were excluded after randomisation. Intervention: a total of 13 and 22 tympanostomy tubes were inserted in groups A and C respectively. They excluded the children that still had unilateral or bilateral tubes at the time of comparison.

Table 4. Characteristics of ongoing studies

Study name	NOA: Netherlands Adenoidectomy Study
Methods	RCT, follow-up of 2 years
Participants	111 children aged 1 to 6 years selected for adenoidectomy with or without myringotomy because of recurrent or chronic upper respiratory tract infections (common colds, rhinosinusitis)
Interventions	1) Adenoidectomy with or without myringotomy within 6 weeks 2) Watchful waiting strategy
Outcomes	· Primary outcome measure: Recurrent upper respiratory tract infections with or without fever · Secundary outcome measures: · Acute otitis media and otitis media with effusion episodes · Exhaled nitric oxide · Nasopharyngeal flora · Health related quality of life · Cost-effectiveness
Starting date	1 April 2007

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Appendix. Search strategies for electronic databases

CENTRAL	PubMed	EMBASE (Ovid)
1 MeSH descriptor Adenoidectomy explode all trees 2 MeSH descriptor Adenoids explode all trees with qulifier : SU 3 adenoidectom* or adenoitonsillectom* or adenotonsilectom* or adeno NEXT tonsillectomy* or adeno NEXT tonsillectom* 4 (1 OR 2 OR 3) 5 MeSH descriptor Adenoids explode all trees 6 adenoid* or adenotonsil* 7 (5 OR 6) 8 MeSH descriptor Surgical Procedures, Operative explode all trees 9 (surg* :ti or operat* :ti or excis* :ti or extract* :ti or remov* :ti or dissect* :ti or ablat* ;ti or coblat* :ti or laser* :ti) 10 (8 OR 9) 11 (7 AND 10) 12 (4 OR 11) 13 (nose OR nasal) NEAR (symptom* OR discharg* OR secret* OR obstruct*) 14 rhinorrhea OR rhinorrhoea 15 MeSH descriptor Nasl Obstruction explode all trees 16 airway* AND obstruct* 17 breath* and impair* 18 MeSH descriptor Otitis Media explode all trees 19 middle NEXT ear NEXT (infect* OR inflam* OR disease*) 20 otitis OR aom OR ome 21 glue AND ear 22 (13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21) 23 (12 AND 22)	1 'Adenoidectomy [Mesh] 2 'Adenoids/surgery [Mesh] 3 adenoidecotm* [tiab] OR adenotonsillectom* [tiab] OR adenotonsilectom* [tiab] OR 'adenotonsillectomy* [tiab] OR 'adenotonsilectom' [tiab] 4 1 OR 2 OR 3 5 'Adenoids'/ [Mesh] 6 adenoid* [tiab] OR adenotonsil* [tiab] 7 5 OR 6 8 'surgical procedures, operative' [Mesh] 9 'surgery' [subheading] 10 surg* [tiab OR operat* [tiab] OR excis* [tiab] OR extract* [tiab] OR remov* [tiab] OR dissect* [tiab] OR ablat* [tiab] OR coblat* [tiab] OR laser* [tiab] 11 8 OR 9 OR 10 12 7 AND 11 13 4 OR 12 14 (nose [tiab] OR nasal [tiab]) AND (symptom*[tiab] OR discharg* [tiab] OR secret* [tiab] OR obstruct* [tiab]) 15 rhinorrhea [tiab] OR rhinorrhoea [tiab] 16 'Nasal Obstruction' [Mesh 17 airway* [tiab] AND obtruct* [tiab] 18 breath* [tiab] AND impair* [tiab] 19 'Otitis Media' [Mesh] 20 middle [tiab] AND ear [tiab] AND (infect* [tiab] OR inflam* [tiab] OR disease* [tiab]) 21 otitis [tiab] OR aom [tiab] OR ome [tiab] 22 glue [tiab] AND ear [tiab] 23 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 22 24 13 AND 24	1 adenoidectomy/ 2 (adenoidectom* or adenotonsillectom* or adenotonsilectom* or 'adenotonsillectomy*' or 'adenotonsilectom*').tw. 3 1 or 2 4 *Adenoid/ 5 (adenoid* or adenotonsil*).ti. 6 4 or 5 7 (surg* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser*).ti. 8 exp *Surgery/ 9 8 or 7 10 6 and 9 11 3 or 10 12 nose obstruction/ or rhinorrhea/ 13 *airway obstruction/ or *upper respiratory tract obstruction/ 14 ((nose or nasal) and (symptom* or discharge* or obstruct* or secret*)).tw. 15 rhinorrhea or rhinorrhoea).tw. 16 (airway* and obstruct*).tw. 17 breath* and impair*).tw. 18 exp Middle Ear Disease/ 19 (middle and ear and (infect* or inflamm* or disease*)).tw. 20 (otitis or aom or raom or ome).tw. 21 (glue and ear).tw. 22 21 or 17 or 12 or 20 or 15 or 14 or 18 or 13 or 16 or 19 23 22 and 11
CINAHL (EBSCO)	**Web of Science**	**BIOSIS Previews/CAB Abstracts (Ovid)**
S1 (MH 'Adenoidectomy') S2 (MH 'Adenoids/SU') S3 adenoidectom* or adenotonsillectom* or adenotonsilectom* or 'adenotonsillectomy*' or adeno tonsilectomy*' S4 (MM 'Adenoids') S5 TI adenoid* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser* S7 (MH 'Surgery, Operative') S8 S6 or S7 S9 S4 or S5 S10 S8 and S9 S11 S1 or S2 or S3 or S10	1 TS=(adenoidectom* or adenotonsillectom* or adenotonsilectom* or 'adeno tonsillectomy*' or 'adeno tonsilectom*') 2 TI=(adenoid* or adenotonsil*) 3 TI=(surg* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser*) 4 2 AND 3 5 1 or 4 6 TS=((nose or nasal) and (symptom* or discharg* or obstruct* or secret*)) 7 TS=(rhinorrhea or rhinorrhoea) 8 TS=(airway* and obstruct*) 9 TS=(breath* and impair*) 10 TS=(middle and ear and (infect* or inflamm* or disease*)) 11 TS=(otitis or aom or raom or ome) 12 TS=(glue and ear) 13 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 14 5 AND 13	1 (adenoidectom* or adenotonsillectom* or adenotonsilectom* or 'adeno tonsillectomy*' or adeno tonsilectom*').tw. 2 (adenoid* or adentonsil*).ti. 3 (surg* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser*).ti. 4 ((nose or nasal) and (symptom* or discharg* or obstruct* or secret*)).tw 5 (rhinorrhea or rhinorrhoea).tw. 6 (airway* and obstruct*).tw. 7 (breath* and impair*).tw. 8 (middle and ear and (infect* or inflamm* or disease*)).tw. 9 (otitis or aom or raom or ome).tw. 10 (glue and ear).tw. 11 3 and 2 12 11 or 1 13 8 or 6 or 4 or 7 or 10 or 9 or 5 14 13 and 12

Chapter 4

Adenoidectomy for otitis media in children

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CD007810

Plain language summary

Both acute and chronic middle ear infections (acute otitis media and chronic otitis media with effusion or 'glue ear') are very common in children. Adenoidectomy is a surgical procedure to remove the adenoids and is often performed in these children as it is thought to prevent these problems.

Our review, which includes 14 studies and 2712 children, shows that adenoidectomy is effective in getting rid of middle ear fluid ('glue') but does not have a significant effect on acute otitis media or the child's hearing.

Abstract

Background: Adenoidectomy, surgical removal of the adenoids, is a common ENT operation worldwide in children with otitis media. A systematic review on the effectiveness of adenoidectomy in this specific group has not previously been performed.

Objectives: To assess the effectiveness of adenoidectomy versus non-surgical management or tympanostomy tubes in children with otitis media.

Search methods: We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT and additional sources for published and unpublished trials. The date of the most recent search was 30 March 2009.

Selection criteria: Randomised controlled trials comparing adenoidectomy, with or without tympanostomy tubes, versus non-surgical management or tympanostomy tubes only in children with otitis media.
The primary outcome studied was the proportion of time with otitis media with effusion (OME). Secondary outcomes were mean number of episodes, mean number of days per episode and per year, and proportion of children with either acute otitis media (AOM) or otitis media with effusion (OME), as well as mean hearing level. Tertiary outcome measures included atrophy of the tympanic membrane, tympanosclerosis, retraction of the pars tensa and pars flaccid and cholesteatoma.

Data collection and analysis: Two authors assessed trial quality and extracted data independently.

Results: Fourteen randomised controlled trials (2712 children) studying the effectiveness of adenoidectomy in children with otitis media were evaluated. Most of these trials were too heterogeneous to pool in a meta-analysis. Loss to follow up varied from 0% to 63% after two years.
Adenoidectomy in combination with a unilateral tympanostomy tube has a beneficial effect on the resolution of OME (risk difference (RD) 22% (95% CI 12% to 32%) and 29% (95% CI 19% to 39%) for the non-operated ear at six and 12 months, respectively (n = 3 trials)) and a very small (< 5 dB) effect on hearing, compared to a unilateral tympanostomy tube only. The results of studies of adenoidectomy with or without myringotomy versus non-surgical treatment or myringotomy only, and those of adenoidectomy in combination with bilateral tympanostomy tubes versus bilateral tympanostomy tubes only, also showed a small beneficial effect of adenoidectomy on the resolution of the effusion. The latter results could not be pooled due to large heterogeneity of the trials.
Regarding AOM, the results of none of the trials including this outcome indicate a significant beneficial effect of adenoidectomy. The trials were too heterogeneous to pool in a meta-analysis.
The effects of adenoidectomy on changes of the tympanic membrane or cholesteatoma have not been studied.

Conclusion: Our review shows a significant benefit of adenoidectomy as far as the *resolution* of middle ear effusion in children with OME is concerned. However, the benefit to hearing is small and the effects on changes in the tympanic membrane are unknown. The risks of operating should be weighed against these potential benefits.
The absence of a significant benefit of adenoidectomy on AOM suggests that routine surgery for this indication is not warranted.

Background

Incidence

Adenoidectomy is one of the most frequently performed surgical procedures in children in Western countries. Annual adenoidectomy rates, however, differ between countries, from 127/10 000 children per year in Belgium, 101/10 000 children per year in the Netherlands and 39/10 000 children per year in England to 24/10 000 and 17/10 000 children per year in the United States and Canada, respectively (Schilder (2004)).

Adenoidectomy

Indications for adenoidectomy include recurrent episodes of acute otitis media (AOM) and persistent otitis media with effusion (OME). The operation involves removing the adenoids - a nasopharyngeal reservoir of potential respiratory pathogens and a potential cause of obstruction of the nasal airway. As such, Eustachian tube function is thought to improve.

Evidence for adenoidectomy

At present the effectiveness of adenoidectomy in children with otitis media remains uncertain and practice is experience-based rather than evidence-based. Some surgeons prefer to perform adenoidectomy in these children, whereas others do not. In previous systematic reviews for The Cochrane Library the effectiveness of 1) grommets (ventilation tubes) for recurrent acute otitis media in children (McDonald (2008)) and 2) grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children (Lous (2005)) and 3) tonsillectomy or adeno-tonsillectomy versus non-surgical treatment for chronic/recurrent acute tonsillitis (Burton (2009)) have all been assessed. For adenoidectomy in children with otitis media no such review is available. This study therefore provides a comprehensive systematic review and meta-analysis of randomised controlled trials evaluating the effectiveness of adenoidectomy in children with otitis media.

Objectives

To assess the effectiveness of adenoidectomy compared with non-surgical management in children up to 18 years of age with otitis media.

Methods

Criteria for considering studies for this review

Types of studies

We considered all identified randomised controlled trials of adenoidectomy for otitis media compared with non-surgical treatment or tympanostomy tubes alone for inclusion in this review. We included trials in which the method of randomisation was not specified in detail, but we excluded quasi-randomised trials (e.g. allocation by date of birth or record number). Studies had to have a follow up of at least six months. Studies with a follow up of six to 12 months were reported separately from those with a follow up of 12 months or more. Desirable time points of outcome assessment were six months, 12 months, 24 months and 36 months.

Types of participants
Children up to 18 years of age diagnosed with otitis media.

Types of interventions
To evaluate the effects of adenoidectomy we compared the following interventions:
1. adenoidectomy (with or without myringotomy) versus non-surgical treatment or myringotomy only;
2. adenoidectomy with unilateral tympanostomy tube versus unilateral tympanostomy tube only (in studies of this type it is the ear without the tympanostomy tube that is evaluated to study the effect of adenoidectomy);
3. adenoidectomy with bilateral tympanostomy tubes versus bilateral tympanostomy tubes only.

Non-surgical management included watchful waiting and medical treatment including antibiotics (intermittent and long-term), steroids, antihistamines and analgesics.

Types of outcome measures

Primary outcomes
The primary outcome measure was the proportion of time with effusion, diagnosed with and without tympanometry.

Secondary outcomes
Secondary outcomes are as follows:

- Acute otitis media (AOM).
  - Number of episodes per year.
  - Number of days per episode and per year.
  - Proportion of children with recurrent episodes.

- Otitis media with effusion (OME).
  - Number of episodes per year.
  - Number of days per episode and per year.
  - Proportion of children with recurrent episodes.

- Mean hearing level.

Definitions of secondary outcome measures
AOM and OME were defined according to the definitions issued by the American Association of Family Physicians (AAFP) and the American Academy of Pediatrics (AAP).
For AOM this is: acute onset of signs and symptoms, the presence of middle ear effusion (bulging of the tympanic membrane, or limited or absent mobility of the tympanic membrane, or air-fluid level behind the tympanic membrane, or otorrhoea), and signs and symptoms of middle ear inflammation (distinct erythema of the tympanic membrane or distinct otalgia (AAFP (2009)a).
For OME this is: presence of fluid in the middle ear, without signs and symptoms of acute ear infection as diagnosed by (pneumatic) otoscopy or tympanometry (AAFP (2009)b).
Recurrent was defined as the patient having three or more episodes of OME or AOM in a period of six months, or four or more episodes in a period of 12 months (Rosenfeld (2000)).

Tertiary outcome measures
Tertiary outcome measures include:

- the proportion of children with atrophy of the tympanic membrane
- the proportion of children with tympanosclerosis of the tympanic membrane
- the proportion of children with retraction of the pars tensa and pars flaccida
- the proportion of children with cholesteatoma

Search methods for identification of studies
We conducted systematic searches for randomised controlled trials on the effectiveness of adenoidectomy in children up to 18 years of age with otitis media. There were no language, publication year or publication status restrictions. We contacted original authors for clarification and further data if trial reports were unclear and arranged translations of papers where necessary. The date of the last search was 30 March 2009.

Electronic searches
We searched the following databases from their inception: the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library Issue 1, 2009); PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; mRCT (Current Controlled Trials); ClinicalTrials.gov; ICTRP (International Clinical Trials Registry Platform); ClinicalStudyResults.org and Google.
We modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, we combined subject strategies with adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1, Box 6.4.b. (Handbook (2008)). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources
We checked the reference lists of identified publications for additional trials. We searched PubMed; TRIPdatabase; NHS Evidence - ENT and Audiology and Google to retrieve existing systematic reviews possibly relevant to this systematic review, in order to search their

reference lists for additional trials. We scanned abstracts of conference proceedings via the Cochrane Ear, Nose and Throat Disorders Group Trials Register and CENTRAL.

Data collection and analysis

We conducted the review according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions 5.0.1 (Handbook (2008)).

Selection of studies

Two review authors (MvdA, EH) scanned the abstracts to identify relevant randomised controlled trials. The same two authors obtained and reviewed the full texts of these articles. We assessed the eligibility of the trials independently and resolved any differences in opinion by discussion between the two authors. Reasons for exclusion of potentially relevant studies are given in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (MvdA, EH) also performed data extraction independently, followed by a consensus conference to resolve differences. We extracted the following data from each study: total number of children in each trial, description of participants (mean age, country of origin, inclusion and exclusion criteria, allergy status, adenoid size), follow-up time in months, description of intervention and control therapy, number of patients per intervention group, primary and secondary outcomes, the use of tympanometry as an objective outcome measure and the authors conclusion.

Assessment of risk of bias in included studies

Two authors (MvdA, CB) assessed the quality of all included trials independently using the Cochrane Collaboration's tool for assessing risk of bias ('Risk of bias' table, Cochrane Handbook for Systematic Reviews of Interventions, chapter 5 (Handbook (2008)). Six specific domains were addressed, i.e. sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other biases. By answering pre-specified questions we reported the execution of the study and judged the risk of bias for each domain. The outcome for each domain was either 1) yes, a high risk, 2) no, a low risk or 3) an unknown or unclear risk of bias. We resolved disagreement by discussion (MvdA, CB, MR).

Data synthesis

We planned to assess publication bias with a scatter plot (funnel plot) of the log rate ratios (x-axis) versus precision defined as 1/standard error (y-axis) (Handbook (2008)).

Data synthesis

We used RevMan version 5.0 (RevMan (2008)) to carry out the meta-analyses for comparable trials and outcomes. For continuous outcomes (i.e. number of episodes, number of days per episode, number of days per year, and mean hearing loss) we calculated standard mean differences (SMD) and their corresponding 95% confidence intervals (CI).
For dichotomous outcomes we measured the estimates of effect as risk differences (RD) with their corresponding 95% confidence intervals. Risk differences were calculated using: (proportion of children with outcome present in adenoidectomy group) - (proportion of children with outcome present in control group).

If heterogeneity was low (I^2 < 25%) we calculated the summary weighted risk differences and 95% confidence intervals (random-effects model) by the Mantel-Haenszel method, which weighs studies by the number of events in the control group, using the Cochrane statistical package in RevMan (version 5.0).
We planned to perform sensitivity analyses excluding the studies with the lowest methodological quality according to the Cochrane Collaboration's risk of bias assessment, and by including and excluding studies using tympanometry as an objective measure in the diagnosis of OME, to investigate whether these factors influenced the final outcome. We intended to perform subgroup analyses for age groups and adenoid size. Ultimately this was impossible because the original papers did not report the effects for these subgroups separately. Data allowing, we hope to include sensitivity and subgroup analyses in future updates of this review.

Results

Results of the search

Our search of CENTRAL, PubMed, EMBASE and other databases retrieved a total of 204 articles. We first sifted the articles by title/abstract and this left us 31 articles to read in full text. A total of 14 studies (n = 2712 children) were included in this review. No additional trials were identified by checking the bibliographies of the selected trials and reviews, nor by contacting the first or corresponding author of the eligible trials. One study by Sagnelli et al (Sagnelli (1990)) could not be retrieved.
We excluded eleven of the publications because the same data are presented in more recent articles included in this review (Black (1986); Gates (1988); Gates (1989); Maw (1983); Maw (1985)a; Maw (1985)b; Maw (1987); Maw (1988); Maw (1993); Maw (1994)a; Maw (1994)b). Publications which focused on the intervention adenotonsillectomy were also excluded except for those in which a separate analysis for adenoidectomy was performed (Paradise (1999)). Reasons for exclusion are described in the 'Characteristics of excluded studies' table.

Included studies

The included studies used a wide range of interventions and outcome measures. Therefore studies will be described by type of intervention. The 'Characteristics of included studies' table shows the characteristics in summary. The inclusion and exclusion criteria for participants of all included trials in this review are shown in table 2.

1) Adenoidectomy with or without myringotomy versus non-surgical treatment or myringotomy only.
   - Koivunen (2004)
   - Paradise (1999)
   - Paradise (1990)
   - Gates (1987)
   - Fiellau-Nikolajsen (1980)
   - Rynnel-Dagöo (1978)

2) Adenoidectomy with unilateral tympanostomy tube versus a unilateral tympanostomy tube only; non-operated ear examined for comparison.
   - Dempster (1993)
   - Black (1990)
   - Maw (1986)

3) Adenoidectomy with bilateral tympanostomy tubes versus bilateral tympanostomy tubes only.
   - Casselbrant (2009)
   - Hammarén-Malmi (2005)
   - Nguyen (2004)
   - Mattila (2003)
   - Gates (1987)
   - Roydhouse (1980)

Adenoidectomy (with or without myringotomy) versus non-surgical treatment or myringotomy only

Koivunen (2004) reported on 180 children aged 10 months to two years with at least three episodes of acute otitis media during the previous six months. They were randomly allocated to 1) adenoidectomy (n = 60), 2) chemoprophylaxis (n = 60) or 3) placebo (n = 60). The primary outcome was intervention failure in the first six months, which was defined as two or more episodes of acute otitis media in two months or at least three in six months, or middle ear effusion for at least two months. Secondary outcomes were mean number of 1) episodes of acute otitis media, 2) visits to a doctor, 3) antibiotic prescriptions and 4) days with symptoms (rhinitis, earache, fever). Follow up was two years.

Paradise (1999) reported on 304 children aged three to 15 years with recurrent acute otitis media or persistent otitis media with effusion. They were randomly allocated to 1) adenoidectomy (n = 100), 2) adenotonsillectomy (n = 103) or 3) the control group (n = 101). The primary outcome was the mean number of episodes of acute otitis media measured at 12, 24 and 36 months. Secondary outcomes were estimated proportion of time with acute otitis media, mean number of days with ear pain, mean number of days with antimicrobial treatment and the number of myringotomy and tympanostomy tube procedures. Follow up was three years.

Paradise (1990) reported on 99 children aged one to 15 years with recurrent acute otitis media after tympanostomy tube extrusion. They were randomly allocated to 1) adenoidectomy (n = 52) or 2) the control group (n = 47). The primary outcome was the proportion of time with otitis media and the number of episodes of otitis media with effusion. The secondary outcome measures were the number of tympanostomy tube procedures, the number of episodes of otorrhoea, and the numbers of days, respectively, on which ear pain occurred and antimicrobial treatment was received. Follow up was three years.

Gates (1987) reported on 491 children aged four to eight years with chronic effusion. They were randomly allocated to 1) bilateral myringotomy (n = 107), 2) bilateral tympanostomy tubes (n = 129), 3) adenoidectomy and bilateral myringotomy (n = 130) and 4) adenoidectomy and bilateral tympanostomy tubes (n = 125). Primary outcomes were time with effusion and time with hearing loss > 20 dB. Secondary outcome measures were median days to first

recurrence of OME and number of surgical re-treatments. Follow up was two years.

Fiellau-Nikolajsen (1980) screened 463 three-year-old children with recurrent or persistent OME by tympanometry and otoscopy. Forty-two children with an abnormal tympanogram, i.e. type B or C1/C2 for at least six months, were included in the trial. The children were randomly assigned to 1) myringotomy with adenoidectomy (n = 20) or to 2) myringotomy without adenoidectomy (n = 22). Primary outcome was type of tympanogram (A, C1, C2 or B). Secondary outcome was recovery time in months. Follow up was six months.

Rynnel-Dagöo (1978) reported on 105 children aged less than 12 years with recurrent serous and purulent otitis media, frequent upper airway infections and nasal obstruction. After randomisation 29 children were excluded for various reasons, i.e. 76 children remained for analysis: 37 in the adenoidectomy group and 39 in the control group. Outcomes were change (better, deteriorated or unchanged) in frequency of common colds, purulent or serous otitis media and nasal obstruction. The follow up was two years.
In summary, the selected studies differed regarding the inclusion criteria and the outcomes measured.

Adenoidectomy with a unilateral tympanostomy tube versus a unilateral tympanostomy tube only; non-operated ear examined for comparison
Dempster (1993) reported on 78 children, aged three to 12 years with bilateral otitis media with effusion based on otoscopy, an air bone gap > 15 dB, hearing levels > 25 dB HL and a type B tympanogram in both ears at two examinations with an interval of 12 weeks. The children were randomly assigned to 1) adenoidectomy with unilateral tube insertion (n = 37) or 2) unilateral tube insertion (n = 35). The primary outcomes were resolution of otitis media and improvement in hearing recorded at six and 12 months postoperatively by a validated otoscopist, tympanometry and pure-tone audiometry. Follow up was one year.

Black (1990) reported on 149 children aged four to nine years with bilateral otitis media with effusion. All children were randomly assigned to 1) adenoidectomy with bilateral myringotomy and unilateral tympanostomy tube insertion (n = 37), 2) adenoidectomy with unilateral tympanostomy tube insertion (n = 38), 3) bilateral myringotomy and unilateral tympanostomy tube insertion (n = 37) and 4) unilateral tympanostomy tube insertion (n = 37). Outcome measures were mean hearing loss (dB) of the three worst heard frequencies between 250 Hz and 4000 Hz, resolution of effusion and parental views on their child's progress. Follow up was two years.

Maw (1986) reported on 150 children aged two to nine years with bilateral OME, subjective hearing loss, a mean hearing loss of > 25 dB and tympanograms other than type A, for at least three months. The children were randomised to 1) adenotonsillectomy (n = 47), 2) adenoidectomy (n = 47) or 3) neither (n = 56). Furthermore, all children received a tympanostomy tube in either the left or right ear by random allocation. Outcomes were resolution of effusion based on otoscopy and tympanometry. Pure tone audiometry was also performed. Follow up was one year.
In summary, inclusion criteria and outcome measures of the included studies were comparable.

Adenoidectomy with bilateral tympanostomy tubes versus bilateral tympanostomy tubes only

Casselbrant (2009) reported on 98 children aged 24 months to 47 months with bilateral or unilateral middle ear effusion. They were randomly assigned to 1) myringotomy and tympanostomy tube insertion (n = 32), 2) adenoidectomy with myringotomy and tympanostomy tube insertion (n = 32) or 3) adenoidectomy with myringotomy alone (n = 34). The primary outcome was percentage of time with middle ear effusion. Secondary outcomes were episodes of AOM, otorrhoea and OME, time to first recurrence, number of surgical procedures, treatment failures, complications and treatment sequelae. Follow up was 3 years.

Hammarén-Malmi (2005) reported on 217 children aged one to four years with recurrent acute otitis media (162 children) or persistent otitis media with effusion (55 children) examined for at least six to eight weeks. They were randomly assigned to 1) adenoidectomy with insertion of bilateral tympanostomy tubes (n = 109) or 2) bilateral tympanostomy tube insertion without adenoidectomy (n = 108). The outcome was the mean number of otitis media episodes. Follow up was one year.

Nguyen (2004) reported on 72 patients aged 18 months to 18 years with recurrent acute otitis media and/or otitis media with effusion causing a conductive hearing loss > 30 dB. The children were randomly assigned to 1) bilateral tympanostomy tube insertion with adenoidectomy (n = 23) or 2) bilateral tympanostomy tube insertion without adenoidectomy (n = 40). The outcome measure was the rate of treatment failure (recurrence of AOM, persistent OME or reinsertion of ventilation tubes). Follow up was one year.

Mattila (2003) included 137 children aged one to two years out of 2497 children who were participating in a pneumococcal vaccine study (the Finnish Otitis Media Vaccine Trial). All included children experienced recurrent episodes of acute otitis media (with or without effusion); more than three to five events of AOM during the last six months, or four to six events during the last year. The children were randomly allocated to 1) bilateral tympanostomy tubes (n = 63) and 2) bilateral tympanostomy tubes and adenoidectomy (n = 74). Primary outcomes were the rate of all acute otitis media episodes (per person-year) and the rates of acute otitis media episodes caused by *S pneumonia*, *H influenza* and *M catarrhalis*. The secondary outcome measure was the number of days with otorrhoea. Follow up was one year.

Gates (1987) reported on 491 children aged four to eight years with chronic effusion. They were randomly allocated to 1) bilateral myringotomy (n = 107), 2) bilateral tympanostomy tubes (n = 129), 3) adenoidectomy and bilateral myringotomy (n = 130) and 4) adenoidectomy and bilateral tympanostomy tubes (n = 125). Primary outcomes were time with effusion and time with hearing loss > 20 dB. Secondary outcome measures were median days to first recurrence of OME and number of surgical re-treatments. Follow up was two years.

Roydhouse (1980) assessed 169 children aged two to 14 years with OME for at least two months. The 100 eligible children were randomly assigned to 1) bilateral tympanostomy tubes with adenoidectomy (n = 50) or 2) bilateral tympanostomy tubes without adenoidectomy (n = 50). The outcome measure was presence or absence of effusion. Absence of effusion was defined as type A or C1/C2 tympanogram or tympanostomy tubes in situ. Follow up was three years.

In summary, the included studies differed regarding the inclusion criteria and outcome measures.

Risk of bias in included studies

Figure 1 and Figure 2 show the results of the quality assessment according to the Cochrane Collaboration s tool for assessing risk of bias. Figure 1 shows the judgements about each methodological quality item presented as percentages across all included trials; Figure 2 shows the judgements for each included trial separately.

Sequence generation and allocation concealment

In four out of 14 studies (29%) the risk of bias for sequence generation was classified as unclear (Fiellau-Nikolajsen (1980); Mattila (2003); Nguyen (2004); Roydhouse (1980)). In five out of 14 studies (36%) allocation concealment was classified as unclear (Casselbrant (2009); Fiellau-Nikolajsen (1980); Mattila (2003); Nguyen (2004); Roydhouse (1980)). The reasons are reported in the 'Risk of bias' tables under 'Characteristics of included studies'. Ten out of the 14 studies (71%) had a low risk of bias for sequence generation (Black (1990); Casselbrant (2009); Dempster (1993); Gates (1987); Hammarén-Malmi (2005); Koivunen (2004); Maw (1986), Paradise (1990); Paradise (1999); Rynnel-Dagöo (1978)) and nine out of 14 studies (64%) had a low risk of bias for allocation concealment (Black (1990); Dempster (1993); Gates (1987); Hammarén-Malmi (2005); Koivunen (2004); Maw (1986); Paradise (1990); Paradise (1999); Rynnel-Dagöo (1978)).

Blinding

Seven out of 14 studies (50%) had a high risk of bias for blinding (Gates (1987); Koivunen (2004); Mattila (2003); Nguyen (2004); Paradise (1990); Paradise (1999); Rynnel-Dagöo (1978)). In six out of 14 studies (43%) the risk of bias for blinding was unclear (Black (1990); Casselbrant (2009); Fiellau-Nikolajsen (1980); Hammarén-Malmi (2005); Maw (1986); Roydhouse (1980)). Blinding was performed for the outcome assessor of the primary outcome in one study (7%) (Dempster (1993)).

Incomplete outcome data

There was a high risk of bias for incomplete outcome data in three out of 14 studies (21%) (Mattila (2003); Nguyen (2004); Rynnel-Dagöo (1978)). The risk of bias was unclear in five studies (36%) (Black (1990); Dempster (1993); Koivunen (2004); Maw (1986); Paradise (1999)) and low in six studies (43%) (Casselbrant (2009); Fiellau-Nikolajsen (1980); Gates (1987); Hammarén-Malmi (2005); Paradise (1990); Roydhouse (1980)).

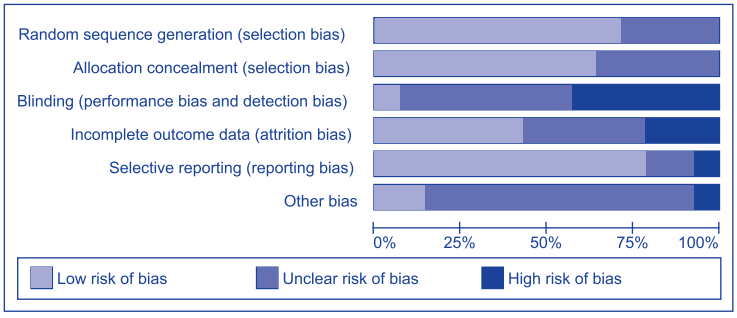

Figure 1. risk of bias methodological quality graph: review authors judgement about each methodological quality item presented as percentages across all included studies.

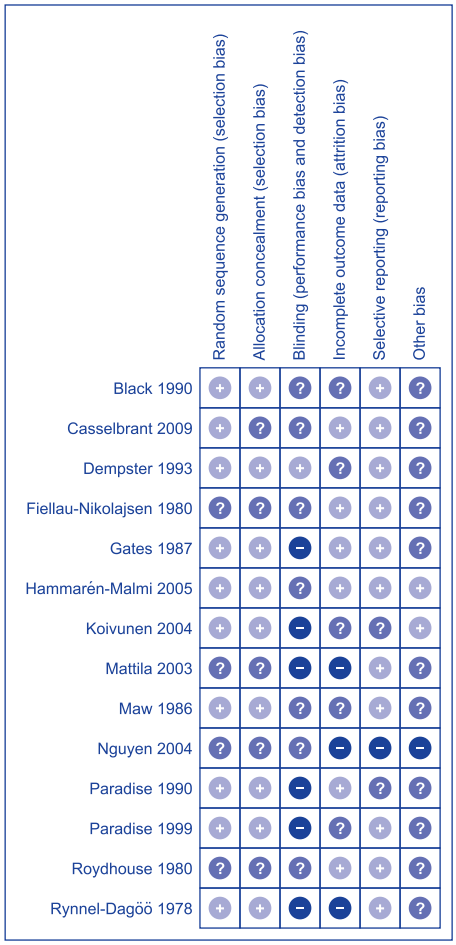

Figure 2. risk of bias methodological quality graph: review authors judgement about each methodological quality item for each included study.

Selective outcome reporting

One study (7%) had a high risk of selective outcome reporting (Nguyen (2004)). In two studies (14%) the risk of bias was unclear (Koivunen (2004); Paradise (1990)). Eleven studies (79%) had a low risk of bias for selective outcome reporting (Black (1990); Casselbrant (2009); Dempster (1993); Fiellau-Nikolajsen (1980); Gates (1987); Hammarén-Malmi (2005); Maw (1986); Paradise (1999); Roydhouse (1980); Rynnel-Dagöo (1978)).

Other sources of bias

One study (7%) had a high risk of bias for other sources of bias (Nguyen (2004)). In ten studies (71%) the risk of bias was unclear (Black (1990); Casselbrant (2009); Dempster (1993); Gates (1987); Fiellau-Nikolajsen (1980); Mattila (2003); Maw (1986); Paradise (1999); Roydhouse (1980); Rynnel-Dagöo (1978)) and in three low (21%) (Hammarén-Malmi (2005); Koivunen (2004); Paradise (1990)).

Effects of interventions

Adenoidectomy (with or without myringotomy) versus non-surgical treatment or myringotomy only

Koivunen (2004) showed that 26 children (43%) in the adenoidectomy group still had otitis media at six months and 43 children (76%) at 24 months. In the control group these numbers were 32 children (58%) at six months and 41 (79%) at 24 months. The corresponding difference rates, are -15% (95% confidence interval (CI) -3 to 33) and -3% (95% CI -13 to 19) at six and 24 months, respectively.

Differences at six months were calculated for the mean number of acute otitis media (AOM) episodes (0; 95% CI -0.4 to 0.4), sick child visits (0.6; 95% CI -0.3 to 1.5), antimicrobial prescriptions (-0.1; 95% CI -0.6 to 0.5), days with earache (-0.3; 95% CI -1.6 to 1.0) and days with fever (1.6; 95% CI -4.5 to 1.2).

Paradise (1999) reported that the mean rate of AOM episodes (> 10 days) during the first year was 1.8 per subject in the adenoidectomy group and 2.1 per subject in the control group. After two and three years the episode rates were 1.7 versus 1.2 and 1.3 versus 1.5, respectively.

The difference between the groups in percentage of subjects without AOM episodes was 9.6% (95% CI -5.1% to 24.4%) after one year; -10.9% (95% CI -28.0% to 6.2%) after two years; and -0.9% (95% CI -22.0% to 20.3%) after three years.

The mean number of days with earache per subject in the adenoidectomy and control group was 7.0 versus 8.1, 6.8 versus 6.8, and 5.4 versus 6.1 in the first, second and third year, respectively.

The number of days that subjects were treated with antibiotics was 50.2 versus 61.9, 44.6 versus 44.0, and 46.1 versus 42.1 in the first, second and third year, respectively. Since no standard deviations were reported we could not calculate standardised mean differences.

Paradise (1990) reported a mean proportion of time with otitis media during the first year of 15% in the adenoidectomy group and 27.4% in the control group. After two years this was 18% versus 27.2% respectively. The difference between the groups in proportion of time with otitis media was -12.2% (95% CI -31.4 to 6.9) after one year and -10.4% (95% CI -31.4 to 10.6) after two years. The mean number of episodes of otitis media with effusion in the adenoidectomy group and the control group was 1.06 versus 1.45, 1.09 versus 1.67, and 0.89 versus 0.87 in the first, second and third follow-up year respectively

The number of tympanostomy tube procedures per subject in the adenoidectomy and the control group were 0.13 versus 0.29, 0.13 versus 0.26, and 0.08 versus 0.13 in the first, second and third year, respectively. The number of secondary otorrhoea episodes per subject in the adenoidectomy and the control group was 0.13 versus 0.13, 0.09 versus 0.04, and 0.05 versus 0.07 in the first, second and third year, respectively. The mean number of days with earache per subject was 3.99 versus 4.54, 4.21 versus 4.28, and 3.94 versus 5.08 in the first, second and third year, respectively. The mean number of days with antimicrobial treatment was 30.7 versus 43.2, 28.6 versus 45.3, and 30.8 versus 25.8 in the first, second and third year, respectively.

Gates (1987) reported that the mean time with effusion (± SD) in the myringotomy with adenoidectomy group was 0.302 (± 0.250) and in the myringotomy group 0.491 (± 0.252).

The corresponding standardised mean difference (SMD) is -0.76 (95% CI -1.02 to -0.49).
The mean time with hearing loss > 20 dB (SD) for the better ear was 0.078 (± 0.131) in the myringotomy with adenoidectomy group and 0.186 (± 0.195) in the myringotomy group. The standardised mean difference (SMD) is -0.66 (95% CI -0.93 to -0.40). For the poorer ear these numbers were 0.220 (± 0.239) and 0.375 (± 0.253), respectively. The standardised mean difference (SMD) is -0.65 (95% CI -0.91 to -0.39).

Fiellau-Nikolajsen (1980) showed that 68% of the children in the adenoidectomy group had normal ears (type A tympanogram) compared to 52% in the control group after six months of follow up. The risk differences (RD) were 15% (95% CI -5% to 36%) for a type A tympanogram and -2% (95% CI -30% to 26%) for recovery of effusion.

Rynnel-Dagöo (1978) found an overall improvement regarding the frequency of common colds and otitis media in both the adenoidectomy and control group, but no difference was found between intervention groups.
Improvement in episodes of purulent otitis media, meaning a reduction in number of more than two episodes of illness, was found in 47% versus 49% after 12 months, and in 46% versus 52% after 24 months in the adenoidectomy and control group, respectively. The risk differences were -1% (95% CI -24% to 21%) and -6% (95% CI -30% to 18%).
Improvement in episodes of serous otitis media, defined as a change from existing to non-existing serous secretion, was found in 19% versus 30% after 12 months, and in 31% versus 30% after 24 months in the adenoidectomy and control group, respectively. The risk differences were -10% (95% CI -30% to 9%) and 1% (95% CI -21% to 23%).

Three trials reported similar outcomes (Koivunen (2004); Paradise (1990); Paradise (1999)), i.e. mean number of AOM episodes, mean number of antimicrobial prescriptions and mean number of days with earache, but the inclusion criteria and time of follow-up measurements differed. Therefore, we could not perform a meta-analysis.

Adenoidectomy with a unilateral tympanostomy tube versus a unilateral tympanostomy tube only; non-operated ear examined for comparison
Meta-analysis could be performed for the following:
1) Resolution of OME based on otoscopy.
   - Dempster (1993) (at six and 12 months).
   - Maw (1986) (at six and 12 months).

2) Resolution of OME measured by tympanometry.
   - Dempster (1993) (at six and 12 months).
   - Black (1990) (at seven weeks, six, 12 and 24 months).
   - Maw (1986) (at six and 12 months).

Resolution of OME based on otoscopy

Dempster (1993) reported that in 49% of the children in the adenoidectomy group the effusion had resolved after six months. In the control group this percentage was 26%. The risk difference was 23% (95% CI 1% to 45%).

Maw (1986) reported that the effusion had resolved in 49% of the children in the adenoidectomy group after six months. In the control group this was 17%. The risk difference was 31% (95% CI 11% to 51%).

Analysis 1.1 shows no heterogeneity (I^2 value 0%) between the two studies when considering number of children with resolution of OME by otoscopy at six months. The overall risk difference is 27% (95% CI 13% to 42%) (Figure 3).

The analysis considering this outcome at 12 months showed a high heterogeneity ($I^2 > 50\%$), suggesting that these trials differ too much to pool into a meta-analysis.

Dempster (1993) showed 54% resolution of OME in the adenoidectomy group and 37% in the control group after 12 months. The risk difference was 17% (95% CI -6% to 40%).

Maw (1986) reported that in 69.4% of the children the effusion had resolved in the adenoidectomy group after 12 months. In the control group this percentage was 27.7%. The risk difference was 42% (95% CI 22% to 62%).

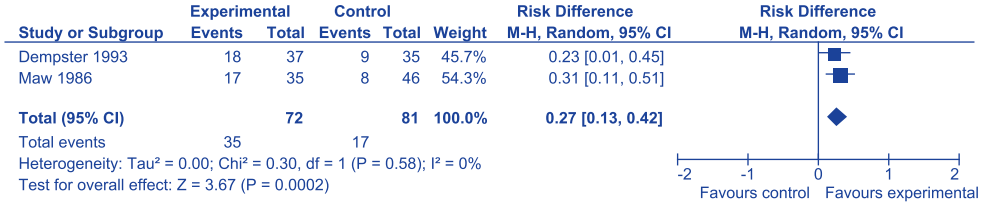

Figure 3. analysis 1.1: Forest plot of comparison.

Adenoidectomy with unilateral tympanostomy tube vs a unilateral tympanostomy tube.

Outcome: Resolution of OME based on otoscopy at 6 months.

Resolution of OME measured by tympanometry

Dempster (1993) reported resolution of effusion in 41% of the children in the adenoidectomy group after six months compared to 20% in the control group. The risk difference was 21% (95% CI 0% to 41%). After 12 months the effusion had resolved in 51% of the children in the adenoidectomy group versus 31% of the control group. The risk difference was 20% (95% CI -2% to 42%).

Black (1990) reported resolution of effusion in 37% of the children in the adenoidectomy group versus 15% in the control group after six months. The risk difference was 22% (95% CI 9% to 36%). After 12 months the effusion had resolved in 41% of the children in the adenoidectomy group versus 9% in the control group. The risk difference was 32% (95% CI 19% to 45%).

Maw (1986) reported resolution of effusion in 41% of the children in the adenoidectomy group after six months compared to 18% of the control group. The risk difference was 22% (95% CI 2% to 43%). After 12 months the effusion had resolved in 58% of the children in the adenoidectomy group versus 28% in the control group. The risk difference was 30% (95% CI 8% to 52%).

According to Analysis 1.2 there is no heterogeneity (I^2 value 0%) between studies when resolution of OME measured by tympanometry is considered at six months. The overall risk difference (RD) is 22% (95% CI 12% to 32%) (Figure 4).

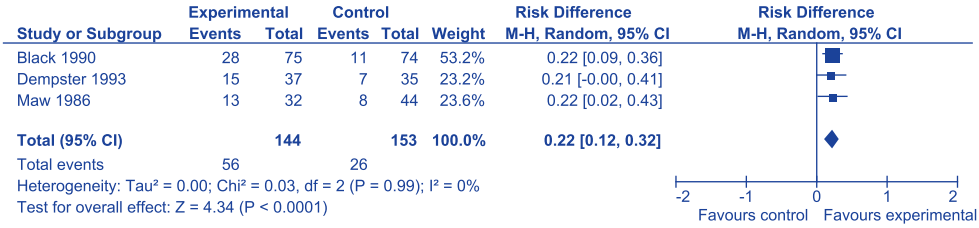

Figure 4. analysis 1.2: Forest plot of comparison.
Adenoidectomy with unilateral tympanostomy tube vs a unilateral tympanostomy tube.
Outcome: Resolution of OME based on tympanometry at 6 months.

According to Analysis 1.3 there is no heterogeneity (I^2 value 0%) between studies when resolution of OME measured by tympanometry is considered at 12 months. The overall risk difference (RD) is 29% (95% CI 19% to 39%) (Figure 5).

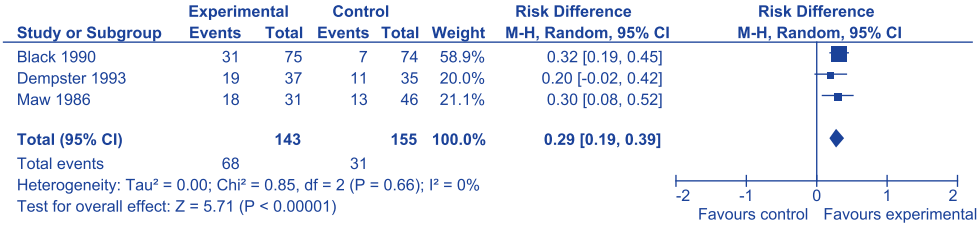

Figure 5. analysis 1.3: Forest plot of comparison.
Adenoidectomy with unilateral tympanostomy tube vs a unilateral tympanostomy tube.
Outcome: Resolution of OME based on tympanometry at 12 months.

Hearing loss (air conduction measured in dB HL) in children with OME

The analysis considering this outcome showed high heterogeneity ($I^2 > 50\%$), so these trials differ too much to pool into a meta-analysis.

Dempster (1993) reported a mean air conduction HL of 18.0 dB (± 13.0) versus 21.1 dB (± 11.7) at six months, and 15.6 dB (± 8.4) versus 18.4 dB (± 10.6) at 12 months in the adenoidectomy and control group, respectively. The standardised mean differences (SMD) were -0.25 dB (95% CI -0.71 to 0.22) and -0.29 dB (95% CI -0.76 to 0.17), respectively.

Black (1990) reported only treatment group comparisons of change in mean audiometry scores (dB). Differences of 4.3 dB (95% CI -1.4 to 9.9) and 4.3 dB (95% CI -3.1 to 11.6) were found between the group with adenoidectomy and the group without adenoidectomy after six and 12 months, respectively.

Maw (1986) reported a mean air conduction HL of 20.4 dB (± 11.27) versus 36.5 dB (± 11.87) at six months, and 19.7 dB (± 10.36) versus 27.4 dB (± 12.13) after 12 months in the adenoidectomy and control group, respectively. The standardised mean differences (SMD) were -1.37 dB (95% CI -1.87 to -0.88) and -0.67 dB (95% CI -1.12 to -0.22).

Adenoidectomy with bilateral tympanostomy tubes versus bilateral tympanostomy tubes

Casselbrant (2009) reported the percentage of time with middle ear effusion of 18% in the adenoidectomy group and 12% in the control group during the first 18 months. After three years this was 21% and 19%, respectively. The difference in proportion of time was 6% (95% CI -12 to 24) after 18 months and 2% (95% CI -19 to 23) after 36 months.
After 18 months the number of episodes of AOM was seven and six in the adenoidectomy and the control group, respectively. The risk difference is 5% (95% CI -22 to 32). After 36 months the number of AOM episodes was 17 and 21 in the adenoidectomy and the control group. The risk difference is -18% (95% CI -37 to 1).
Hammarén-Malmi (2005) reported a mean number of otitis media episodes of 1.73 (SD ± 1.8) in the tympanostomy tube with adenoidectomy group versus 1.44 (SD ± 1.5) in the tympanostomy tubes group. The standardised mean difference (SMD) was 0.17 (95% CI -0.11 to 0.45).

Nguyen (2004) reported 21.7% failures in the PET (pressure equalisation tubes) with adenoidectomy group and 42.5% failures in the PET group, with a risk difference (RD) of -21% (95% CI -44% to 2%) regarding treatment failure.

Mattila (2003) reported 2.05 episodes of acute otitis media per person-year in the tympanostomy tubes with adenoidectomy group and 2.40 in the tympanostomy tubes group. Since no standard deviations were reported, we could not calculate standardised mean differences (SMD). The estimate efficacy, determined as 1 minus the RR adjusted for vaccination status, sex, number of siblings, and the preoperative number of otitis media episodes, of adenoidectomy with tympanostomy tubes versus tympanostomy tubes was 0.19 (95% CI -0.14 to 0.43).

Gates (1987) reported the mean time with effusion (± SD) in the tympanostomy tubes with adenoidectomy group was 0.258 (± 0.212) and in the tympanostomy tubes group 0.349 (± 0.235). The corresponding standardised mean difference (SMD) is -0.40 (95% CI -0.65 to -0.15). The mean time with hearing loss > 20 dB (± SD) for the better ear was 0.065 (± 0.116) in the tympanostomy tubes with adenoidectomy group and 0.101 (± 0.141) in the tympanostomy tubes group. The standardised mean difference (SMD) is -0.23 (95% CI -0.48 to 0.02). For the poorer ear these numbers were 0.224 (± 0.221) and 0.304 (± 0.227), respectively. The standardised mean difference (SMD) is -0.35 (95% CI -0.60 to -0.11).

Roydhouse (1980) reported that 18% and 23% of all ears had effusion at 12 months in the tympanostomy tubes with adenoidectomy group and tympanostomy tubes group, respectively. These numbers were 15% and 18% after 24 months in both intervention groups, respectively. The risk differences were -5% (95% CI -8% to 17%) and -3% (95% CI -10% to 15%).

The trials were too heterogeneous to pool into a meta-analysis.

Subgroup and sensitivity analysis
Since all three studies included in the meta-analysis (Black (1990); Dempster (1993); Maw (1986)) were of high quality and all used the best available non-invasive objective diagnostic test for OME (tympanometry) as an objective outcome measure, sensitivity analysis excluding studies of either low quality or those not using tympanometry as an objective outcome measure was not possible.
For the other studies pooling was impossible and the outcome measures differed too much to perform sensitivity analysis. Due to the lack of data in the included studies concerning age, adenoid size and allergic rhinitis, factors that may modify the effect of adenoidectomy, it was not possible to perform subgroup analyses.

Complications and adverse effects
Five studies (Dempster (1993); Gates (1987); Koivunen (2004); Paradise (1999); Rynnel-Dagöo (1978)) reported information about postoperative complications. Gates (1987) reported on one child with recurring haemorrhage; Paradise (1999) reported on one patient with incipient malignant hyperthermia, one with postoperative pneumonia and two with transient postoperative velopharyngeal insufficiency. No haemorrhage occurred. In the studies by Koivunen (2004), Dempster (1993) and Rynnel-Dagöo (1978) no complications occurred.

Discussion

Summary of main results
The most important findings are the 22% (95% CI 12% to 32%) and 29% (95% CI 19% to 39%) risk differences at six months and 12 months for children with persistent otitis media with effusion (OME) in the three pooled trials that compared adenoidectomy with unilateral tympanostomy tubes versus a unilateral tympanostomy tube alone, in which the non-operated ears were used as the comparator.
The trials comparing adenoidectomy with or without myringotomy versus non-surgical treatment or myringotomy alone, and adenoidectomy with bilateral tympanostomy tubes versus bilateral tympanostomy tubes alone, are more difficult to interpret because they

include a heterogeneous patient population: some children had primarily recurrent acute otitis media (AOM), some had only OME and some had a combination of the two. Nevertheless, the effect of adenoidectomy on both AOM and hearing appears to be small and non-significant.
The effects of adenoidectomy on changes of the tympanic membrane or cholesteatoma were not reported in any of the included trials.

Potential biases in the review process

During the review process potential biases were identified both in the individual trials and in the review process itself.
In only four trials a power analysis was provided and adequate numbers included (Black (1990); Dempster (1993); Gates (1987); Koivunen (2004)). As the other trials included relatively few patients, their power may have been too low, leading to either a type I or type II error.
Loss to follow up was significant in most studies. This can be associated with either good or poor outcome. In three trials children were excluded after randomisation, which may have led to residual confounding (Mattila (2003); Paradise (1999); Rynnel-Dagöo (1978)).
Eight studies were analysed per protocol and no data were available to perform intention-to-treat analyses (Black (1990); Dempster (1993); Hammarén-Malmi (2005); Mattila (2003); Maw (1986); Nguyen (2004); Paradise (1999); Rynnel-Dagöo (1978)). Per protocol analyses in which children who change groups are excluded may underestimate the treatment effect. In surgical trials only children in the watchful waiting group with severe complaints can change treatment group, whereas children in the surgical group who may experience similarly severe complaints cannot change treatment group. Analysing children on the basis of time spent in a treatment arm may over or underestimate the treatment effect.
Information bias may be considerable since trials on adenoidectomy, like most surgical trials, cannot be performed in a true double-blind fashion. Such bias will overestimate the effect of the intervention.
All three studies included in the meta-analysis for 'adenoidectomy with a unilateral tympanostomy tube versus unilateral tympanostomy tube only; non-operated ear examined for comparison' (Black (1990); Dempster (1993); Maw (1986)) randomised which ear (left or right) would receive the tympanostomy tube. Eustachian tube function has been shown to vary greatly between ears in individuals (Heerbeek (2003)), therefore the validity of a paired organ design for otitis media may be limited.
Generalisability of the trials can be questioned since only a very small proportion of the eligible children undergoing adenoidectomy were included in the trials.
Due to the large variety of outcome measures used it was not possible to make a funnel plot to explore publication bias.
Due to the lack of data on factors that may modify the effect of adenoidectomy, such as age, adenoid size or allergic rhinitis, it was not possible to perform subgroup analyses and identify children that may benefit more or less from the operation.
The authors of this review were not blinded to authorship and origin of the included studies, since they knew most of the literature before embarking on this review.
Lastly, we could not include the results of the TARGET trial (TARGET), the largest and highest quality study to date on the effectiveness of adenoidectomy and tympanostomy tubes in children with otitis media with effusion, as the results have not yet been published. We expect to be able to include these results in the next update of this review.

Conclusion

Implications for practice

Our review shows a significant benefit of adenoidectomy as far as the resolution of middle ear effusion in children with otitis media with effusion (OME) is concerned. However, the benefit to hearing is small and the effects on changes in the tympanic membrane are unknown. The risks of operating should be weighed against these potential benefits.

The absence of a significant benefit of adenoidectomy for acute otitis media (AOM) suggests that routine surgery for this indication is not warranted.

Implications for research

There is a need for good quality evidence on the effectiveness of adenoidectomy in children with otitis media. An individual patient data meta-analysis, pooling the original data of trials performed in this area, could identify the subgroups that will benefit most from adenoidectomy.

Tables

Table 1. Characteristics of included studies including risk of bias table per author.

Black (1990)

Methods	RCT
Participants	149 children aged 4 to 9 years with bilateral OME
Interventions	Adenoidectomy with bilateral myringotomy (n=37), adenoidectomy with a unilateral tube (n=38), bilateral myringotomy (n=37), and a unilateral tube (=37)
Outcomes	Measured at 7 weeks, 6, 12 and 24 months: · Resolution of OME measured by tympanometry · Hearing loss · Parents'opinion on their child's symptoms
Notes	15% of the children were lost to follow-up after 12 months follow-up and 39% after 24 months 48 children (32%) underwent further surgery during 24 months follow-up Children who had undergone adenoidectomy were less likely to have further surgery (19% versus 45%) No intention to treat method was used for analysis

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote 1: 'we randomly divided the children in to one of our four groups.' 'Randomisation between the right ear and the left ear for grommet insertion was also carried out.' Quote 2: 'Instructions about the treatment allocation were contained in sealed numbered envelopes. The contents of the envelopes were determined with a table of random numbers.'
Allocation concealment?	Yes	Quote 1: 'we randomly divided the children in to one of our four groups.' 'Randomisation between the right ear and the left ear for grommet insertion was also carried out.' Quote 2: 'Instructions about the treatment allocation were contained in sealed numbered envelopes. The contents of the envelopes were determined with a table of random numbers.'
Blinding?	Unclear	Quote: 'The audiometricians were blind to treatment the children had received.' Comment: no information is provided about blinding of the otolaryngologist who retrieved the remaining data. Probably not since it is a surgical trial.
Incompelete outcome data addressed?	Unclear	Quote 1: 'Audiometric data were not obtained on every occasion in 22 children and therefore these children were omitted from the analysis.' Quote 2: 'The data were initially analysed without taking into account any loss to follow-up. The results are shown in table IV (raw data).'
Free of selective reporting?	Yes	Comment: the main outcome measures 1) mean hearing loss (dB), 2) results of impedance tympanometry and 3) parental views on their child s progress are reported.
Free of other bias?	Unclear	Quote: 'The only important methodological problem was the higher than predicted number of children who we were unable to follow up for two years. The principal reason for this was the clinicians dissatisfaction with a child s progress, which they believed warranted further surgical intervention.'

Casselbrant (2009)

Methods	RCT
Participants	98 children aged 24 to 47 months, with a history of bilateral middle ear effusion (MEE) for at least 3 months, unilateral for 6 months or longer or unilateral for 3 months after extrusion of a tympanostomy tube, unresponsive to recent antibiotic.
Interventions	1) Myringotomy and tympanostomy tubes, 2) adenoidectomy, myringotomy and tympanostomy tube, 3) adenoidectomy and myringotomy
Outcomes	Measured at 18 months and 36 months: · Primary outcome: proportion of time with MEE · Secondary outcome: time after insertion a tube became permanently non-functional, acute otitis media episodes, otorrhoea episodes, and additional surgical procedures
Notes	Analysed with intention to treat principle If MEE persisted bilaterally for 4 consecutive months or cumulatively for 6 of the previous 12 months, or unilateral MEE for 6 consecutive months or cumulatively for 8 months in the past 12 months, myringotomy and tympanostomy tube placement was performed in all children irrespective of initial random assignment and adenoidectomy was recommended to children initially randomised to myringotomy and tympanostomy tube placement.

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote: 'The children were randomly assigned within strata to defined by age (...), nasal obstruction (...), and previous history of M&T into one of three treatment groups (...). Children with one functioning tympanostomy tube were assigned to one of two treatment groups'. Comment: the randomisation method was not specifically mentioned; one can assume that the randomisation was computer generated, since this was stratified.
Allocation concealment?	Unclear	Comment: no information provided
Blinding?	Unclear	Comment: no information provided
Incompelete outcome data addressed?	Yes	Comment: the study was terminated before the number of the estimated sample size was reached due to low accrual rate and ending of the funding period. The length of follow up was equal in all three groups. For the analysis of 18 and 36 months only those children with full follow up were analysed.
Free of selective reporting?	Yes	Comment: all reported outcome measures are reported on.
Free of other bias?	Unclear	Comment: no information provided

Dempster (1993)

Methods	RCT
Participants	78 children aged 3 to 12 years with bilateral OME associated with hearing loss
Interventions	Adenoidectomy with unilateral tube (n = 37), unilateral tube (n = 35)
Outcomes	Measured at 6 and 12 months: · Otoscopy · Tympanometry · Mean hearing loss
Notes	6 children (8%) were lost to follow-up after 12 months follow up No re-treatments occurred No intention to treat method was used for analysis No immediate postoperative complications were reported by surgeons

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote:'These 78 children were then (...) randomly allocated by a serially numbered envelope system. (...) The ears in each child were then randomly allocated by a similar process to have no ear surgery or to have a unilateral Shah grommet inserted following a radial myringotomy with aspiration of fluid.'
Allocation concealment?	Yes	Quote: 'These 78 children were then (...) randomly allocated by a serially numbered envelope system. (...) The ears in each child were then randomly allocated by a similar process to have no ear surgery or to have a unilateral Shah grommet inserted following a radial myringotomy with aspiration of fluid.'
Blinding?	Yes	Quote: 'At six and 12 months post-surgery, the presence or absence or otitis media in the non-grommeted ear was recorded by the validated otoscopist who was blinded as to whether adenoidectomy had been performed and bytympanometry.'
Incompelete outcome data addressed?	Unclear	Quote: '(...) parents of 78 of them agreed to participate. Six children defaulted either at the six or 12 month assessment visits, leaving 72 children with complete clinical, audiometric and tympanometric data for the pre-operative and these post-operative visits.' Comment: these 6 children seem to be evenly distributed over both groups, however it is unclear whether they are clinically similar to the 72 children analysed.
Free of selective reporting?	Yes	Quote: '(...) the effect of adenoidectomy on resolution of otitis media with effusion, (...) the effect on the hearing of grommet insertion alone, adenoidectomy alone, and of adenoidectomy with grommet insertion could be assessed.' Comment: all outcome measures are reported on.
Free of other bias?	Unclear	Comment: each group consisted of a small number of children

Fiellau-Nikolajsen (1980)

Methods	RCT
Participants	42 children aged 3 years with persistent or recurrent OME
Interventions	Myringotomy with adenoidectomy (n = 20), myringotomy only (n = 22)
Outcomes	Measured at 1, 3 and 6 months: Tympanometry Time to recover
Notes	No children were lost to follow up Intention to treat method was used for analysis

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Unclear	Quote: 'The children were divided by randomized, blind allocation (...).' Comment: no information provided on randomisation process
Allocation concealment?	Unclear	Quote: 'The children were divided by randomized, blind allocation (...).' Comment: no information provided on randomisation process
Blinding?	Unclear	Quote: 'The children were divided by randomized, blind allocation (...).' Comment: no further information provided who was blinded (parents, outcome assessor?), however tympanometry was used as an objective measure to asses the primary outcome.
Incompelete outcome data addressed?	Yes	Comment: all 42 children included in the trial are reported on and shown in the outcome tables.
Free of selective reporting?	Yes	Comment: the results of the pure tone audiometry and otomicroscopy at 1, 3 and 6 months postoperatively are reported on in Table 3
Free of other bias?	Unclear	Comment: each group consisted of a small number of children

Gates (1987)

Methods	RCT
Participants	491 children aged 4 to 8 years with persistent bilateral OME
Interventions	Bilateral myringotomy (n = 107), tympanostomy tubes (n = 129), bilateral myringotomy with adenoidectomy (n = 130), tympanostomy tubes with adenoidectomy (n = 125)
Outcomes	Measured until 24 months: · Time with effusion · Time with abnormal hearing · Time to first recurrence of effusion · Number of surgical re-treatments
Notes	17% of the children were lost to follow-up after 12 months and 63% after 24 months follow-up Surgical re-treatment occurred and reported as an outcome Intention to treat method was used for analysis Complications: 1 patient had recurring haemorrhage

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote 1: '(...) the child was assigned by the statistician (who used tables of random numbers) to one of the four groups (...).' Quote 2: 'Randomization was done in blocks of 16 with each stratum to ensure even distribution of patients within the four groups across time.'
Allocation concealment?	Yes	Quote 1: '(...) the child was assigned by the statistician (who used tables of random numbers) to one of the four groups (...).' Quote 2:'Randomization was done in blocks of 16 with each stratum to ensure even distribution of patients within the four groups across time.'
Blinding?	No	Quote:'An otolaryngologist in the study advised parents about the known advantages and disadvantages of the assigned treatment.'
Incompelete outcome data addressed?	Yes	Quote:'Eighty-seven patients who were randomly assigned were not included in the analysis because they did not have an operation; the effusion cleared in 46 of them and parents of 41 refused to allow surgical treatment. These children were distributed equally across treatment groups and did not differ in any clinically important way from the other 491.'
Free of selective reporting?	Yes	Quote:'The outcome measures, established a priori, were time with effusion, time with abnormal hearing, time to first recurrence of effusion, and number of surgical retreatments.' Comment: all outcome measures are reported in the results section
Free of other bias?	Unclear	Quote:'A potential source of bias is the six-week period between observations. Thus, it is possible that the duration of effusion, time to first recurrence, and tube-retention time were overestimated and that the number of recurrent effusions and the time to first recurrence after the tubes fell out were underestimated. Since the follow-up procedures were applied uniformly to all groups, it is unlikely that this source of bias influenced the conclusions.' Quote 2: 'Entry into Group 1 was closed in November 1983 because of increased morbidity.' Comment: it is unclear how this information was obtained and what consequences it had for the objectivity of the following data collection

Hammarén-Malmi (2005)

Methods	RCT
Participants	217 children aged 1 to 4 years with recurrent AOM or persistent OME
Interventions	Tympanostomy tubes with adenoidectomy (n = 109), tympanostomy tubes (n = 108)
Outcomes	Measured at 12 months: · Number of episodes with otitis media
Notes	19 children (9%) were lost to follow-up after 12 months follow-up 18 children (8%) underwent reinsertion of tympanostomy tubes No intention to treat method was used; patients who did not receive intervention as allocated were excluded from analysis

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote: 'These children were randomised in blocks of 8.'
Allocation concealment?	Yes	Quote: 'These children were randomised in blocks of 8.'
Blinding?	Unclear	Comment: no information provided. Could be possible.
Incompelete outcome data addressed?	Yes	Quote: 'The two randomisation groups were similar at the end of the follow-up? (Table 1)'
Free of selective reporting?	Yes	Quote: 'The outcome measure was the number of otitis media episodes.' Comment: this is reported
Free of other bias?	Yes	Comment: not including the data of 4 children in the tympanostomy-only treatment arm who underwent adenoidectomy for recurrent otitis media did not influence the final outcome

Koivunen (2004)

Methods	RCT
Participants	180 children aged 10 months to 2 years with recurrent acute otitis media
Interventions	Adenoidectomy (n=60), chemoprofylaxis (n=60), placebo (n=60)
Outcomes	Primary outcome measured at 12 and 24 months: · Intervention failure Secondary outcomes measured until intervention failure, drop-out, or 6 months of follow-up, whichever came first: · Mean number of episodes of acute otitis media · Sick child visits · Antimicrobial prescriptions · Day with rhinitis · Days with earache · Days with fever
Notes	Duration of an episode is not described. Follow-up 24 months; 34 children (28%) were lost to follow-up in the non-adenoidectomy groups and 2 children (3%) were lost to follow-up in the adenoidectomy group after 24 months follow-up. At the beginning of the study 12 children in the adenoidectomy group concurrently received tympanostomy tubes. During follow-up 23 children (13%) (6 adenoidectomy, 6 chemoprofylaxis, 11 placebo) received tympanostomy tubes because of persistent middle ear fluid. Intention to treat method was used for analysis. No complications in the adenoidectomy procedures were reported by the surgeons.

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote: 'We randomly assigned children to receive (...). We performed block randomisation with a block size of six using numbered containers so that allocation was concealed from the investigator.'
Allocation concealment?	Yes	Quote: 'We performed block randomisation with a block size of six using numbered containers so that allocation was concealed from the investigator.'
Blinding?	No	Quote: 'The sulfafurazole and placebo suspensions were given in a double blind fashion.' Comment: blinding for adenoidectomy versus placebo was not possible. Outcome measures are subjective.
Incompelete outcome data addressed?	Unclear	Quote: 'Children in the sulfafurazole and placebo groups discontinued intervention and received another profylaxis more often than children in the adenoidectomy group (fig.1).' Comment: 1 child was lost to follow-up in the adenoidectomy group whereas 15 and 14 children were lost to follow-up in the sulfafurozole and placebo group respectively. However, intention to treat analysis with all 180 randomised children was performed.
Free of selective reporting?	Unclear	Comment: all outcome measures are presented. The primary outcome in table 2 and the secondary outcome measures in table 3.
Free of other bias?	Yes	Quote 1: 'However, as the children in the placebo group and sulfafurazole groups discontinued the allocated intervention mor often than the children in the adenoidectomy group (...), as these children may have had more severe otitis media, this could have caused some bias by weakening the true effect of adenoidectomy.' Quote 2: 'There are two other important sources of bias that may have diminished the true effects of the treatments: firstly, the use of symptom diaries to collect the outcome, and, secondly, the possibility of misdiagnosis.' Comment: 12 children in the adenoidectomy group also received tympanostomy tubes.

Mattila (2003)

Methods	A prospective trial with a randomised and non-randomised arm; the randomised arm only was evaluated
Participants	137 children aged 1 to 2 years with recurrent AOM
Interventions	Tympanostomy tubes (n = 63), tympanostomy tubes with adenoidectomy (n = 74)
Outcomes	Measured until 24 months, per person-year: · Rates of all acute otitis media episodes · Rates of acute otitis media episodes caused by *S. pneumonia*, *H. influenza* and *M.catarrhalis* · Number of days with otorrhoea
Notes	All children received a pneumococcal vaccine (PncCRM or PncOMPC) before entering the trial 3 children (2%) were lost to follow-up after 24 months follow-up No intention to treat method was used for analysis

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Unclear	Quote: '(...) he or she was randomized into 1 of 2 treatment groups.' Comment: no information provided
Allocation concealment?	Unclear	Quote: 'The allocated treatment was not exposed to the parents or to the operation surgeon before the study was introduced and explained to the parents. If the parents showed willingness to participate, the randomly allocated treatment was revealed to them. At this point the parents were given the chance to not participate. (...) those children whose parents gave written consent were enrolled in the randomized trial (...).'
Blinding?	No	Quote: 'If the parents showed willingness to participate, the randomly allocated treatment was revealed to them. At this point the parents were given the chance to not participate.'
Incompelete outcome data addressed?	No	Quote: 'Of the 306 children randomized, 137 were enrolled in the trial. Of those enrolled, 63 were assigned to be treated with tympanostomy tubes (39% of the 162 randomized to have tympanostomy only) and 74 were assigned to be treated with concurrent tympanostomy tube placement and adenoidectomy (51% of the 144 children randomized to have concurrent tympanostomy and adenoidectomy).'
Free of selective reporting?	No	Quote: 'The main outcome measures were the rate of all acute otitis media episodes and the rates of otitis media episodes caused by S. pneumoniae, H.influenzae and M. Catarrhalis. The secondary outcome measure was the number of days with otorrhea.' Comment: all these outcomes are reported
Free of other bias?	No	Quote 1: 'Thus, the design of the trial was unconventional in that the eligible children were randomized before the study subjects were enrolled.' Comment: baseline values between study groups are not equal for number of siblings and vaccination status Quote 2: 'Thus, in the analysis the 5 children were transferred from the tympanostomy group to the tympanostomy and adenoidectomy group at the time of adenoidectomy.'

Maw (1986)

Methods	RCT
Participants	150 children aged 2 to 9 years with persistent bilateral OME
Interventions	Adenotonsillectomy with unilateral tube (n = 47), adenoidectomy with unilateral tube (n = 47), unilateral tube (n = 56)
Outcomes	Measured at 6 and 12 months: · Otoscopy · Tympanometry · Pure tone audiometry
Notes	15 children (10%) were lost to follow-up after 24 months follow-up 12 children (26%) in the adenoidectomy group and 30 children (54%) in the control group had re-insertion of tympanostomy tubes Method of analysis was unknown

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote: 'From tables of random numbers the children were allocated (...).'
Allocation concealment?	Yes	Quote: 'From tables of random numbers the children were allocated (...).'
Blinding?	Unclear	Quote: 'Post operatively clinical otoscopic examinations were done in standard fashion by the same observer, who did not look at the case notes beforehand and was not aware of the operative subgroup.'
Incompelete outcome data addressed?	Unclear	Quote: '13 cases were excluded at operation, either because an ear proved to be dry at myringotomy or because the contralateral ear was suspected to be dry.' Comment: however, 150 children were randomised and reported on in the baseline table Quote 2: '2 cases were excluded before six months because of gross nasal obstruction requiring adenoidectomy.'
Free of selective reporting?	Yes	Comment: otoscopic and audiometric findings and tympanometric peak - no peak conversion are reported
Free of other bias?	Unclear	Quote: '(...) of those having adenoidectomy 12 (26%) had 16 reinsertions; and in the no-surgery group 30 (54%) had 47 reinsertions. (...) the difference between surgery and no-surgery is significant at the 1% level.'

Nguyen (2004)

Methods	RCT
Participants	72 patients aged 18 months to 18 years with recurrent AOM or OME
Interventions	Tympanostomy tubes (n = 40), tympanostomy tubes with adenoidectomy (n = 23)
Outcomes	Measured at 12 months: · Rate of intervention failure
Notes	9 children (12%) were lost to follow-up after 12 months follow-up Nothing known about re-treatments Incidences of OM related to patient noncompliance with water-protection (i.e. swimming-related) were excluded from final analysis. No intention to treat method was used for analysis

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Unclear	Quote: 'patients were randomised to two groups.'
Allocation concealment?	Unclear	Comment: no information provided
Blinding?	Unclear	Comment: no information provided
Incompelete outcome data addressed?	No	Quote 1: 'Two patients were not included in the final analysis because their adenoids were found to be completely obstructing their nasopharynx and subsequently underwent adenoidectomy.' Quote 2: 'Seven patients did not complete the study because of incomplete follow-up of less than 12 months. Of these seven patients, 5 (71%) were randomized to the experimental group.' Comment: experimental group is tympanostomy tubes and adenoidectomy Comment: these 9 children were excluded from all analyses
Free of selective reporting?	No	Quote 1: 'Selective demographic and clinical characteristics of patients in each subgroup are summarised in Table 1.' Comment: only the mean age, percentage of males, and the degree of adenoid hypertrophy in percentage are mentioned. No absolute numbers, therefore it is unclear whether this is data on 72 or 63 children. It is also unlikely that these are the only baseline data. Quote 2: 'Incidences of otitis media related to patient non-compliance with water protection were excluded from the final analysis.'
Free of other bias?	No	Quote 1: 'For ethical reasons, patients found to have adenoids completely obstructing their nasopharynx underwent adenoidectomy, despite their initial randomisation.' Comment: randomisation did not successfully create two equal groups. Age and degree of adenoid hypertrophy differed between the two groups (Table 1). Comment: follow-up data were obtained by retrospectively filled out questionnaires at least every 6 months. This could have lead to recall bias.

Paradise (1990)

Methods	Two parallel randomised clinical trials; one-arm RCT only valued
Participants	99 children aged 1 to 15 years with either recurrent AOM or persistent OME after tympanostomy tube extrusion
Interventions	Adenoidectomy (n = 52), control group (n = 47)
Outcomes	Measured at 12, 24 and 36 months: · Proportion of time with otitis media · Mean number of episodes of OME · Mean number of tympanostomy tube procedures · Mean number of days with secondary otorrhea · Mean number of days with earache · Mean number of days with antimicrobial treatment
Notes	13% of the children were lost to follow-up after 12 months, 27% after 24 months and 47% after 36 months follow-up Children with OME at inclusion who did not respond to antibiotic therapy underwent tympanostomy tube placement In the adenoidectomy group 1 child underwent repeat adenoidectomy, in the control group 17 children underwent adenoidectomy The data were analysed in 2 modes: per protocol (i.e. the children who switched treatment arm or were lost to follow-up without completing the full year were not analysed for the whole year outcomes) and intention to treat for the primary outcome measure

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote: 'The 99 of these children whose parents gave consent were assigned randomly.' Comment: probably done since other similar trial reports separate computer generated random number lists were used for the assignments
Allocation concealment?	Yes	Comment: no information provided, probably done since other similar trial reports separate computer generated random number lists were used for the assignments.
Blinding?	No	Comment: no information provided, probably not done since it is a surgical intervention trial. However, tympanometry was performed during most visits to objectively confirm the primary outcome measure
Incompelete outcome data addressed?	Yes	Quote 1: 'Not included in the tables are data derived from experiences of less than a full year in an assigned treatment group that resulted from either failure to complete the year or a change in treatment group.' Quote 2: 'An alternative 'intention-to-treat analysis', (...) gave closely similar results.'
Free of selective reporting?	Unclear	Quote: '(...) not included in the tables are data derived from experiences of less than a full year in an assigned treatment group that resulted from either failure to complete the year or a change in treatment group.'
Free of other bias?	Unclear	Comment: no information provided. For all children to start the trial without OME, children with OME at assignment received antibiotic therapy. This occurred more often in the control group. However, data collection for the adenoidectomy group started later than the control group.

Paradise (1999)

Methods	Two parallel randomised clinical trials; 3-way trial only valued
Participants	304 children aged 3 to 15 years with either recurrent AOM or persistent OME
Interventions	Adenoidectomy (n = 100), adenotonsillectomy (n = 103), control group (n = 101)
Outcomes	Measured at 12, 24 and 36 months: · Mean rate of episodes (> 10 days) per subject of AOM · Total number of episodes of AOM · Mean number of days with earache · Mean number of days with antimicrobial treatment · Number of myringotomy procedures
Notes	23% of the children were lost to follow-up after 12 months, 34% after 24 months and 47% after 36 months follow-up 11 children (4%) had insertion of tympanostomy tubes during follow-up The author noted data were analysed in 2 modes, published data not according intention to treat method

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote: 'The children were then assigned randomly (...). Separate, computer generated random number lists were used for the assignments.'
Allocation concealment?	Yes	Quote: 'The children were then assigned randomly (...). Separate, computer generated random number lists were used for the assignments.'
Blinding?	No	Comment: no information provided, probably not done since it is a surgical intervention trial. However, tympanometry was performed during most visits to objectively confirm the primary outcome measure
Incompelete outcome data addressed?	Unclear	Quote: '304 were eligible for the 3-way trial. (...) A total of 47 subjects assigned to surgical treatment groups were withdrawn from the trials without undergoing surgery, in some instances because the parents lacked insurance coverage. (...) Four subjects assigned to control status were also withdrawn. To conserve resources, these 51 withdrawn subjects were discharged from the study. (...) Accordingly, follow-up data were available for 266 children in the 3-way trial.' Comment: it is possible that the children withdrawn from the study with a lower socio-economic status have a higher risk of AOM and OME. This might possibly have influenced the outcome. Intention to treat analysis was performed for the primary outcome measure
Free of selective reporting?	Yes	Quote: 'Data concerning the remaining outcome measures are summarized in table 4.'
Free of other bias?	Unclear	Comment: no information provided. For all children to start the trial without OME, children with OME at assignment received antibiotic therapy. This occurred more often in the control group. However, data collection for the adenoidectomy group started later than the control group.

Roydhouse (1980)

Methods	RCT
Participants	169 children aged 2 to 14 years with persistent OME
Interventions	Tympanostomy tubes with adenoidectomy (n = 50), tympanostomy tubes (n = 50), control group (n = 69)
Outcomes	Measured at 12, 24 and 36 months: · Presence or absence of OME on ear level
Notes	5 children (3%) were lost to follow-up after 12 months, 22 children (13%) after 24 months and 38 (22%) after 36 months follow-up 24 children (53%) required repeat insertions in the adenoidectomy group and 31 children (62%) in control group 'Children without effusion were defined as children with type A or type C tympanograms, children who had tympanostomy tubes in place or children who had persistent perforations following extrusion of the tube.'

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Unclear	Quote: 'Group A includes those cases who by random selection underwent adenoidectomy and insertion of aeration tubes.' Comment: no information provided
Allocation concealment?	Unclear	Quote: 'Group A includes those cases who by random selection underwent adenoidectomy and insertion of aeration tubes.' Comment: no information provided
Blinding?	Unclear	Comment: no information provided
Incompelete outcome data addressed?	Yes	Comment: all information is provided for all patients still included per year. The reasons for loss to follow-up are reported and equal in both groups.
Free of selective reporting?	Yes	Comment: all outcomes are reported. Extra outcomes reported are number of relapses and the relation to adenoid size.
Free of other bias?	Unclear	Comment: no information provided

Rynell-Dagöo (1978)

Methods	Prospective controlled study
Participants	105 children aged less than 12 years with recurrent acute otitis media/otitis media with effusion, frequent upper respiratory airway infections and nasal obstruction.
Interventions	Adenoidectomy (n=37), control group (n=39)
Outcomes	Measured at 12 and 24 months: · Change in frequency of commons colds, purulent otitis media, serous otitis media and nasal obstruction
Notes	11% of the children were lost to follow-up (8% in the adenoidectomy group and 13% in the control group) after 24 months follow-up. 35% of the children in the adenoidectomy group and 56% of the children in the control group had insertion of tympanostomy tubes. When those children still had tubes at the end of the trial they were excluded from analysis (8% in the adenoidectomy group and 3% in the control group). No intention to treat method was used for analysis. No complications were reported by surgeons.

Risk of bias

Item	Judgement	Description
Adequate sequence generation?	Yes	Quote: 'All children (...) received a number between 0-105 randomly acquired by casting of lots. Children with even numbers came to belong to the adenoidectomy group and those with odd numbers to the control group.'
Allocation concealment?	Yes	Quote: 'All children (...) received a number between 0-105 randomly acquired by casting of lots. Children with even numbers came to belong to the adenoidectomy group and those with odd numbers to the control group.'
Blinding?	No	Quote: '(...) we were naturally aware of whether the children belonged to the A- or C-group.'
Incomplete outcome data addressed?	No	Quote: 'Twenty-nine children were omitted for reasons shown in table 1, leaving 76 children to participate in the investigation.' Comment: these children were excluded after randomisation. The most common reasons were severe nasal obstruction and administrative mishaps. It is unclear whether the 29 omitted children were otherwise clinically similar to the 76 children included in the study.
Free of selective reporting?	Yes	Comment: all outcomes are reported on (nasopharyngeal flora, improvement, unchanged or deterioration in episodes of common colds, purulent otitis media, serous otitis media, and nasal obstruction)
Free of other bias?	Unclear	Quote: '(...) data concerning frequency of illnesses were obtained retrospectively by interviews with the parents.' Comment: each group consisted of a small number of children

Table 2. Inclusion and exclusion criteria of studies included in this review.

Author	Inclusion criteria	Exclusion criteria
Black (1990)	Children with an operation indication for glue ear (secretory otitis media) based on the clinical judgement of the otolaryngologist	Children who had previous operations on their tonsils, adenoids or ears. Children with evidence of cleft palate or any sensorineural deafness. Children with conditions other than glue ear, such as gross nasal obstruction (where also adenoidectomy is indicated)
Casselbrant (2009)	Children aged 24 to 47 months, with a history of bilateral middle ear effusion (MEE) for at least 3 months, unilateral for 6 months or longer, or unilateral for 3 months after extrusion of one tympanostomy tube with the other still in place and patent, and who had completed a 10-day course of a broad spectrum antimicrobial agent within the past month	Children with previous tonsillectomy and/or adenoidectomy, previous ear surgery other than tympanocentesis or myringotomy with or without tube insertion; history of seizure disorder, diabetes mellitus, asthma requiring daily medication, or any health condition that would make entry potentially disadvantageous to the child; medical conditions with predisposition for MEE, such as cleft plate, Down's syndrome, congenital malformations of the ear; cholesteatoma or chronic mastoiditis; severe retraction pockets; acute or chronic diffuse external otitis; perforation of the tympanic membrane; intracranial or intratemporal complications of MEE; upper respiratory obstruction attributable to tonsil or adenoid enlargement or both with cor pulmonale, sleep apnoea or severe dysphagia; conductive hearing loss attributable to destructive changes in the middle ear; sensorineural hearing loss; distance from CHP that would make follow up difficult
Dempster (1993)	Otoscopic evidence of bilateral otitis media with effusion with a pure tone air conduction thresholds average over 0.5, 1 and 2 kHz of > 25 dB HL, and with an air bone gap over 0.5, 1 and 2 kHz of >25 dB, and a type B tympanogram	Children with previous adenoidectomy or aural surgery, or additional symptoms requiring surgical intervention, e.g. recurrent sore throat, or children with a cleft palate
Fiellau-Nikolajsen (1980)	Persistent or recurrent secretory otitis media and tubal dysfunction at 3-years old. Abnormal (type B, C1 or C2) tympanograms must be present at the 4 preoperative follow-up points (duration preoperative follow-up time was 7 months)	Parents refusal to operate on their children, cholesteatoma, previous operation for cleft palate
Gates (1987)	Bilateral chronic effusion diagnosed by otoscopists	Childrenwith a history of previous tonsil or adenoid surgery, placement of TT (within 2 years), or cleft palate, or children with any severe chronic illness, were excluded. Also children with advanced or irreversible structural damage of the tympanum (such as cholesteatoma, perforation, atelectasis) were excluded
Hammarén-Malmi (2005)	Children with recurrent AOM (> 3 episodes of AOM during the preceding 6 months or > 5 episodes of AOM during the preceding 12 months) or a suspicion of chronic OME as judged by examination with a pneumatic otoscope	Previous adenotonsillar surgery or placement of tympanostomy tubes. Children with asthma, cleft palate, or diabetes or children who were judged to require prompt removal of adenoids because of obstructive symptoms resulting in continues mouth breathing or sleep apnoea, were excluded

Author	Inclusion criteria	Exclusion criteria
Koivunen (2004)	3 or more episodes of acute otitis media in the last 6 months	Previously performed adenoidectomy or tympanostomy tube placement, cranial anomalies, documented immunological disorders and ongoing antimicrobial chemoprophylaxis
Mattila (2003)	3 to 5 events of acute otitis media during the last 6 months or 4 to 6 events of acute otitis media during the last year	Nothing known about exclusion criteria
Maw (1986)	1) Persistent subjective hearing difficulty 2) Pneumatic otoscopic confirmation of bilateral effusions 3) Symmetrical audiometric hearing loss, in excess of 25 dB at one or more frequencies 4) Impedance measurements not showing a peak A type of curve	1) Resolution of effusions in 1 or both ears during 3 months preoperative follow up 2) Upper airway obstruction from gross adenoidal hyperplasia 3) Parents refusal of randomisation 4) Reappraisal of audiometric data, either because the loss was asymmetrical or because superadded sensorineural loss 5) Loss to preoperative follow up 6) At operation because either ear proved to be dry at myringotomy or because the contralateral ear was suspected to be dry
Nguyen (2004)	Children who required PET insertion as their first surgical treatment of OM with the following indications: 1) Recurrent OM with more than 3 episodes during the preceding 6 months or more than 4 during the preceding 12 months 2) OM with effusion persisting for more than 3 months or producing a conducting hearing loss >30 dB with a type B tympanogram or 3) Both	1) Previous PET insertion 2) Down's syndrome 3) Craniofacial anomalies such as cleft palate 4) Immune deficiency 5) Bleeding disorders 6) Ciliary dyskinesia 7) A follow-up period of less than 6 months
Paradise (1990)	1) A history of persistent and/or recurrent otitis media 2) To have thereafter received tympanostomy-tube placement in one or both ears on one or more occasions, and to have 3) developed, after extrusion and within the year that preceded enrolment, one or more additional, well-documented episodes of either suppurative (acute) otitis media or non-suppurative (acute) otitis media	Children with overt or submucous palatal clefts
Paradise (1999)	1) At least 3 episodes of AOMduring the preceding 6months, or at least 4 episodes during the preceding 12 months including at least 1 episode during the preceding 6 months, with at least 1 of the episodes having been documented with recorded description of symptoms and tympanic membrane findings or confirmed by tympanometry or myringotomy; or 2) Middle ear effusion in one or both ears extending over at least 180 days during the preceding year and documented by at least 2 clinical observations at least 6 months apart, the most recent by a studyteam clinician and/or confirmed by tympanometry	Children with overt or submucous palatal clefts and children who have undergone previous tympanostomy tube placement
Roydhouse (1980)	Children with OME diagnosed on clinical grounds and with impedance audiometry	Children with a primary bias towards recurrent tonsillitis were not taken into this study

Author	Inclusion criteria	Exclusion criteria
Rynnel-Dagöo (1978)	Recurrent serous/purulent otitis media, frequent upper airway infections and nasal obstruction	Cases of severe nasal obstruction, previous operation performed, refused operation by parents, cases of recurring adenoids, diabetes or administrative mishaps

Table 3. Characteristics of excluded studies; reasons for exclusion.

Author	Reason for exclusion
Black (1986)	Same study as Black 1990; first 100 children were analysed. No additional data were published.
Bulman (1984)	Allocation: not concealed Participants: selection of patients not restricted by clear boundaries; not all had bilateral OME and bilateral similar deafness. Preoperative middle ear effusion only measured for 6 weeks. Outcome measures: 'Adenoidectomy only' versus 'Control' are the only two groups that can be compared; 15 versus 14 patients were allocated to those groups. Overall, results of the different intervention groups are impossible to differentiate.
Fiellau-Nikolajsen (1982)	Same study as Fiellau-Nikolajsen 1980
Gates (1988)	Same study as Gates 1987
Gates (1989)	Same study as Gates 1987; Outcome measures: results are specified in adenoid size (in our study this is not an outcome measure).
Marshak (1980)	Allocation: non-randomised controlled study
Maw (1983)	Same study as Maw 1986
Maw (1985)a	Same study as Maw 1986
Maw (1985)b	Same study as Maw 1986
Maw (1987)	Same study as Maw 1986
Maw (1988)	Same study as Maw 1986
Maw (1993)	This study was excluded because data from the adenoidectomy group could not be analysed separately from those undergoing adenotonsillectomy. The authors combined the adenoidectomy group and the adenotonsillectomy group because in the study Maw 1986 adenotonsillectomy appeared to have no additional benefit compared to adenoidectomy alone.
Maw (1994)a	Same study as Maw 1993, long-term effect
Maw (1994)b	Same study as Maw 1986
Widemar (1982)	Allocation: randomisation process (used date of birth to randomise). Same study as Widemar 1985. The first year follow-up of 44 children is presented.
Widemar (1985)	Allocation: randomisation process (used date of birth to randomise). Participants: only data from 59 children were used for analysis because 19 children were excluded after randomisation. Intervention: a total of 13 and 22 tympanostomy tubes were inserted in groups A and C respectively. They excluded the children that still had unilateral or bilateral tubes at the time of comparison.

Table 4. Characteristics of ongoing studies.

FATA

Study name	FATA: Food Allergy – Tubes – Adenoids trial
Methods	RCT
Participants	Children up to 4 years of age, with otoscopic and tympanometric signs of OME for 3 months or more, with lack of improvement after antibiotics for 3 months, with > 3 episodes of AOM in the preceding 6 months or > 5 in the preceding 12 months, bilateral conductive hearing loss of 15 dB or more and without previous adenotonsillar surgery or tympanostomy tube placement, or inhalent allergies including asthma
Interventions	1) Bilateral myringotomy with tympanostomy tubes 2) Bilateral myringotomy with tympanostomy tubes and food allergy testing and management 3) Bilateral myringotomy with tympanostomy tubes, adenoidectomy and food allergy testing and management
Outcomes	Number of otitis media episodes
Starting date	1 October 2008

NOA

Study name	NOA: Netherlands Adenoidectomy Study
Methods	RCT, follow-up of 2 years
Participants	111 children aged 1 to 6 years selected for adenoidectomy with or without myringotomy because of recurrent or chronic upper respiratory tract infections (common colds, rhinosinusitis)
Interventions	1) Adenoidectomy with or without myringotomy within 6 weeks 2) Watchful waiting strategy
Outcomes	Primary outcome measure: · Recurrent upper respiratory tract infections with or without fever Secundary outcome measures: · Acute otitis media and otitis media with effusion episodes · Exhaled nitric oxide · Nasopharyngeal flora · Health related quality of life · Cost-effectiveness
Starting date	1 April 2007

TARGET

Study name	TARGET: trial of alternative regimens in glue ear treatment - effectiveness of surgery for otitis media with effusion in 3.5 to 7-year olds using multiple developmental and economic measures combined with classical clinical measures
Methods	RCT
Participants	Children aged 3.5 to 7 years without previous ear or adenoid surgery, with B+B or B+C2 tympanograms and a bilateral average hearing threshold > 20 dB and an air-bone gap > 10 dB HL
Interventions	1) Ventilation tube insertion alone 2) Ventilation tube insertion plus adenoidectomy 3) Observation + medical management
Outcomes	Clinical measures - otoscopy, audiometry, tympanometry and questionnaire measures, (hearing and predictive factors, general health, economic impact, behavioural assessment and quality of life
Starting date	1 April 1994

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Appendix. Search strategies for electronic databases

CENTRAL	PubMed	EMBASE (Ovid)
1 MeSH descriptor Adenoidectomy explode all trees 2 MeSH descriptor Adenoids explode all trees with qulifier : SU 3 adenoidectom* or adenoitonsillectom* or adenotonsilectom* or adeno NEXT tonsillectomy* or adeno NEXT tonsillectom* 4 (1 OR 2 OR 3) 5 MeSH descriptor Adenoids explode all trees 6 adenoid* or adenotonsil* 7 (5 OR 6) 8 MeSH descriptor Surgical Procedures, Operative explode all trees 9 (surg* :ti or operat* :ti or excis* :ti or extract* :ti or remov* :ti or dissect* :ti or ablat* ;ti or coblat* :ti or laser* :ti) 10 (8 OR 9) 11 (7 AND 10) 12 (4 OR 11) 13 (nose OR nasal) NEAR (symptom* OR discharg* OR secret* OR obstruct*) 14 rhinorrhea OR rhinorrhoea 15 MeSH descriptor Nasl Obstruction explode all trees 16 airway* AND obstruct* 17 breath* and impair* 18 MeSH descriptor Otitis Media explode all trees 19 middle NEXT ear NEXT (infect* OR inflam* OR disease*) 20 otitis OR aom OR ome 21 glue AND ear 22 (13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21) 23 (12 AND 22)	1 'Adenoidectomy [Mesh] 2 'Adenoids/surgery [Mesh] 3 adenoidecotm* [tiab] OR adenotonsillectom* [tiab] OR adenotonsilectom* [tiab] OR 'adenotonsillectomy* [tiab] OR 'adenotonsilectom' [tiab] 4 1 OR 2 OR 3 5 'Adenoids'/ [Mesh] 6 adenoid* [tiab] OR adenotonsil* [tiab] 7 5 OR 6 8 'surgical procedures, operative' [Mesh] 9 'surgery' [subheading] 10 surg* [tiab OR operat* [tiab] OR excis* [tiab] OR extract* [tiab] OR remov* [tiab] OR dissect* [tiab] OR ablat* [tiab] OR coblat* [tiab] OR laser* [tiab] 11 8 OR 9 OR 10 12 7 AND 11 13 4 OR 12 14 (nose [tiab] OR nasal [tiab]) AND (symptom*[tiab] OR discharg* [tiab] OR secret* [tiab] OR obstruct* [tiab]) 15 rhinorrhea [tiab] OR rhinorrhoea [tiab] 16 'Nasal Obstruction' [Mesh 17 airway* [tiab] AND obtruct* [tiab] 18 breath* [tiab] AND impair* [tiab] 19 'Otitis Media' [Mesh] 20 middle [tiab] AND ear [tiab] AND (infect* [tiab] OR inflam* [tiab] OR disease* [tiab]) 21 otitis [tiab] OR aom [tiab] OR ome [tiab] 22 glue [tiab] AND ear [tiab] 23 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 22 24 13 AND 24	1 adenoidectomy/ 2 (adenoidectom* or adenotonsillectom* or adenotonsilectom* or 'adenotonsillectomy*' or 'adenotonsilectom*').tw. 3 1 or 2 4 *Adenoid/ 5 (adenoid* or adenotonsil*).ti. 6 4 or 5 7 (surg* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser*).ti. 8 exp *Surgery/ 9 8 or 7 10 6 and 9 11 3 or 10 12 nose obstruction/ or rhinorrhea/ 13 *airway obstruction/ or *upper respiratory tract obstruction/ 14 ((nose or nasal) and (symptom* or discharge* or obstruct* or secret*)).tw. 15 rhinorrhea or rhinorrhoea).tw. 16 (airway* and obstruct*).tw. 17 breath* and impair*).tw. 18 exp Middle Ear Disease/ 19 (middle and ear and (infect* or inflamm* or disease*)).tw. 20 (otitis or aom or raom or ome).tw. 21 (glue and ear).tw. 22 21 or 17 or 12 or 20 or 15 or 14 or 18 or 13 or 16 or 19 23 22 and 11
CINAHL (EBSCO)	**Web of Science**	**BIOSIS Previews/CAB Abstracts (Ovid)**
S1 (MH 'Adenoidectomy') S2 (MH 'Adenoids/SU') S3 adenoidectom* or adenotonsillectom* or adenotonsilectom* or 'adenotonsillectomy*' or adeno tonsilectomy*' S4 (MM 'Adenoids') S5 TI adenoid* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser* S7 (MH 'Surgery, Operative') S8 S6 or S7 S9 S4 or S5 S10 S8 and S9 S11 S1 or S2 or S3 or S10	1 TS=(adenoidectom* or adenotonsillectom* or adenotonsilectom* or 'adeno tonsillectomy*' or 'adeno tonsilectom*') 2 TI=(adenoid* or adenotonsil*) 3 TI=(surg* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser*) 4 2 AND 3 5 1 or 4 6 TS=((nose or nasal) and (symptom* or discharg* or obstruct* or secret*)) 7 TS=(rhinorrhea or rhinorrhoea) 8 TS=(airway* and obstruct*) 9 TS=(breath* and impair*) 10 TS=(middle and ear and (infect* or inflamm* or disease*)) 11 TS=(otitis or aom or raom or ome) 12 TS=(glue and ear) 13 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 14 5 AND 13	1 (adenoidectom* or adenotonsillectom* or adenotonsilectom* or 'adeno tonsillectomy*' or adeno tonsilectom*').tw. 2 (adenoid* or adentonsil*).ti. 3 (surg* or operat* or excis* or extract* or remov* or dissect* or ablat* or coblat* or laser*).ti. 4 ((nose or nasal) and (symptom* or discharg* or obstruct* or secret*)).tw 5 (rhinorrhea or rhinorrhoea).tw. 6 (airway* and obstruct*).tw. 7 (breath* and impair*).tw. 8 (middle and ear and (infect* or inflamm* or disease*)).tw. 9 (otitis or aom or raom or ome).tw. 10 (glue and ear).tw. 11 3 and 2 12 11 or 1 13 8 or 6 or 4 or 7 or 10 or 9 or 5 14 13 and 12

Chapter 5

Alterations in the nasopharyngeal flora after adenoidectomy in children: a systematic review

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Abstract

Objective: To review the current literature on alterations in the nasopharyngeal bacterial flora in relation to adenoidectomy in children with recurrent upper respiratory tract infections (rURTIs).

Data sources: A systematic literature search of PubMed (from 1966 on) and EMBASE (from 1974 on) to May 3 2008.

Methods: A study was selected if it included children aged less than 18 years who had undergone adenoidectomy or adenotonsillectomy, and in whom nasopharyngeal bacterial flora was studied before and after or only after surgery.
Data from eight studies were included in this review. We extracted from each study which potentially pathogenic and nonpathogenic nasopharyngeal flora were cultured before and after surgery.

Results: *Streptococcus pneumoniae* and *Haemophilus influenzae* were most often detected in the nasopharynx of children with rURTI. Carriage of these bacteria decreased after adenoidectomy in the majority of studies. In contrast, carriage of bacteria belonging to the nonpathogenic nasopharyngeal flora increased after surgery.

Conclusion: Adenoidectomy seems to have a beneficial effect on the nasopharyngeal bacterial flora. Because the overall quality of the available evidence is low, it is important that controlled studies are initiated into the short- and long-term effect of adenoidectomy on the nasopharyngeal bacterial flora and its relationship with the recurrence of URTIs in children.

Introduction

Upper respiratory tract infections (URTIs) including middle ear infections are the most common infectious diseases in children. They are generally caused by commensal bacteria of the nasopharyngeal flora.[1-3] Although the mechanisms that cause these bacteria to become invasive are unknown, there is some evidence that interference between the so called potential pathogenic flora (*Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis*) and nonpathogenic flora (alpha-hemolytic streptococci, and *Neisseria* and *Corynebacterium* species)[1,4] plays a role.

Adenoidectomy (i.e., surgical removal of the adenoid) may influence the composition/balance of the nasopharyngeal flora and is one of the most frequently performed procedures in children with recurrent URTIs.[5] This procedure may decrease carriage of potential pathogenic bacteria in favor of nonpathogens in the nasopharynx. As such, recurrence of URTIs should decrease.

We systematically reviewed the current literature on alterations in the nasopharyngeal bacterial flora in relation to adenoidectomy in children.

Methods

Literature Search

A systematic search of the literature was conducted to identify studies on the effect of adenoidectomy on the nasopharyngeal bacterial flora published up to May 3, 2008. The electronic databases PubMed and EMBASE were searched by using the syntax listed in the appendix. Reference lists of identified articles were screened for additional relevant studies.

Study Selection

All titles and abstracts selected were reviewed by two of the coauthors (J.W.M.A., M.T.A.v.d.A.), who further selected studies using the following inclusion criteria: 1) children aged less than 18 years were addressed, 2) children who had undergone adenoidectomy or adenotonsillectomy were included, 3) nasopharyngeal bacterial flora was studied before and after or only after surgery, 4) and the study contained original data. All studies not fulfilling these criteria were excluded from the review. No studies were excluded on the basis of the methodological quality.

Methodological Quality of Studies

The methodological quality of included studies was assessed with the checklist designed by Downs and Black[6] for randomized and nonrandomized studies. It assesses the internal and external validity and contains 27 questions, for example on randomization, blinding, confounding, loss to follow-up, representativeness of the study population, and reporting bias. As such an overall score (maximum of 30 points) for the study quality is given.

Data Extraction

The following data were extracted: study type, inclusion period, number of patients, group characteristics, age at inclusion, methods of bacteriological sampling, time of outcome assessment, the use of antibiotics after surgery, and the potentially pathogenic and nonpathogenic nasopharyngeal bacteria assessed. *Streptococcus pneumoniae, Haemophilus*

influenzae, Staphylococcus aureus, Moraxella catarrhalis and beta-hemolytic streptococci group A are considered to be potential pathogens of the nasopharynx. All other hemolytic and nonhemolytic streptococci as well as *Neisseria* species and *Haemophilus parainfluenzae* are defined as nonpathogenic nasopharyngeal bacteria.
The outcome measure was the percentage of children with a positive culture for potentially pathogenic and nonpathogenic nasopharyngeal bacteria before and after surgery. Because of heterogeneity of the studies included, no attempts were made to perform further statistical analysis on the data extracted.

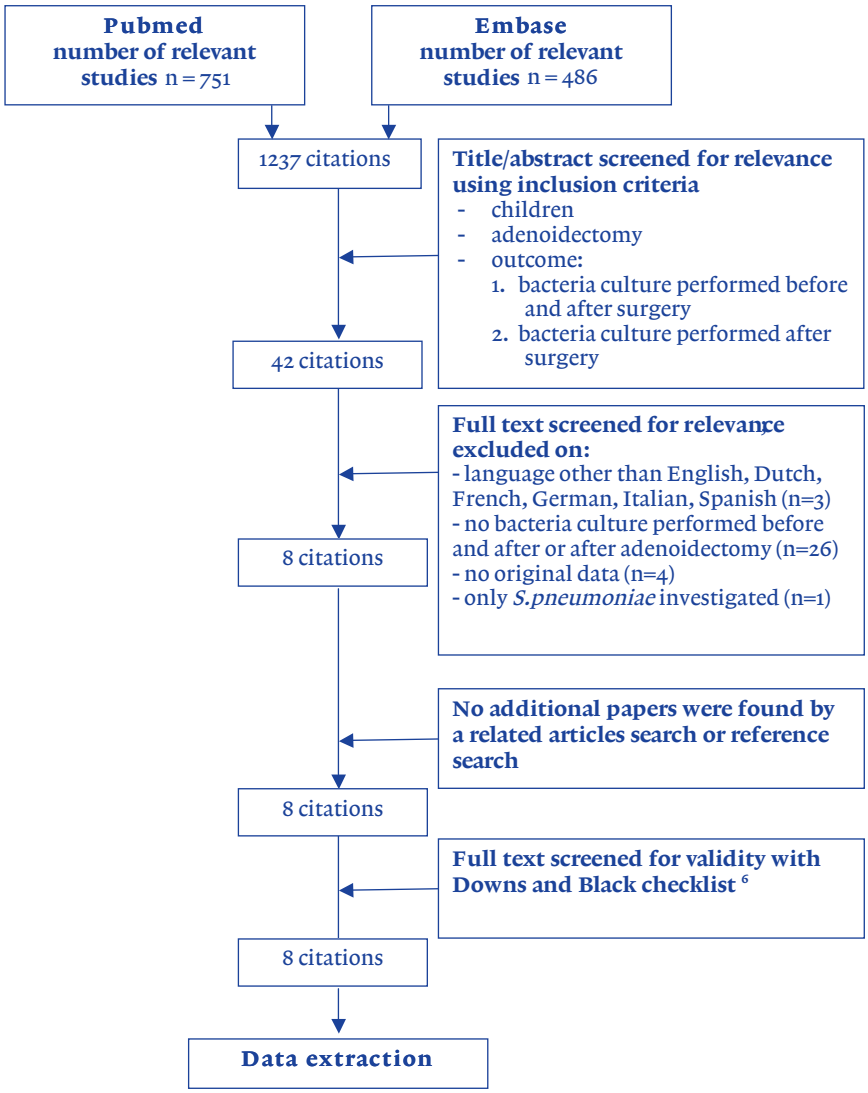

Figure 1. Study selection

Table 1. Characteristics of studies inlcuded in this review.

First author	Study design	N	Inclusion criteria	Age at inclusion	Treatment	Methods	Time of outcome assessment before and after surgery	Use of AB after surgery	Val-idity score
Veltri 1972 USA	cohort	34	acute or recurrent tonsillitis, OM ±tonsillitis, peritonsillar abcess, retro-pharyngeal abcess	2 – 17 yrs	T&A	tonsil and adenoid surface swab	Before: surgery day After: 3 – 5 wks 3 mo 9-12 mo	Yes	11
Palva 1986 Finland	cohort	78	chronic OME	6mo – 15 yrs	A	Pernasal swab of naso-pharynx	Before: 7-8 days and peroperative After: 1 mo (n=44)	NR	13
Talaat 1989 Egypt	case control	70	-chronic hypertrophy and infection of adenoid -healthy controls	3 – 10 yrs	A (n=50) Control (n=20)	pernasal swab of adenoid surface	Before: unknown After: 1 mo (n=40)	No	9
Tomonaga 1989 Japan	cohort	38	adenoid hypertrophy ± OME	2 – 12 yrs	A	pernasal swab	Before: unknown After: unknown	NR	7
Manolis 1994 Greece	RCT	20	Chronic hypertrophy and infection of adenoid and tonsils	2 – 10 yrs	A	adenoid surface swab	Before: 1 day After: 10 and 30 days	NR	16
Lacosta 1995 Spain	cohort	90	adenoid and/or tonsil related pathology	until 14 yrs	A and T&A	pernasal swab of naso-pharynx	Before: surgery day After: 3 and 6 mo (n = 44)	NR	16
Garcia 1997 Spain	cohort	85	radiological hypertrophy of adenoid	2 – 6 yrs	A (n=40) T&A (n=45)	adenoid surface swab	Before: 1 day After: 10 and 30 days	NR	14
Dhooge 1999 Belgium	case control	70	-otitis prone children free of rURTI at inclusion -controls: surgery for other reasons	11 – 47 mo	A + TT (n=35) Non-ENT (n=35)	two swabs of naso-pharynx	Before: surgery day After: 1 mo	Yes	17

Abbreviations: RCT= Randomized Controlled Trial; OM = otitis media; OME = otitis media with effusion; rURTI = recurrent upper respiratory tract infections; wks = weeks; mo = month(s); yrs = years; A = adenoidectomy; T&A = adenotonsillectomy; TT = tympanostomy tube placement; Non-ENT = no ear nose throat surgery; AB = antibiotics; NR = Not Reported

Results

Study Selection

The literature search yielded 1237 citations. Screening of titles and abstracts using the inclusion criteria identified 42 studies, of which 34 were excluded after reading the full text. No additional relevant papers were identified from the references or a related article search. In eight studies the nasopharyngeal flora was studied before and after surgery (Fig 1).

Methodological Quality

In general, the methodological quality (design and report) of the studies was poor (Table 1). The only randomized controlled trial did not provide an adequate description of the allocation concealment.[7] Data of the adenoidectomy group only were analyzed. Two studies were case-control studies;[2,8] the remaining five citations were prospective observational studies.[4,9-12]

Characteristics of Populations Studied

The children population in the studies included can be distinguished into three subgroups. The first subgroup concerns children with sinonasal symptoms, that is, those with a chronically hypertrophied and infected adenoid.[4,7,8] The second concerns children with middle ear disease, i.e., otitis prone[2] or those with otitis media with effusion.[10,11] The third subgroup includes children with diverse symptoms related to the adenoid and/or tonsils.[9,10] Besides adenoidectomy[9-11] some studies also included children who underwent the placement of tympanostomy tubes[2] and tonsillectomy.[4,7,9,12]

Nasopharyngeal Carriage

Bacterial carriage varied across the different subgroups (Tables 2-5): *Streptococcus pneumoniae* and *Staphylococcus aureus* were most common in children with sinonasal symptoms, whereas *Haemophilus influenzae* was most common in children with diverse symptoms related to the adenoid and/or tonsils. *Neisseria species* and alpha-hemolytic streptococci appear to make up the greatest part of the nonpathogenic flora of the nasopharynx.

In most studies[2,4,7,8,11,12] carriage of potential pathogens decreased following adenoidectomy. Within approximately 1 month (Tables 2 and 3), the carriage rate of *Streptococcus pneumoniae* and *Haemophilus influenzae* decreased in six of seven studies.[2,4,7,8,11,12] Nasopharyngeal colonization of *Staphylococcus aureus* decreased in four of six studies.[4,7,8,12] A pronounced decrease of group A beta-hemolytic streptococci carriage was observed in all studies.[4,7,8,10-12] Carriage of *Moraxella catarrhalis*, however, barely changed following surgery. In contrast, the prevalence of nonpathogenic nasopharyngeal flora increased after adenoidectomy in all studies[2,4,7-10,12] but one.[11]

Table 2. Percentage of potential pathogenic bacteria detected per author: before surgery and 10 days or 1 month after surgery.

	Veltri		Palva		Talaat		Tomonaga		Manolis		Garcia		Dhooge	
	Pre (n=34)	Post (n=34)	Pre (n=78)	Post (n=44)	Pre (n=50)	Post (n=40)	Pre (n=38)	Post (n=38)	Pre (n=20)	Post (n=20)	Pre (n=85)	Post (n=85)	Pre (n=35)	Post (n=35)
Streptococcus pneumoniae	41	41[b]	12	20[b]	38	8[b]	21	16[c]	55	20[a] 10[b]	54	20[a] 7[b]	23	11[b]
Haemophilus influenzae	50	24[b]	28	36[b]	18	5[b]	45	34[c]	45	25[a] 30[b]	42	27[a] 31[b]	74	49[b]
Moraxella catarrhalis			27	30[b]	12	23[b]	5	8[c]	45	45[a] 25[b]	46	45[a] 26[b]	54	37[b]
Staphylococcus aureus	41	14[b]	19	20[b]	38	18[b]	16	16[c]	55	35[a] 40[b]	55	33[a] 39[b]		
B-hemolytic streptococcus group A	24	0[b]	10	7[b]	10	0[b]	5	0[c]	35	10[a] 15[b]	33	11[a] 17[b]		

All preoperative swabs are performed within 1 week before surgery
a = 10 days postoperatively; b = 1 month postoperatively; c = time of outcome assessment unknown, underlined numbers represent statistically significant results at p<0.05, significance was not reported in Veltri, Palva, Talaat or Tamonaga

Table 3. Percentage of nonpathogenic bacteria detected per author: before surgery and 10 days or 1 month after surgery.

	Talaat		Tomonaga		Garcia		Dhooge	
	Pre (n=50)	Post (n=40)	Pre (n=38)	Post (n=38)	Pre (n=85)	Post (n=85)	Pre (n=35)	Post (n=35)
Alfa streptococcus			61	61[c]				
Gamma Streptococcus			16	21[c]				
Alfa hemolytic streptococcus	38	60[b]			37	22[a] 53[b]		
Streptococcus sanguis II					42	28[a] 48[b]		
Non-hemolytic streptococcus	14	23[b]						
Pepto-streptococcus					29	52[a] 33[b]		
Streptococcus salivarius					27	39[a] 34[b]		
Diphteroid bacilli	38	60[b]						
***Neisseria* species**	36	40[b]	71	53[c]	24	51[a] 54[b]		
Haemophilus parainfluenzae			16	8[c]				
Normal flora							71	91[b]
***Veillonella* species (parasite)**					31	40[a] 51[b]		

All preoperative swabs are performed within 1 week before surgery
a = 10 days postoperatively; b = 1 month postoperatively; c = time of outcome assessment unknown, underlined numbers represent statistically significant results at p<0.05, significance was not reported in Talaat or Tamonaga

Semiquantative microbiology results (i.e., density of bacterial growth) were reported in three studies.[4,7,8] Overall, in these three studies the density of bacterial growth marginally declined after adenoidectomy. True quantitative microbiology results were not reported. In the majority of studies the postoperative swab was taken after a short period, varying from 10 days to 1 month. Only Veltri et al[12] and Lacosta et al[9] reported long-term results at three months and longer after adenoidectomy (Tables 4 and 5). Veltri et al found a decrease and Lacosta et al an increase of the carriage of potential nasopharyngeal pathogens after three months. However, at one year[12] and six to nine months[9] after surgery, respectively, both authors observed a (further) decrease in the carriage rate of potential pathogens of the nasopharynx.

Table 4. Percentage of potential pathogenic bacteria detected per author: before surgery and 3 months or more after surgery.

	Veltri		Tomonaga		Lacosta	
	Pre (n=34)	Post (n=34)	Pre (n=38)	Post (n=38)	Pre (n=90)	Post (n=90)
Streptococcus pneumoniae	41	15[c] 26[d]	21	16[e]	10	18[c] 5[d]
Haemophilus influenzae	50	33[c] 16[d]	45	34[e]	10	34[c] 18[d]
Moraxella catarrhalis			5	8[e]	4	3[c] 0[d]
Staphyloccus aureus	41	11[c] 5[d]	16	16[e]	4	8[c] 0[d]
B-hemolytic streptococcus group A	24	7[c] 5[d]	5	0[e]	2	2[c] 5[d]

All preoperative swabs are performed within 1 week before surgery, c = 3 months postoperatively; d = 3 – 12 months postoperatively; e = time of outcome assessment unknown
Significance was not reported in Veltri and Tomonaga; the total percentage of bacteria 3 months and >3 months postoperatively was significantly higher than preoperative values in Lacosta.

Table 5. Percentage of nonpathogenic bacteria detected per author: before surgery and 3 months or more after surgery.

	Tomonaga		Lacosta	
	Pre (n=38)	Post (n=38)	Pre (n=90)	Post (n=90)
Alfa streptococcus	61	61[e]		
Gamma Streptococcus	16	21[e]		
***Neisseria* species**	71	53[e]		
Haemophilus parainfluenzae	16	8[e]		
Normal flora			12	34[c] 72[d]

All preoperative swabs are performed within 1 week before surgery, c = 3 months postoperatively; d = 3 – 12 months postoperatively; e = time of outcome assessment unknown
Significance was not reported in Tomonaga; the total percentage of bacteria 3 months and >3 months postoperatively was significantly higher than preoperative values in Lacosta.

Because of the heterogeneity of the study design, population characteristics, intervention, and time of outcome assessment, it was not possible to perform a meta-analysis.

Discussion

Carriage of potential pathogens in the nasopharynx appears to decrease after adenoidectomy, whereas carriage of nonpathogens increases. It is not clear whether reestablishment of normal flora protects children from rURTI because none of the studies on nasopharyngeal flora before and after adenoidectomy have related their findings to the frequency of URTIs. To our knowledge, this is the first systematic review on the effect of adenoidectomy on the nasopharyngeal bacterial flora. Some possible limitations should be discussed.

First, the methodological quality of the design and report of most of the included studies was poor. In three studies it cannot be determined reliably whether the effect of adenoidectomy on the nasopharyngeal flora was caused by the surgery alone. Palva et al[10] administered antibiotics to all patients before surgery. Tomonaga et al[11] poorly described the methods of microflora assessment after adenoidectomy. Veltri et al[12] took both oropharyngeal and nasopharyngeal swabs and reported numbers of cultured bacteria under the single heading 'oropharyngeal flora.'

Second, other factors may have biased the effect of adenoidectomy on the colonization of bacteria in the nasopharynx, such as age and sex, number of siblings, bottle versus breast-feeding, day care attendance, parental smoking, season, and use of antibiotics after surgery. Two of the studies[2,9] took these factors into account and only one, Lacosta et al,[9] adjusted the outcome data for age, sex, and season. The use of antibiotics after surgery was specifically reported in only three publications. Veltri et al[12] reported that one patient received antibiotics for follicular tonsillitis. Dhooge et al[2] reported that the culture was postponed in patients who had taken antibiotics or were ill in the previous three weeks. Talaat et al[8] explicitly reported that patients were excluded from the study if they had received antibiotics one month before or after surgery. None, however, adjusted outcome data for the use of antibiotics.

Third, the postoperative swabs were taken after a relatively short period, varying from 10 days to three months in almost all included studies.[2,4,7,8,10,11] Therefore, it is impossible to draw conclusions on the long-term effect of adenoidectomy on the nasopharyngeal flora, and the long-term clinical beneficial effect of adenoidectomy remains to be proven.

Fourth, vaccination with the conjugate pneumococcal vaccine was implemented after publication of the studies included in this review. Therefore, current carriage rates of *Streptococcus pneumoniae* may differ from those reported in this review.

Conclusion

On the basis of current literature, adenoidectomy seems to have a beneficial effect on the nasopharyngeal bacterial flora. Carriage of potential pathogens decreases, specifically *Streptococcus pneumoniae* and *Haemophilus influenzae*, and carriage of normal nonpathogenic flora in the nasopharynx is reestablished. Overall, the quality of the reported studies is low, and heterogeneity prevented us from performing a meta-analysis. We therefore believe that it is crucial that controlled studies are initiated to look into the short- and long-term effect of adenoidectomy on the nasopharyngeal bacterial flora and its relationship with recurrence of URTIs in children.

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Appendix.

Search strategies for electronic databases

The databases Pubmed and Embase were searched for relevant literature by using the keywords listed below. The search was performed on May 3, 2008.

child*[Title/Abstract] OR paediatr*[Title/Abstract] OR pediatr*[Title/Abstract] OR infant*[Title/Abstract] OR toddler*[Title/Abstract] OR 'pre school'[Title/Abstract] OR preschool[Title/Abstract] OR adolescent*[Title/Ab- stract] OR Baby [Title/Abstract] OR babies[Title/Abstract] OR Kid[Title/Abstract] OR kids[Title/Abstract] OR Young- ster[Title/Abstract] OR Youngsters[Title/Abstract] OR chil- dren[Title/Abstract] OR child[Title/Abstract] OR pediatrics [Title/Abstract] OR paediatrics[Title/Abstract] OR infant [Title/Abstract] OR infants[Title/Abstract] OR child- hood[Title/Abstract] OR toddler[Title/Abstract] OR toddlers- [Title/Abstract] OR Adolescent[Title/Abstract] OR adolescents- [Title/Abstract] OR Pediatrics[MeSH] OR Child[MeSH] OR Infant[MeSH] OR Adolescent[MeSH] OR Child, pre-school[MeSH]
AND
adenoidectomy[Title/Abstract] OR adenotomy[Title/Ab- stract] OR adenoid removal[Title/Abstract] OR adenoid resection[Title/Abstract] OR adenoid surgery[Title/Ab- stract] OR adenoid excision[Title/Abstract] OR adenoid op- erations[Title/Abstract] OR adenotonsillectomy[Title/Ab- stract] OR ATE[Title/Abstract] OR adenoidectomies[Title/Abstract] OR adenoid[Title/abstract] OR adenoids[Title/ abstract] OR adenoidectomy[MeSH] OR adenoids[MeSH]
AND
Nasopharynx[title/abstract] OR nasopharyn*[title/abstract] OR nasopharyngeal bacterial flora[Title/Abstract] OR naso- pharyngeal bacteria[Title/Abstract] OR nasopharyngeal bacteriology[Title/Abstract] OR nasopharyngeal pathogen[Title/ Abstract] OR nasopharyngeal pathogens[Title/Abstract] OR nasopharyngeal microorganisms[Title/Abstract] OR nasopharyngeal microbial flora[Title/Abstract] OR nasopharyngeal microflora[Title/Abstract] OR nasopharyngeal flora[Title/Ab- stract] OR nasopharyngeal colonization[Title/Abstract] OR na- sopharyngeal colonisation[Title/Abstract] OR nasopharyngeal commensal[Title/Abstract] OR adenoid bacterial flora[Title/ Abstract] OR adenoid bacteriology[Title/Abstract] OR adenoid flora[Title/Abstract] OR 'streptococci pneumoniae' [Ti- tle/Abstract] OR 'streptococcus pneumoniae' [Title/Abstract] OR 'haemophilus influenzae' [Title/Abstract] OR 'hemophi- lus influenzae'[Title/Abstract] OR 'moraxella catarrhalis' [Title/Abstract] OR 'group a beta haemolytic streptococci' [Title/Abstract] OR 'group a beta hemolytic streptococci'[Title/Abstract] OR 'group a beta hemolytic streptococcus'[Title/ Abstract] OR 'group b beta hemolytic streptococcal'[Ti- tle/Abstract] OR 'group b beta hemolytic streptococci' [Title/Abstract] OR 'group b beta hemolytic streptococcus' [Title/Abstract] OR 'group b beta haemolytic streptococ- cus'[Title/Abstract] OR 'group c beta hemolytic strepto- coccus'[Title/Abstract] OR 'group c beta hemolytic streptococci'[Title/Abstract] OR 'group c beta hemolytic streptococcal'[Title/Abstract] OR 'group g beta he- molytic streptococcal'[Title/Abstract] OR 'group g beta he- molytic streptococci'[Title/Abstract] OR 'group g beta hemo- lytic streptococcus'[Title/Abstract] OR 'staphylococci aureus' [Title/Abstract] OR 'staphylococcus aureus' [Title/Abstract] OR diphteroid bacteria[Title/Abstract] OR neisseria species- [Title/Abstract] OR neisseria[Title/Abstract] OR 'streptococci viridans'[Title/Abstract] OR

'streptococcus viridans'[Title/ Abstract] OR coagulase negative cocci[Title/Abstract] OR coagulase negative[Title/Abstract] OR non hemolytic streptoc- occi[Title/Abstract] OR non hemolytic streptococcus[Title/Ab- stract] OR moraxella species[Title/Abstract] OR klebsiella pneumoniae[Title/Abstract] OR 'e coli'[Title/Abstract] OR escherichia coli[Title/Abstract] OR fusobacterium nucleatum- [Title/Abstract] OR bacteroides capillosus[Title/Abstract] OR bacteroides oralis[Title/Abstract] OR bacteroides fragilis[Title/ Abstract] OR bacteroides melaninogenicus[Title/Abstract] OR peptococcus[Title/Abstract] OR actinomyces[Title/ Abstract] OR clostridium[Title/Abstract] OR Bordetella Pertussis[title/ abstract] OR Nasopharynx[MeSH] OR Bacteria[MeSH] OR Microbiology[MeSH] OR microbiology[Subheading] OR Streptococcus pneumoniae[MeSH] OR Streptococcus mil- leri Group[MeSH] OR Staphylococcus aureus[MeSH] OR Haemophilus influenzae[MeSH] OR 'Moraxella (Branha- mella) catarrhalis'[MeSH] OR neisseria[MeSH] OR bacte- roides[MeSH] OR bacteroides fragilis[MeSH] OR viridans streptococci[MeSH] OR escherichia coli[MeSH] xOR kleb- siella pneumoniae[MeSH] OR clostridium[MeSH].

Chapter 6

Effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections: an open randomized controlled trial

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Abstract

Objective: To assess the effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections.

Design: Open randomised controlled trial.

Setting: 11 general hospitals and two academic centres.

Participants: 111 children aged 1-6 with recurrent upper respiratory tract infections selected for adenoidectomy.

Intervention: A strategy of immediate adenoidectomy with or without myringotomy or a strategy of initial watchful waiting.

Main outcome measure: Primary outcome measure: number of upper respiratory tract infections per person year calculated from data obtained during the total follow-up (maximum 24 months).
Secondary outcome measures: days with upper respiratory tract infection per person year, middle ear complaints with fever in episodes and days, days with fever, prevalence of upper respiratory tract infections, and health related quality of life.

Results: During the median follow-up of 24 months, there were 7.91 episodes of upper respiratory tract infections per person year in the adenoidectomy group and 7.84 in the watchful waiting group (difference in incidence rate 0.07, 95% confidence interval −0.70 to 0.85). No relevant differences were found for days of upper respiratory tract infections and middle ear complaints with fever in episodes and days, nor for health related quality of life. The prevalence of upper respiratory tract infections decreased over time in both groups. Children in the adenoidectomy group had significantly more days with fever than the children in the watchful waiting group. Two children had complications related to surgery.

Conclusion: In children selected for adenoidectomy for recurrent upper respiratory tract infections, a strategy of immediate surgery confers no clinical benefits over a strategy of initial watchful waiting.

Introduction

An acute upper respiratory tract infection is the most common diagnosis in children in primary care: every year the diagnosis is made in one in every two children aged 0-4 and in one in 10 of those aged 5-9.[1] The true incidence of the condition in the community is much higher as usually parents do not consult their doctor when their child develops an upper respiratory tract infection. Upper respiratory tract infections not only affect children's health but also account for a large proportion of annual healthcare expenditure and high indirect costs for the family and society.[2-4]

An estimated 20% of children experience recurrent upper respiratory tract infections, and many of these children are referred to the ear, nose, and throat surgeon for surgery.[5-8]

Adenoidectomy is one of the most commonly performed surgical procedures in children in western countries. In 2009 in the Netherlands 15 179 children (16.3 per 1000) aged 0-4 and 5573 children (5.5 per 1000) aged 5-9 underwent adenoidectomy.[9,10] In 60% of these children, recurrent upper respiratory tract infections were the indication for surgery.[11] In 2006 in the United States 129 540 children (1.76 per 1000) up to the age of 18 underwent adenoidectomy. In 12% of these children the operation was performed because of chronic infections.[12] In both countries the figures have remained stable over the past decade.[12,13]

Remarkably, the adenoidectomy rate is more than three times higher in the Netherlands than in the US, and the proportion of children operated on for infections varies fivefold across these two countries, suggesting that there is no international consensus as to which children benefit from the operation.

Evidence for the effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections is indeed scarce and (inter)nationally accepted guidelines are lacking. In our recent Cochrane review we showed that so far only two randomised controlled trials of adenoidectomy in children included upper respiratory tract infections as an outcome measure.[14] One study was methodologically weak,[15] and the other was performed in children with recurrent acute otitis media rather than upper respiratory tract infections.[16] In this open multicentre randomised controlled trial we studied the effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections.

Methods

Patients

We performed an open multicentre randomised controlled trial between April 2007 and October 2010. Ear, nose, and throat surgeons in 11 general hospitals and two academic centres were asked to complete a questionnaire on their patients aged 1-6 whom they selected for adenoidectomy with or without myringotomy. They were asked to list the indication for the operation and any previous ear, nose, and throat surgery. Parents who had expressed interest in the trial were contacted by a member of our study team. Children were eligible to participate in the trial if they were selected for adenoidectomy for recurrent upper respiratory tract infections. The parents were given detailed information about the trial, exclusion criteria were checked, and a standard demographic and disease specific questionnaire was completed. We excluded children who had previously undergone adenoidectomy or adenotonsillectomy and those with tympanostomy tubes (grommets) or who had an indication for insertion of tympanostomy tubes. We also excluded children with Down's syndrome and craniofacial malformation.

Randomisation

Children whose parents gave informed consent were randomly assigned to one of two strategies: adenoidectomy with or without myringotomy within six weeks or initial watchful waiting. For this purpose we used a computerised minimisation strategy—that is, a method of ensuring balance between prognostic factors in small samples[17]; factors that were taken into account were age (<2 and ≥2) and hospital. Treatment allocation was concealed until formal informed consent was obtained and the child was included in the trial.

Baseline measurements

When children entered the study, the study doctor filled in a demographic and disease specific questionnaire including information on the number of upper respiratory tract infections in the year before trial entry, previous ear, nose, and throat operations, and risk factors for upper respiratory tract infections. Parents filled in two generic and three disease specific questionnaires on health related quality of life: the child health questionnaire,[18,19] the RAND general health rating index for children,[20,21] the sinonasal symptoms questionnaire,[22] the OSA-18 quality of life questionnaire,[23] and the otitis media-6 questionnaire.[24] All children underwent an ear, nose, and throat examination including fibreoptic endoscopy of the nasopharynx. Adenoid size was graded as obstructing the choanae for 0-25%, 26-50%, 51-75%, or 76-100%. A blood sample was taken for the Phadiatop test, an allergen specific IgE test to a panel of common food and aeroallergens in children, with the result classified as positive or negative. Finally, data on nasopharyngeal flora, exhaled nitric oxide, and costs were collected at baseline and during follow-up. These results will be reported separately.

Follow-up

During the two year follow-up parents kept a diary, including specific symptoms of upper respiratory tract infections: nasal stuffiness, mouth breathing, nasal discharge, sore throat, cough, and fever. They also noted middle ear complaints and absence from day care or school because of upper respiratory tract infections. They measured their child's temperature every day with a validated tympanic membrane thermometer. To avoid information bias, we had an electronic device built in, which stored date and first temperature measurement of each day.[25] The study doctor collected the diary and thermometer data during the follow-up visits at 3, 6, 12, 18, and 24 months and examined the child's ears, nose, and throat. At those visits parents also filled in questionnaires on health related quality of life.

Parents, general practitioners, and ear, nose, and throat surgeons of the participating children were encouraged to manage upper respiratory tract infections during follow-up according to their regular practice.

Primary and secondary outcomes

The primary outcome measure was the number of upper respiratory tract infections per person year calculated from data obtained during follow-up (maximum 24 months). The definition of upper respiratory tract infection was two or more of the following: fever (a temperature of 38°C or higher as measured by a tympanic thermometer), diary scored symptoms of nasal stuffiness or mouth breathing, nasal discharge, sore throat, or cough. An episode ended when the child was free from symptoms for at least a day. A new episode was recorded after at least seven days without symptoms or fever.

Secondary outcome measures were days with upper respiratory tract infection per person

year, incidences of mild and severe upper respiratory tract infection, and middle ear complaints with fever in episodes and days, days with fever, days of absence from day care or school because of upper respiratory tract infection, prevalence of upper respiratory tract infections, and health related quality of life. Mild upper respiratory tract infection was defined as an infection without fever and resolving within 10 days. Severe upper respiratory tract infection was defined as an infection persisting for more than 10 days or an infection accompanied by fever. Middle ear complaints were defined as acute otorrhoea, earache, or pulling the ear accompanied by fever. To measure the burden of upper respiratory tract infections during follow-up we calculated the prevalence of upper respiratory tract infections per week. Generic health related quality of life was assessed with the child health questionnaire[18,19] and the RAND general health rating index for children[20,21] and disease specific health related quality of life with the sinonasal symptoms questionnaire,[22] the OSA-18 quality of life questionnaire,[23] and the otitis media-6 questionnaire.[24]

Statistical analysis

Our sample size calculation was based on a clinically relevant reduction of upper respiratory tract infections of 33%. Assuming a mean baseline incidence of six (SD three) upper respiratory tract infections each year, and taking α=0.05 and a power of 0.90, we calculated that we would need 49 children in each group. To allow for 10% loss to follow-up we aimed to include 110 children.

The effects of adenoidectomy on upper respiratory tract infection episodes and days were calculated as differences in incidence rates and incidence rate ratios per person year with 95% confidence intervals. Scores on health related quality of life instruments were linearly transformed into 0-100 scales (100 being the best possible score) and presented per subscale. We used Student's *t* tests or Mann-Whitney U tests to evaluate differences between the two groups. Poisson regression analyses with a robust covariance matrix estimator were used to adjust for potential confounding (observed baseline differences in prognostic factors, such as sex, breast feeding for more than three months, family history of upper respiratory tract infections, and passive smoking). The 95% confidence intervals of the adjusted rate differences and ratios were addressed in R by means of bootstrapping, for which we replicated the trial 10 000 times using random replacement samples.

Potential modification of the effect of adenoidectomy was evaluated with Poisson analyses including interaction terms for age (<2 and ≥2), adenoid size (≤75% v >75% obstruction of the choanae), and Phadiatop (positive v negative). Subgroups were further analysed only in case of significant interaction effects.

In addition to the intention to treat analysis, we also performed two sensitivity analyses: a per protocol analysis in which we excluded the children in the watchful waiting group who went on to have surgery, and an as treated analysis in which we added the children in the watchful waiting group who underwent surgery to the adenoidectomy group.

To study the external validity, we compared demographic and disease specific characteristics of the included children with those who were eligible to participate but whose parents did not give informed consent. We used Pearson's χ^2 tests to compare these characteristics.

All analyses were performed according to the intention to treat principle with SPSS version 17 (SPSS, Chicago, IL), Rothman's Episheet (11 June 2008), and R version 2.13.0 (13 April 2011).

Results

Patients

Between April 2007 and April 2009, 373 children aged 1-6 selected for adenoidectomy for recurrent upper respiratory tract infections were referred to our trial centre. Of these, 262 (70%) were ineligible or excluded for various reasons (fig 1), and 111 were randomly assigned to one of two strategies: 54 children to adenoidectomy with or without myringotomy within six weeks and 57 children to initial watchful waiting.

Table 1 shows the baseline characteristics. The mean age was 36 and 38 months and the median number of upper respiratory tract infection episodes in the year before trial entry was 10 in the adenoidectomy group and nine in the watchful waiting group. Median follow-up was 24 months in both groups.

Table 1. Baseline characteristics of 111 children according to treatment allocation.

	Adenoidectomy N=54 (%)	Watchful waiting N=57 (%)
Patient characteristics		
Age (SD), mo	36 (19)	38 (18)
Male sex	37 (69)	29 (51)
Breastfeeding ≥ 3 months	24 (44)	32 (56)
Positive Phadiatop test[a]	12 (24)	16 (30)
Positive family history for recurrent URTIs	31 (57)	41 (72)
Exposure to household nicotine smoke	19 (35)	13 (23)
Children with household pets	33 (61)	36 (63)
Children with siblings	42 (78)	38 (67)
Education level mother		
1) low	10 (19)	9 (16)
2) average	22 (41)	30 (53)
3) high	22 (41)	18 (32)
Daycare attendance of children < 4 years	33 (81)	36 (88)
Disease characteristics		
Median number of episodes of URTI in the year before trial entry (IQR)	10.0 (3 to 17)	9.0 (2 to 17)
OSA score, median (IQR)[b]	-0.99 (-2.41 to 1.13)	-1.70 (-2.42 to 0.42)
Adenoid size 75-100%	13 (26)	11 (23)

Abbreviations: IQR = interquartile range; URTI = upper respiratory tract infection; OSA = obstructive sleep apnea.
a Phadiatop is an allergen-specific IgE test to a panel of common food and aeroallergens in children; its result was classified as positive or negative.
b Brouilette Obstructive Sleep Apnea Score: 1.42 x difficulty breathing + 1.41 x apnea + 0.71 x snoring – 3.83. Range -3.83 to +3.5. Score greater than 3.5 is highly predictive of OSA; score between -1 and 3.5 indicates possible OSA; and score below -1 indicates no OSA.

During the trial period, 11 (10%) children were lost to follow-up for non-medical reasons: four (7%) from the adenoidectomy group and seven (12%) from the watchful waiting group. All children allocated to adenoidectomy underwent surgery within six weeks: 48 (89%) had adenoidectomy alone and six (11%) had adenoidectomy and myringotomy. During follow-up

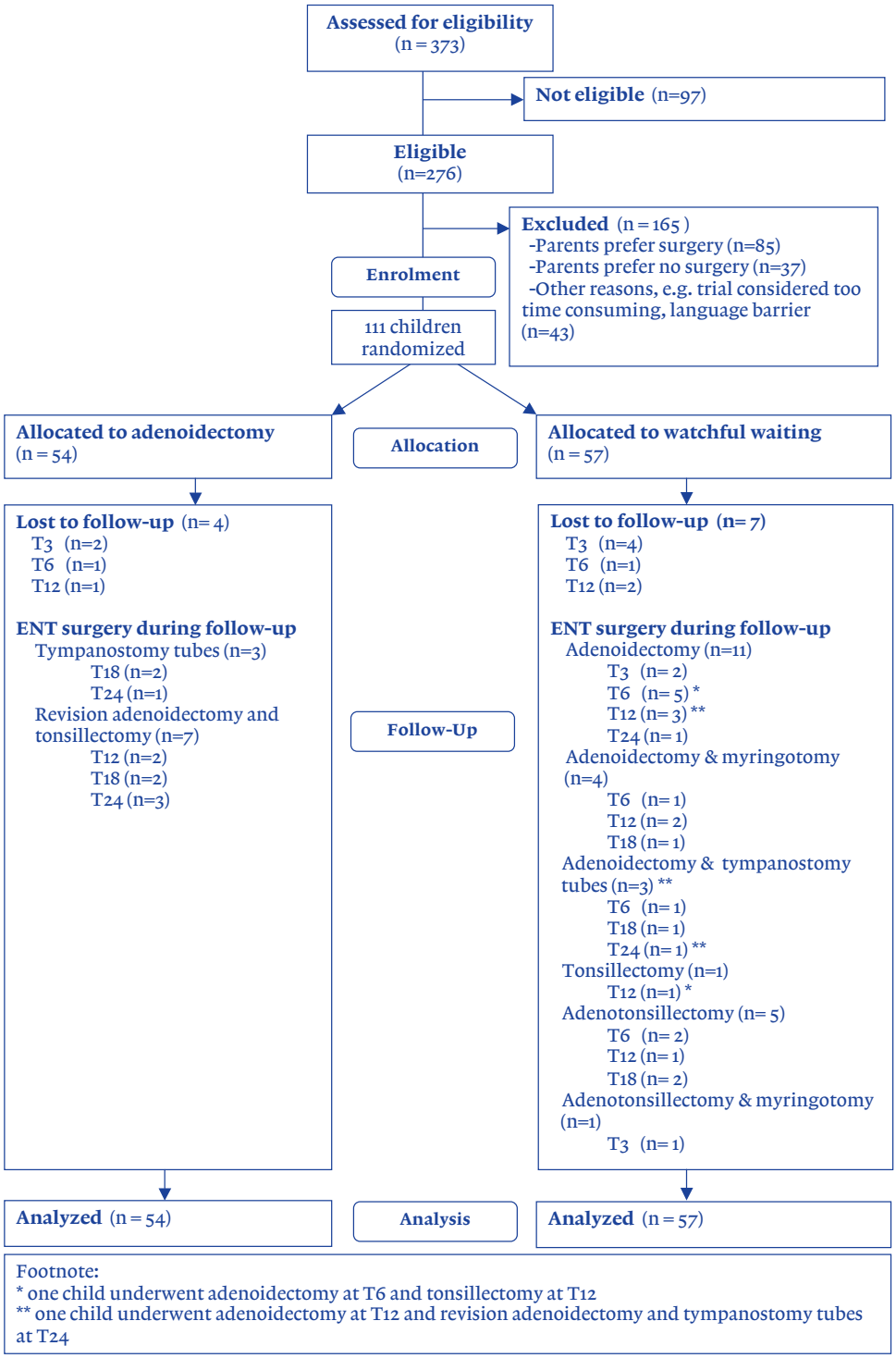

Figure 1. Flow of participants through the trial.

seven (13%) children allocated to adenoidectomy underwent tonsillectomy and revision adenoidectomy and three (6%) had tympanostomy tubes inserted. During follow-up 23 (40%) children allocated to watchful waiting underwent further surgery. Seventeen underwent adenoidectomy (in 11 (19%) it was adenoidectomy only; in four (7%) it was combined with myringotomy and in two (4%) with tympanostomy tubes; one (2%) child underwent adenoidectomy at 12 months and revision adenoidectomy with tympanostomy tubes at 24 months, one (2%) underwent adenoidectomy at six months and tonsillectomy at 12 months). Six (11%) underwent adenotonsillectomy (in one combined with myringotomy).

Primary outcome

During the total follow-up the incidences of upper respiratory tract infections episodes in the adenoidectomy and watchful waiting group were 7.91 and 7.84 per person year (difference in incidence rate 0.07, 95% confidence interval −0.70 to 0.85; table 2).

Table 2. Primary and secondary outcomes for the total follow-up period (maximum 24 months).

	Adenoidectomy	Watchful waiting	Incidence rate difference	Incidence rate ratio
	101 person years	101 person years	(95% CI)	(95% CI)
Primary outcome				
URTI episodes	7.91	7.84	0.07 (-0.70 to 0.85)	1.01 (0.91 to 1.11)
Secondary outcomes				
URTI days	66.10	67.36	-1.27 (-3.52 to 0.99)	0.98 (0.95 to 1.01)
Severe URTI episodes	3.98	3.53	0.45 (-0.08 to 0.99)	1.13 (0.98 to 1.30)
Severe URTI days	48.11	46.56	1.55 (-0.35 to 3.44)	1.03 (0.99 to 1.08)
Mild URTI episodes	3.93	4.31	-0.38 (-0.94 to 0.18)	0.91 (0.80 to 1.04)
Mild URTI days	17.99	20.80	-2.81 (-4.03 to -1.60)	0.86 (0.81 to 0.92)
Fever days	20.00	16.49	3.51 (2.33 to 4.69)	1.21 (1.14 to 1.29)
Middle ear complaints with fever episodes	0.51	0.45	0.05 (-0.14 to 0.24)	1.11 (0.75 to1.65)
Middle ear complaints with fever days	0.86	0.85	0.01 (-0.24 to 0.27)	1.01 (0.75 to1.36)
Absence from day care or school	1.66	2.00	-0.33 (-0.71 to 0.04)	0.83 (0.68 to 1.02)

Abbreviations: URTI = upper respiratory tract infection; 95% CI = 95% confidence interval

These incidences were 9.22 and 9.39 per person year (difference −0.17, −1.34 to 1.00), respectively, during the first year of follow-up and 6.55 and 6.17 per person year (difference 0.37, −0.62 to 1.37), respectively, during the second year of follow-up (table 3).

Table 3. Primary and secondary outcomes for follow-up year 1 and year 2 separately.

	Year 1				Year 2			
	Adenoidectomy, 52 PY	Watchful waiting, 53 PY	Incidence rate difference (95% CI)	Incidence rate ratio (95% CI)	Adenoidectomy, 49 PY	Watchful waiting, 49 PY	Incidence rate difference (95% CI)	Incidence rate ratio (95% CI)
Primary outcome								
URTI episodes	9.22	9.39	-0.17 (-1.34 to 1.00)	0.98 (0.87 to 1.11)	6.55	6.17	0.37 (-0.62 to 1.37)	1.06 (0.91 to 1.24)
Secondary outcomes								
URTI days	52.24	45.22	7.03 (4.35 to 9.71)	1.16 (1.09 to 1.22)	80.60	91.31	-10.71 (-14.38 to -7.03)	0.88 (0.85 to 0.92)
Severe URTI episodes	4.47	4.23	0.25 (-0.55 to 1.05)	1.06 (0.88 to 1.27)	3.47	2.78	0.69 (-0.01 to 1.39)	1.25 (1.00 to 1.56)
Severe URTI days	39.17	31.39	7.78 (5.50 to 10.06)	1.25 (1.17 to 1.33)	57.47	62.96	-5.50 (-8.57 to -2.42)	0.91 (0.87 to 0.96)
Mild URTI episodes	4.74	5.16	-0.42 (-1.27 to 0.44)	0.92 (0.77 to 1.09)	3.08	3.40	-0.31 (-1.03 to 0.40)	0.91 (0.73 to 1.13)
Mild URTI days	13.07	13.82	-0.75 (-2.16 to 0.66)	0.95 (0.85 to 1.05)	23.14	28.34	-5.21 (-7.22 to -3.20)	0.82 (0.75 to 0.88)
Fever days	20.78	16.51	4.27 (2.61 to 5.93)	1.26 (1.15 to 1.38)	19.18	16.47	2.72 (1.04 to 4.39)	1.16 (1.06 to 1.28)
Middle ear complaints with fever episodes	0.64	0.51	0.12 (-0.17 to 0.42)	1.24 (0.75 to 2.07)	0.36	0.39	-0.03 (-0.27 to 0.22)	0.93 (0.49 to 1.78)
Middle ear complaints with fever days	1.01	0.88	0.13 (-0.24 to 0.50)	1.15 (0.77 to 1.71)	0.71	0.82	-0.11 (-0.46 to 0.23)	0.86 (0.55 to 1.36)
Absence from day care or school	1.10	1.33	-0.23 (-0.65 to 0.19)	0.83 (0.58 to 1.17)	2.25	2.72	-0.47 (-1.09 to 0.16)	0.83 (0.64 to 1.07)

Abbreviations: URTI = upper respiratory tract infection; 95% CI = 95% confidence interval PY = person years

Similar results were found after adjustment for observed baseline differences–that is, the adjusted rate differences for the total follow-up, year one, and year two were −0.03 (−1.72 to 1.67), −0.14 (−1.76 to 1.68), and 0.13 (−2.05 to 2.32) (table 4).

Table 4: Primary and secondary outcomes adjusted for observed baseline differences.

	Total follow up				Year 1				Year 2			
	Adenoidectomy	Watchful waiting	Adjusted incidence rate difference (95% CI)	Adjusted incidence rate ratio (95% CI)	Adenoidectomy	Watchful waiting	Adjusted incidence rate difference (95% CI)	Adjusted incidence rate ratio (95% CI)	Adenoidectomy	Watchful waiting	Adjusted incidence rate difference (95% CI)	Adjusted incidence rate ratio (95% CI)
Primary outcome												
URTI episodes	7.86	7.89	-0.03 (-1.72 to 1.67)	1.00 (0.80 to 1.23)	9.23	9.37	-0.14 (-1.76 to 1.68)	0.99 (0.82 to 1.20)	6.43	6.30	0.13 (-2.05 to 2.32)	1.02 (0.71 to 1.42)
Secondary outcomes												
URTI days	66.25	67.20	-0.95 (-20.50 to 4.48)	0.99 (0.73 to 1.31)	52.21	45.24	6.97 (-13.24 to 27.51)	1.15 (0.74 to 1.72)	79.60	89.39	-9.79 (-35.55 to 12.91)	0.89 (0.67 to 1.16)
Severe URTI episodes	3.97	3.54	0.42 (-0.63 to 1.52)	1.12 (0.84 to 1.48)	4.55	4.16	0.40 (-0.68 to 1.48)	1.10 (0.85 to 1.40)	3.34	2.88	0.47 (-0.98 to 1.93)	1.16 (0.71 to 1.82)
Severe URTI days	48.49	46.20	2.28 (-15.62 to 20.17)	1.05 (0.71 to 1.52)	39.18	31.39	7.79 (-11.19 to 26.89)	1.25 (0.71 to 2.13)	57.13	61.70	-4.57 (-26.06 to 16.37)	0.93 (0.64 to 1.32)
Mild URTI episodes	3.89	4.35	-0.46 (-1.31 to 0.35)	0.89 (0.73 to 1.09)	4.68	5.23	-0.55 (-1.62 to 0.48)	0.90 (0.72 to 1.10)	3.08	3.40	-0.32 (-1.35 to 0.65)	0.90 (0.66 to 1.23)
Mild URTI days	17.80	21.01	-3.21 (-7.85 to 1.147)	0.85 (0.66 to 1.06)	13.03	13.86	-0.83 (-5.10 to 3.28)	0.94 (0.68 to 1.28)	22.54	27.64	-5.10 (-11.86 to 1.39)	0.82 (0.61 to 1.05)
Fever days	20.16	16.36	3.80 (-6.75 to 14.20)	1.23 (0.68 to 2.12)	20.70	16.57	4.13 (-10.99 to 18.38)	1.25 (0.49 to 2.66)	19.01	15.81	3.20 (-5.09 to 12.05)	1.20 (0.73 to 1.94)
Middle ear complaints with fever episodes	0.53	0.44	0.09 (-0.26 to 0.43)	1.20 (0.56 to 2.36)	0.68	0.48	0.20 (-0.28 to 0.67)	1.41 (0.60 to 3.07)	0.35	0.41	-0.05 (-0.44 to 0.33)	0.87 (0.18 to 2.08)
Middle ear complaints with fever days	0.91	0.81	0.10 (-0.61 to 0.77)	1.13 (0.48 to 2.60)	1.09	0.81	0.28 (-0.66 to 1.18)	1.34 (0.49 to 3.61)	0.71	0.82	-0.11 (-0.98 to 0.69)	0.86 (0.18 to 2.27)
Absence from day care or school	1.75	1.90	-0.15 (-0.78 to 0.48)	0.92 (0.64 to 1.30)	1.21	1.22	-0.01 (-0.64 to 0.61)	0.99 (0.57 to 1.63)	2.31	2.57	-0.26 (-1.24 to 0.73)	0.90 (0.59 to 1.35)

Abbreviations: URTI = upper respiratory tract infection; 95% CI = 95% confidence interval

Secondary outcomes

During the total follow-up there were 66.10 and 67.36 days with upper respiratory tract infection per person year (difference in incidence rate −1.27, −3.52 to 0.99; table 2) in the adenoidectomy and watchful waiting group, respectively.

Figure 2 shows that the proportion of children with an upper respiratory tract infection (expressed as the prevalence per week) decreased over time in both groups. No differences were found between the two groups for episodes of mild and severe upper respiratory tract infection and days per person year during the total follow-up (table 2). Children in the adenoidectomy group had significantly more days with fever than the children in the watchful waiting group: 20.00 v 16.49 days per person year during the total follow-up (difference 3.51, 2.33 to 4.69).

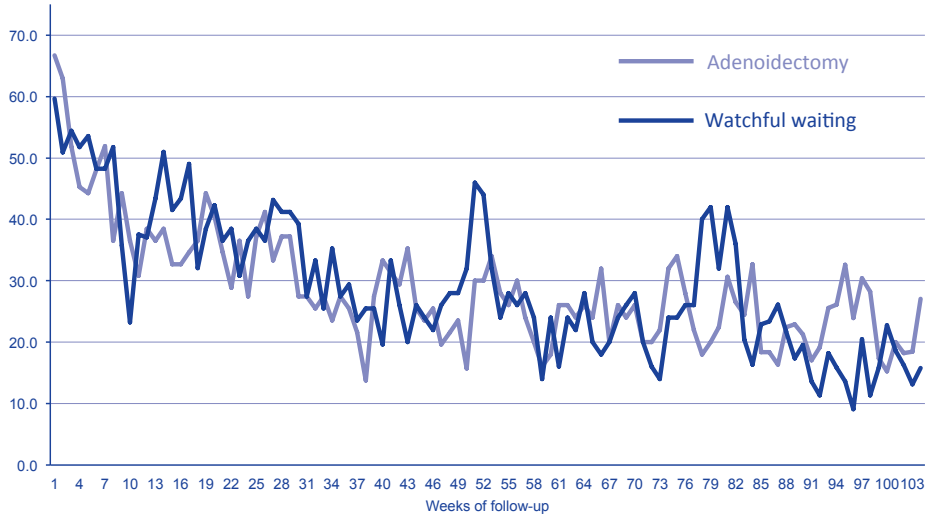

Figure 2. Proportion of children with an upper respiratory tract infection (prevalence per week) in the adenoidectomy (light blue line) and watchful waiting (dark blue line) group.

During the total follow-up there were 0.51 episodes of middle ear complaints with fever per person year in the adenoidectomy group and 0.45 in the watchful waiting group (difference 0.05, −0.14 to 0.24 (table 2). Children in the adenoidectomy group had 0.86 days per person year of middle ear complaints with fever and children in the watchful waiting group had 0.85 (0.01, −0.24 to 0.27). Days of absence from day care or school because of an upper respiratory tract infection were 1.66 and 2.00 (−0.33, −0.71 to 0.04) in the adenoidectomy and watchful waiting groups, respectively. Table 3 shows the results for follow-up year one and two separately. After adjustment for observed baseline differences, we found no significant differences (table 4). Health related quality of life as measured by generic (child health questionnaire,[18,19] and RAND[20,21]) and disease specific (sinonasal symptoms questionnaire,[22] OSA-18 quality of life questionnaire,[23] and otitis media-6 questionnaire[24]) questionnaires, did not differ significantly between both groups over time. Exact numbers can be found in the appendix. As we found no significant interaction terms, we did not further analyse any subgroups of patients.

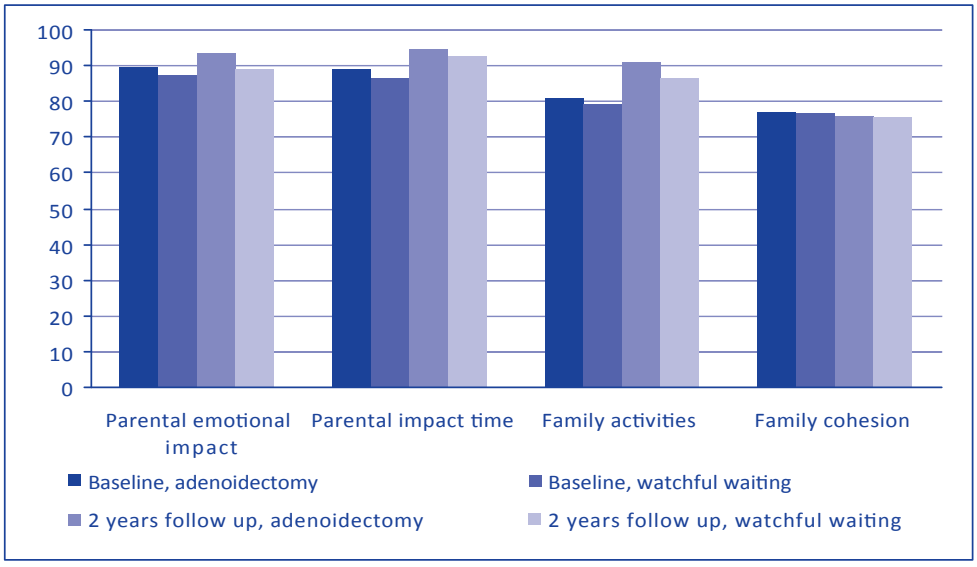

Figure 3A. Generic health related quality of life: Child Health Questionnaire at baseline and 2 year follow-up.

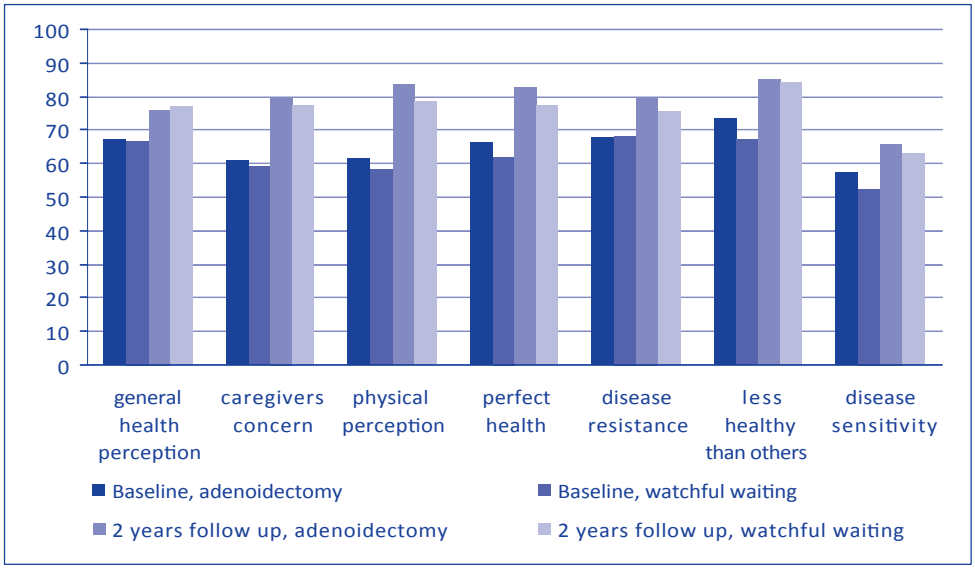

Figure 3B. Generic health related quality of life: RAND at baseline and 2 year follow-up.

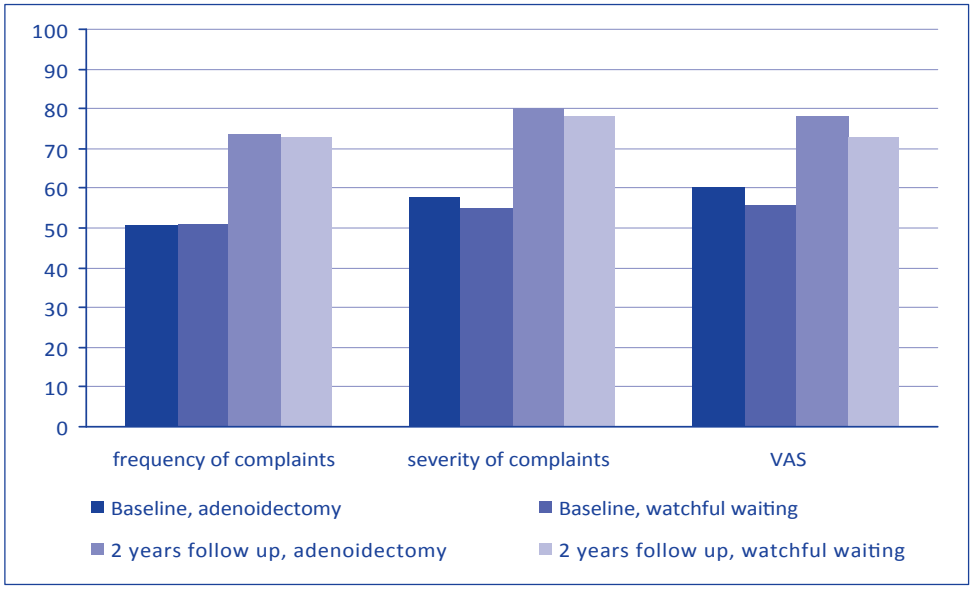

Figure 3C. Disease specific health related quality of life: sinonasal symptoms questionnaire (domain: sinus infection) at baseline and 2 year follow-up.

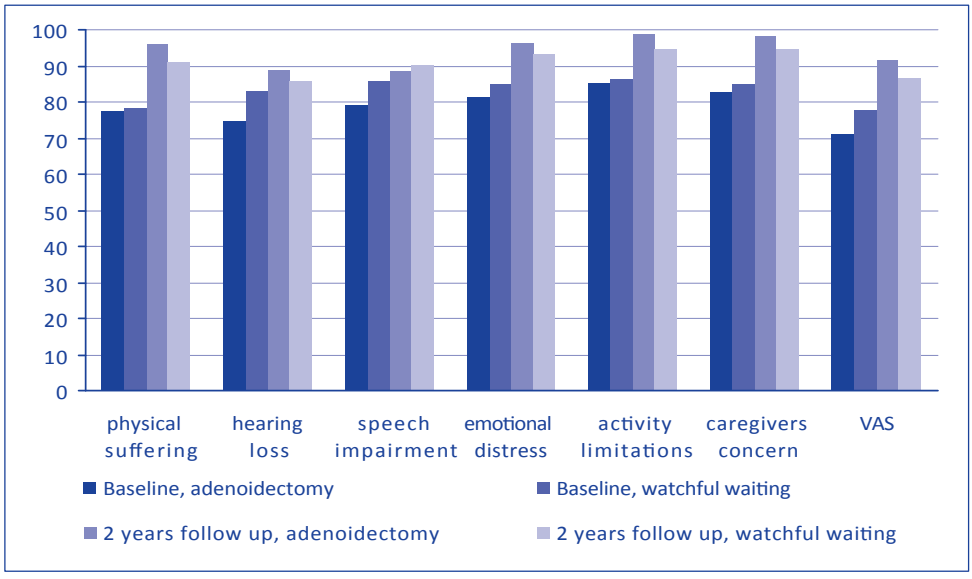

Figure 3D. Disease specific health related quality of life: Otitis Media-6 at baseline and 2 year follow-up.

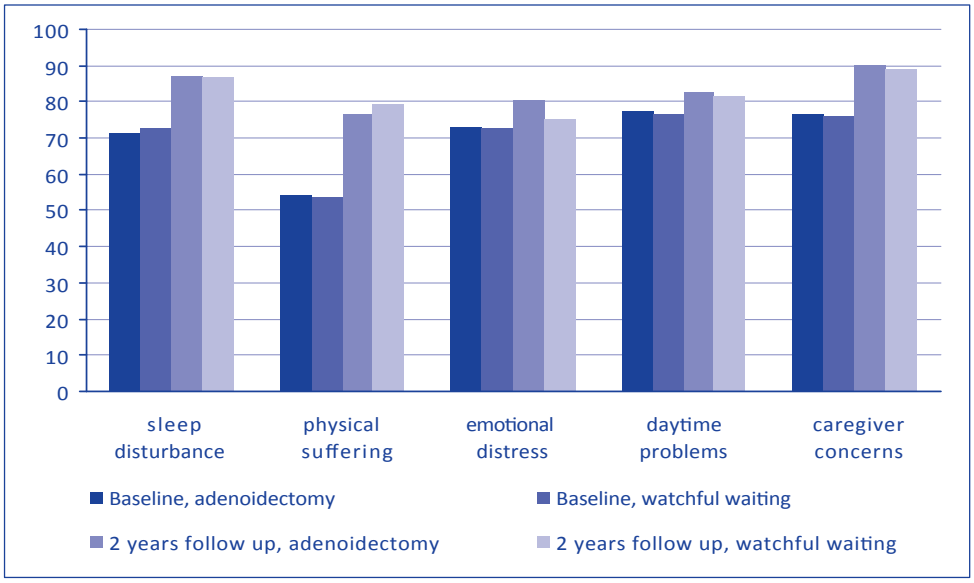

Figure 3E. Disease specific health related quality of life: OSA-18 at baseline and 2 year follow-up

Crossovers

We found no significant differences in baseline variables nor in the number of upper respiratory tract infections during the first year of follow-up between those children in the control group who did and did not cross over (data not shown).

The per protocol and as treated analyses (table 5) yielded the same results as the intention to treat analysis regarding our primary outcome—that is, upper respiratory tract infection episodes during the total follow-up. For example, the difference in incidence rate for episodes of upper respiratory tract infection was −0.13 (−1.02 to 0.77) for the per protocol analysis and −0.23 (−1.08 to 0.62) for the as treated analysis. The adjusted incidence rate differences also showed no significant differences for the primary outcome (table 6).

Adverse events

Two (4%) children in the adenoidectomy group experienced an adverse event: one child was admitted to hospital for an asthma exacerbation during follow-up and in one child a primary tooth was broken when the mouth gag was inserted. One (2%) child in the watchful waiting group who underwent adenotonsillectomy during follow-up was admitted to hospital for a postoperative haemorrhage.

Generalisability

To assess the external validity of our results we compared demographic and disease specific characteristics of the children participating in the trial with those of the 165 (60%) children who were eligible for the trial but did not participate for various reasons. In the trial participants and eligible but non-participating children, respectively, the mean age at referral was 36 and 34 months, 59% and 56% were boys, 57% and 45% had symptoms of snoring or obstructive apnoea, 78% and 84% had nasal discharge on examination, and 67% and 69% had nasal obstruction on examination. Importantly, none of these variables differed significantly.

Table 5. Results for the per protocol and as treated analyses.

	Full follow-up period (max 24 months)							
	Per protocol				As treated			
	Adenoidectomy, 101 PY	Watchful waiting, 61 PY	Incidence rate difference (95% CI)	Incidence rate ratio (95% CI)	Adenoidectomy, 141 PY	Watchful waiting, 61 PY	Incidence rate difference (95% CI)	Incidence rate ratio (95% CI)
Primary outcome								
URTI episodes	7.91	8.04	-0.13 (-1.02 to 0.77)	0.98 (0.88 to 1.10)	7.81	8.04	-0.23 (-1.08 to 0.62)	0.97 (0.87 to 1.08)
Secondary outcomes								
URTI days	66.10	57.63	8.47 (5.99 to 10.95)	1.15 (1.10 to 1.19)	70.67	57.63	13.04 (10.69 to 15.40)	1.23 (1.18 to 1.27)
Severe URTI episodes	3.98	3.50	0.48 (-0.13 to 1.09)	1.14 (0.96 to 1.34)	3.93	3.50	0.42 (-0.15 to 1.00)	1.12 (0.96 to 1.31)
Severe URTI days	48.11	35.42	12.69 (10.67 to 14.70)	1.36 (1.29 to 1.43)	52.49	35.42	17.07 (15.16 to 18.99)	1.48 (1.41 to 1.55)
Mild URTI episodes	3.93	4.54	-0.60 (-1.26 to 0.06)	0.87 (0.74 to 1.01)	3.94	4.54	-0.59 (-1.22 to 0.03)	0.87 (0.75 to 1.00)
Mild URTI days	17.99	22.21	-4.22 (-5.66 to -2.77)	0.81 (0.76 to 0.87)	18.18	22.21	-4.03 (-5.40 to -2.65)	0.82 (0.77 to 0.87)
Fever days	20.00	15.11	4.88 (3.58 to 6.19)	1.32 (1.22 to 1.43)	19.59	15.11	4.48 (3.26 to 5.70)	1.30 (1.20 to 1.40)
Middle ear complaints with fever episodes	0.51	0.46	0.05 (-0.17 to 0.27)	1.10 (0.69 to 1.75)	0.49	0.46	0.03 (-0.17 to 0.24)	1.07 (0.69 to 1.66)
Middle ear complaints with fever days	0.86	0.87	-0.10 (-0.39 to 0.19)	0.89 (0.63 to 1.26)	0.85	0.87	-0.02 (-0.30 to 0.26)	0.98 (0.71 to 1.35)
Absence from day care or school	1.66	1.83	-0.17 (-0.59 to 0.25)	0.91 (0.71 to 1.15)	1.83	1.83	0.00 (-0.41 to 0.40)	1.00 (0.80 to 1.25)

Abbreviations: URTI = upper respiratory tract infection; PY = person years; 95% CI = 95% confidence interval

Table 6. Results for the per protocol and as treated analyses adjusted for observed baseline differences.

	Full follow-up period (max 24 months)							
	Per protocol				As treated			
	Adenoidectomy, 101 PY	Watchful waiting, 61 PY	Incidence rate difference (95% CI)	Incidence rate ratio (95% CI)	Adenoidectomy, 141 PY	Watchful waiting, 61 PY	Incidence rate difference (95% CI)	Incidence rate ratio (95% CI)
Primary outcome								
URTI episodes	7.89	8.01	-0.19 (-2.27 to 1.83)	0.97 (0.75 to 1.26)	7.78	8.10	-0.31 (-2.16 to 1.47)	0.96 (0.77 to 1.21)
Secondary outcomes								
URTI days	66.23	57.44	8.78 (-12.98 to 30.34)	1.15 (0.81 to 1.63)	71.02	56.98	14.04 (-4.35 to 31.87)	1.25 (0.94 to 1.68)
Severe URTI episodes	3.97	3.53	0.44 (-0.82 to 1.72)	1.12 (0.81 to 1.60)	3.84	3.55	0.29 (-0.82 to 1.39)	1.08 (0.81 to 1.49)
Severe URTI days	48.34	35.15	13.19 (-6.31 to 32.62)	1.38 (0.86 to 2.23)	52.84	34.90	17.93 (0.34 to 34.44)	1.51 (1.02 to 2.33)
Mild URTI episodes	3.92	4.56	-0.63 (-1.68 to 0.33)	0.86 (0.67 to 1.08)	3.94	4.54	-0.60 (-1.56 to 0.32)	0.87 (0.70 to 1.08)
Mild URTI days	17.89	22.40	-4.58 (-10.31 to 0.72)	0.80 (0.60 to 1.04)	18.19	22.17	-3.99 (-9.48 to 1.13)	0.82 (0.63 to 1.06)
Fever days	20.36	14.69	5.67 (-4.76 to 15.43)	1.39 (0.77 to 2.45)	19.71	14.90	4.81 (-4.42 to 13.28)	1.32 (0.78 to 2.23)
Middle ear complaints with fever episodes	0.52	0.44	0.08 (-0.36 to 0.47)	1.18 (0.50 to 3.08)	0.49	0.45	0.04 (-0.34 to 0.37)	1.10 (0.53 to 2.63)
Middle ear complaints with fever days	0.90	0.81	0.09 (-0.91 to 0.87)	1.11 (0.41 to 3.84)	0.86	0.84	0.02 (-0.87 to 0.72)	1.03 (0.44 to 3.30)
Absence from day care or school	1.73	1.72	0.01 (-0.71 to 0.74)	1.01 (0.67 to 1.56)	1.87	1.75	0.12 (-0.54 to 0.75)	1.07 (0.75 to 1.56)

Abbreviations: URTI = upper respiratory tract infection; PY = person years; 95% CI = 95% confidence interval

Discussion

In children selected for adenoidectomy for recurrent upper respiratory tract infections, a strategy of immediate surgery did not reduce the number of upper respiratory tract infections compared with a strategy of initial watchful waiting. The prevalence of upper respiratory tract infections decreased similarly over time in both groups, suggesting that the contribution of surgery to the favourable natural course of upper respiratory tract infections is trivial.

We found no relevant differences between the two strategies for days of upper respiratory tract infections, days and episodes of mild and severe upper respiratory tract infections and middle ear complaints with fever, days of absence from day care or school, and health related quality of life. There was a significant difference for days with fever.

Forty per cent of children in the initial watchful waiting group underwent surgery during the course of the trial. These children, however, were not more severely affected by upper respiratory tract infections than the 60% who did not undergo surgery nor did they do better after surgery.

Comparison with literature

So far, most trials of adenoidectomy have been performed in children with recurrent acute otitis media or persistent otitis media with effusion and otitis media was studied as the primary outcome. These studies showed a benefit of adenoidectomy regarding the resolution of middle ear effusion and also a small benefit regarding hearing but did not observe a beneficial effect on recurrence of acute otitis media.[26]

The one study (n=76) that did include children selected for adenoidectomy because of frequent upper respiratory tract infections showed that at 12 months' follow-up 75% of children in the adenoidectomy group and 73% of children in the control group improved during follow-up regarding common colds (risk difference 2%, 95% confidence interval −18% to 22%). At 24 months' follow-up these figures were 77% and 88%, respectively (−11%, −28% to 7%).[15] Another study (n=180) of adenoidectomy versus chemoprophylaxis and placebo in children with recurrent acute otitis media included days with rhinitis as a secondary outcome. Children in the adenoidectomy group had four fewer days with rhinitis during six months of follow-up than those in the control groups (95% confidence interval −13 to 7 days).[16]

All trials of adenoidectomy performed so far have had methodological limitations.[14,26] Firstly, only three trials provided a power analysis and included adequate numbers. As the other trials included relatively few patients, their power might have been too low, leading to a type II error. Secondly, most studies had significant loss to follow-up. This can be associated with either good or poor outcome. Thirdly, three studies were analysed per protocol rather than by intention to treat. Per protocol analyses underestimate the treatment effect as in surgical trials only children in the watchful waiting group with persisting complaints can change treatment group, whereas children of the surgical group, who might experience similar complaints, cannot change treatment group. Fourthly, information bias might have been considerable because trials on adenoidectomy, as most surgical trials, cannot be performed in a true double blind fashion. Such bias will overestimate the effect of the intervention. None of the trials tried to minimise information bias by choosing an objective outcome measure, such as fever. Finally, the generalisability of the trials can be questioned as only a small

proportion of children undergoing adenoidectomy were included in the trials.

Possible limitations

Our trial has several limitations. Firstly, we emphasise that we compared two strategies (immediate adenoidectomy or initial watchful waiting). As in other surgical trials, such as our previous study on adenotonsillectomy,[27] the fact that some patients in the surgery group undergo additional surgical interventions and some patients in the watchful waiting group eventually undergo adenoidectomy mimics daily practice.[28,29] This is part of the two strategies we compared. We studied whether the children in the control group who went on to undergo adenoidectomy were more severely affected than those who did not. There were no significant differences in baseline variables nor in the number of upper respiratory tract infections during the first year of follow-up between those children in the control group who did and did not cross over (data not shown). Furthermore, the per protocol and as treated analyses yielded the same results as the intention to treat analysis regarding our primary outcome—that is, the number of upper respiratory tract infections during the total follow-up. Secondly, we chose 33% as indicating a clinically relevant difference (in absolute terms a decrease from six to four upper respiratory tract infections a year) as the incidence of upper respiratory tract infections in young children is high and is known to decrease over time spontaneously. Nevertheless, we looked into the probability that, given our results, a difference of 20-25%—that is, a difference of 1.5 upper respiratory tract infections a year—could have occurred. Looking at the confidence interval of the total follow-up, the value −1.5 is not within the 99% confidence interval, which means that we can also confidently rule out a difference of 1.5 episodes. Therefore, it seems unlikely that the results and conclusions would change if we had chosen another clinically relevant difference in our power calculation. Thirdly, we question whether our results are generalisable to all children with recurrent upper respiratory tract infections. As we found no statistical differences between the trial participants and those eligible but non-participating, and none of the studied characteristics modified the effect of adenoidectomy, we think that these results are generalisable to all children selected for adenoidectomy for recurrent upper respiratory tract infections.

Strengths of the study

As our randomised controlled trial of adenoidectomy focused on children with recurrent upper respiratory tract infections, it provides important evidence for the many children selected for adenoidectomy for this indication. To our knowledge this is the first randomised controlled trial focusing specifically on these children. We included an objective method to study the effect of adenoidectomy—that is, fever measured daily by a validated thermometer that automatically stored data. Fever is an important physical sign in childhood infections, and most episodes of fever in young children aged under 8 are related to upper respiratory tract infections.[30,31]

For the randomisation process we applied a minimisation strategy that accounted for age and hospital. As such, we ensured that the children within each centre were equally distributed over the two groups. Therefore potential bias from possible differences in 'traditions' of treating these children is precluded.

Conclusion

In children selected for adenoidectomy for recurrent upper respiratory tract infections, a strategy of immediate surgery confers no clinical benefits over a strategy of initial watchful waiting.

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Appendix.

Tables with specific data of quality of life figures expressed as percentage out of 100%. (0% is minimum quality of life, 100% is maximum quality of life).

Table 5A. Child Health Questionnaire at inclusion and 2 year follow-up.

	Adenoidectomy	Watchful waiting	Difference	95% CI
Inclusion				
Parental emotional impact	89.5	87.4	2.1	(-1.5 to 5.6)
Parental impact time	89.1	86.3	2.8	(-2.0 to 7.4)
Family activities	80.8	79.3	1.5	(-4.3 to 7.3)
Family cohesion	76.9	77.0	-0.1	(-6.4 to 6.3)
2 year follow-up				
Parental emotional impact	93.7	89.2	4.5	(-1.3 to 10.3)
Parental impact time	94.4	92.9	1.5	(-4.2 to 7.2)
Family activities	90.8	86.2	4.6	(-1.6 to 10.8)
Family cohesion	76.1	75.5	0.6	(-5.5 to 6.8)

Table 5B. RAND at baseline and 2 year follow-up.

	Adenoidectomy	Watchful waiting	Difference	95% CI
Inclusion				
General health perception	67.2	66.7	0.5	(-4.8 to 5.8)
Caregivers concern	61.1	59.3	1.8	(-6.2 to 10.0)
Physical perception	61.5	58.3	3.2	(-5.5 to 11.9)
Perfect health	66.2	62.2	4.0	(-2.8 to 10.7)
Disease resistance	67.7	68.1	-0.4	(-7.8 to 6.9)
Less healthy than others	73.5	67.4	6.1	(-3.1 to 15.2)
Disease sensitivity	57.0	52.6	4.4	(-4.6 to 14.0)
2 year follow-up				
General health perception	76.1	76.7	-0.6	(-6.2 to 4.9)
Caregivers concern	79.9	77.3	2.6	(-6.9 to 12.2)
Physical perception	83.7	78.4	5.3	(-4.0 to 4.6)
Perfect health	82.6	77.3	5.3	(-0.9 to 11.6)
Disease resistance	80.0	75.5	4.5	(-3.2 to 12.3)
Less healthy than others	85.2	84.1	1.1	(-8.2 to 10.4)
Disease sensitivity	65.7	63.2	2.5	(-7.2 to 12.1)

Table 5C. Sinonasal symptoms questionnaire at baseline and 2 year follow-up.

	Adenoidectomy	Watchful waiting	Difference	95% CI
Inclusion				
Frequency of complaints	50.8	50.8	0.0	(-7.8 to 7.9)
Severity of complaints	57.7	54.8	2.9	(-4.9 to 10.8)
VAS	60.0	55.7	4.3	(-3.2 to 11.7)
2 year follow-up				
Frequency of complaints	73.6	72.7	0.9	(-9.9 to 11.6)
Severity of complaints	80.1	77.9	2.2	(-7.0 to 11.4)
VAS	78.0	72.7	5.3	(-3.3 to 14.0)

Table 5D. Otitis Media-6 at baseline and 2 year follow-up.

	Adenoidectomy	Watchful waiting	Difference	95% CI
Inclusion				
Physical suffering	77.5	78.3	-0.8	(-11.3 to 9.6)
Hearing loss	74.5	83.3	-8.8	(-18.5 to 0.7)
Speech impairment	79.3	86.0	-6.7	(-15.5 to 2.0)
Emotional distress	81.3	84.7	-3.4	(-11.6 to 4.9)
Activity limitations	85.2	86.2	-1.0	(-8.9 to 6.7)
Caregivers concern	82.7	84.7	-2.0	(-10.3 to 6.3)
VAS	71.0	78.0	-7.0	(-16.8 to 2.8)
2 year follow-up				
Physical suffering	96.0	91.2	4.8	(-1.6 to 11.0)
Hearing loss	88.8	85.7	3.1	(-4.8 to 11.0)
Speech impairment	88.3	90.3	-2.0	(-9.9 to 5.8)
Emotional distress	96.6	93.2	3.4	(-2.4 to 9.2)
Activity limitations	98.8	94.8	4.0	(-0.2 to 8.1)
Caregivers concern	98.1	94.8	3.3	(-1.0 to 7.6)
VAS	91.6	86.6	5.0	(-2.1 to 12.0)

Table 5E. OSA-18 at baseline and 2 year follow-up.

	Adenoidectomy	Watchful waiting	Difference	95% CI
Inclusion				
Sleep disturbance	71.3	72.9	-1.6	(-0.8 to 4.9)
Physical suffering	54.1	53.7	0.4	(-6.4 to 7.2)
Emotional distress	73.3	72.9	0.4	(-6.5 to 7.2)
Daytime problems	77.7	76.7	1.0	(-4.8 to 6.9)
Caregiver concerns	76.7	76.0	0.7	(-5.2 to 6.6)
2 year follow-up				
Sleep disturbance	87.4	86.7	0.7	(-4.2 to 5.8)
Physical suffering	76.6	79.1	-2.5	(-10.6 to 5.5)
Emotional distress	80.4	75.5	4.9	(-10.6 to 5.5)
Daytime problems	82.8	81.7	1.1	(-5.1 to 7.3)
Caregiver concerns	90.5	89.0	1.5	(-3.6 to 6.7)

Chapter 7

Alterations of the nasopharyngeal flora after adenoidectomy in children with recurrent upper respiratory tract infections: a randomized controlled trial

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Submission phase

Abstract

Background: Adenoidectomy is one of the most frequently performed procedures in children with recurrent upper respiratory tract infections. Its effect on nasopharyngeal colonization of potential pathogenic bacteria (pathobionts) and subsequent recurrence of upper respiratory tract infections, however, is unknown.

Objective: To establish 1) the effect of adenoidectomy on nasopharyngeal colonization of pathobionts in children with recurrent upper respiratory tract infections and 2) its association with recurrence of these infections.

Methods: During a randomized trial comparing adenoidectomy with watchful waiting in 111 children aged 1 – 6 years with recurrent upper respiratory tract infections we sampled the nasopharyngeal flora at baseline, 3 and 12 months follow-up. The samples were cultured for *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus haemolyticus* and gram negative rods. We studied the association between nasopharyngeal colonization of these pathobionts and subsequent recurrence of upper respiratory tract infections.

Results: Prevalence of each single and multiple pathobionts were similar in the adenoidectomy and watchful waiting group throughout follow-up. Colonization of each single and multiple (1 vs ≥ 2) pathobionts at baseline and/or 3 months was not associated with recurrence of upper respiratory tract infections during 12 months follow-up.

Conclusion: This RCT shows that adenoidectomy has no effect on nasopharyngeal colonization of the most common pathobionts in children with recurrent upper respiratory tract infections, and colonization is not associated with recurrence of these infections.

Introduction

Adenoidectomy is one of the most common surgical procedures in children. Indications include upper airway obstruction, recurrent or chronic otitis media and recurrent upper respiratory tract infections (URTIs), with the latter being the most frequent indication in the Netherlands.[1] The rationale for adenoidectomy is removing the reservoir of potential pathogenic bacteria (pathobionts) causing otitis media and URTIs. The true effect of adenoidectomy on nasopharyngeal colonization of pathobionts and subsequent recurrence of URTIs, however, is unknown. The two cohort studies with long term follow-up of children who had had adenoidectomy reported inconsistent results.[2,3] A randomized controlled trial of adenoidectomy in children who received tympanostomy tubes for otitis media reported higher colonization of *Streptococcus pneumoniae* in the adenoidectomy group than in the non-adenoidectomy group at 12 months follow-up.[4] In this study no baseline samples were taken and only the main pathobionts *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis* were studied.
The aim of this study is to establish the effect of adenoidectomy on the nasopharyngeal colonization of pathobionts in children with recurrent URTIs and its association with recurrence of these infections.

Material and methods

Patients

The present study is part of an open, multi-center randomized controlled trial investigating the effectiveness of adenoidectomy in children with recurrent URTIs. The trial is described in more detail elsewhere.[5] In short, between April 2007 and March 2009 otolaryngologists from 11 general hospitals and 2 academic centers referred children selected for adenoidectomy for recurrent URTIs to the trial center. We excluded children who had previously undergone adenoidectomy or adenotonsillectomy and those with tympanostomy tubes (grommets) present or who had an indication for insertion of tympanostomy tubes. Children with Down's syndrome and craniofacial malformation were also excluded.

Randomization

Children, whose parents gave informed consent, were randomly assigned to one of two strategies: 1) adenoidectomy with or without myringotomy within 6 weeks or 2) watchful waiting. Treatment allocation was concealed until formal informed consent was obtained and the child was included in the study.

Baseline measurements and follow-up

At baseline the study physician filled out a standard questionnaire including the number of URTIs and antibiotic prescriptions in the year before trial entry, recent antibiotic use and risk factors for URTIs. The children underwent an ENT examination and a nasopharyngeal swab was taken.
During 24 months of follow-up parents recorded daily symptoms of URTIs and antibiotic use in a diary. During the home visits by the study physician after 3 and 12 months a nasopharyngeal swab was taken. This paper focuses on the first 12 months of follow-up.

Bacteriologic procedure

For the nasopharyngeal swabs a sterile flexible dry cotton wool swab was inserted in one nostril until the mucosa of the nasopharynx could be firmly swiped. After sampling the swab was immediately stabbed in Amies gel transport medium and transported at room temperature to the Clinical Microbiology Laboratory of the University Medical Center Utrecht. Within 24 hours after collection, the samples were inoculated onto Trypticase Soya Agar with 5% sheepsblood (BA, Becton Dickson), HAE2 Agar (HC, BioMerieux) and MacConckey agar (McC, Oxoid). The plates were incubated aerobically (McConckey) and under 5% carbon dioxide (Trypticase Soya Agar and HAE2 Agar) at 35 degrees Celsius and examined at 24 and 48 hours and longer if necessary.
The following pathobionts were identified: *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus haemolyticus* and gram negative rods. Gram negative rods included *Haemophilus species, Pseudomonas species, Acinetobacter baumanii, Acinetobacter calcoaceticus complex, Strenotrophomonas maltophilia.*

Outcome

We studied the prevalence of these pathobionts and multiple colonization in the nasopharynx at 3 and 12 months after randomization.
Additionally we studied the association between colonization of the most common pathobionts at baseline and/or 3 months and recurrence of URTI during 12 months follow-up. URTI was defined as two or more of the following: fever (a temperature of 38°C or higher), diary scored symptoms of nasal stuffiness or mouth breathing, nasal discharge, sore throat, or cough.

Statistical analysis

We calculated rate differences and the corresponding 95% CI between the adenoidectomy and watchful waiting group for the colonization of each pathobiont and multiple pathobiont colonization. Time trends were analyzed using GEE modeling.
The Students T-test was used to compare the average number of URTIs during 12 months follow-up for children who were and those who were not colonized by each pathobiont and those with and without multiple colonization at baseline and/or 3 months in both groups.
We calculated the proportion of children with an upper respiratory tract infection (expressed as the prevalence per week) for those who were and those who were not colonized by each pathobiont and for those with and without multiple pathobiont colonization (1 vs ≥2) at baseline and/or 3 months.
We studied whether the potential effects of adenoidectomy on colonization were modified by age (<2 years and ≥2 years) or adenoid size (≤75% and >75% obstruction of the choanae) with Poisson analyses.
All analyses were performed according to the intention-to-treat principle using SPSS software, version 15 (SPSS Inc., Chicago, Illinois) and Rothman's Episheet (11 June 2008).

Results

111 children were randomly assigned to one of two strategies: 54 children to adenoidectomy with or without myringotomy within 6 weeks, and 57 children to watchful waiting. Baseline characteristics are shown in Table 1: mean age was 36 and 38 months and the median number of URTI episodes in the year before trial entry was 10 and 9 in the adenoidectomy group and watchful waiting group, respectively. Twelve children (23%) in the adenoidectomy group and 14 (25%) in the watchful waiting group had previously received the 7-valent CRM 197 conjugated pneumococcal vaccine Prevenar® according to the national immunization program for newborns. The median number of antibiotic prescriptions in the year before trial entry was 1 in both groups. Median follow-up was 12 months in both groups.

Table 1. Baseline characteristics of 111 study participants according to treatment allocation.

	Adenoidectomy group N=54 (%)	Watchful waiting group N=57 (%)
Patient characteristics		
Mean age (SD) in months	36 (19)	38 (18)
Male sex	37 (69)	29 (51)
Breastfeeding ≥ 3 months	24 (44)	32 (56)
Positive result Phadiatop test[a]	12 (24)	16 (30)
Vaccinated with 7-valent Pneumococcal vaccine[b]	12 (23)	14 (25)
Day care attendance of children aged <4 years	33 (81)	36 (88)
Median number of URTIs in the year before trial entry (IQR)	10 (3 to 17)	9 (2 to 17)
Median number of antibiotic prescriptions in the year before trial entry (IQR)	1.0 (0.5 to 2.0)	1.0 (0.0 to 3.0)
Antibiotics in 2 weeks prior to swab	5 (9%)	4 (7%)
Adenoid size obstructing 76-100% of choanae	13 (26)	11 (23)

Abbreviations: IQR = interquartile range; URTI = upper respiratory tract infection;

a Phadiatop is an allergen-specific IgE test to a panel of common food and aeroallergens in children; its result was classified as positive or negative.

b The 7-valent CRM 197 conjugated pneumococcal vaccine Prevenar® was introduced to the Dutch vaccination programme in June 2006.

During the trial period, 11 children were lost to follow-up for non-medical reasons: 4 children from the adenoidectomy group and 7 children from the watchful waiting group. During 12 months follow-up two (4%) children allocated to adenoidectomy underwent further ENT surgery. Eighteen (32%) children allocated to watchful waiting underwent ENT-surgery. Further details on the flow of participants through the trial can be found in figure 1. At 3 months 2 (4%) children in the adenoidectomy group and 3 (6%) in the watchful waiting group had used antibiotics in the two weeks prior to the bacteriological swab. At 12 months this was 2 (4%) in both groups.

During the total follow-up of 12 months 23 children in the adenoidectomy group and 26 children in the watchful waiting group used antibiotics. The median number of days with antibiotics was 7.0 (Inter Quartile Range 3 to 14) and 7.5 (IQR 5.8 to 11.5) in the adenoidectomy and watchful waiting group, respectively.

Adenoidectomy did not affect colonization of *Haemophilus influenzae, Streptococcus pneumoniae,*

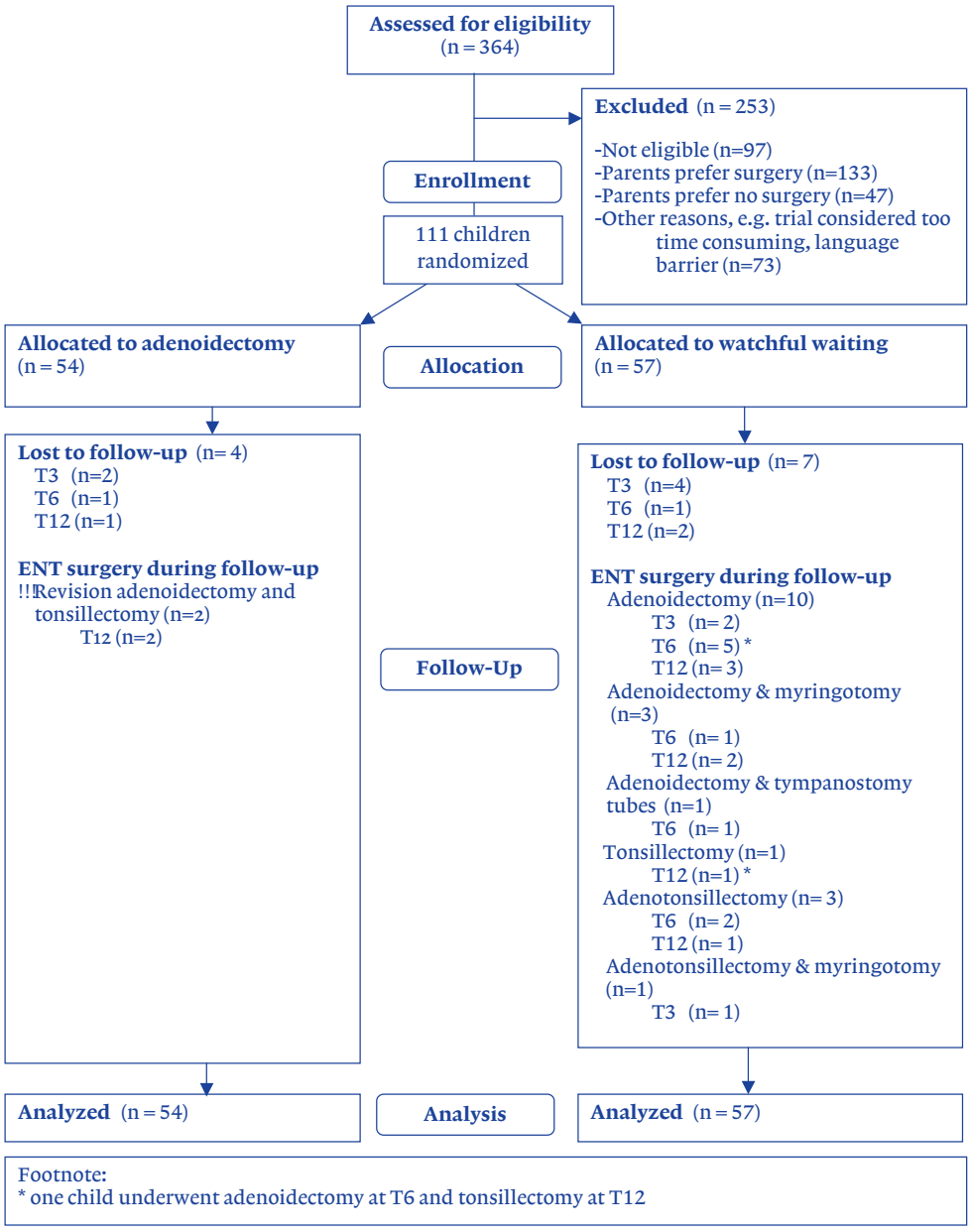

Figure 1. Flow of participants through the trial.

Moraxella catarrhalis, Staphylococcus aureus, Streptococcus haemolyticus and gram negative rods, nor multiple colonization: the prevalence of these pathobionts was similar in the adenoidectomy and the watchful waiting group at 3 and 12 months follow-up. (tables 2 and 3) Colonization with pathobionts did not change over time in both groups (p value for trend = 0.57). For example, at baseline the proportion of children in the adenoidectomy group who were colonized with *Streptococcus pneumoniae* was 50%, at 3 months 45% and at 12 months 36%. For the watchful waiting group these numbers were 54%, 41% and 40%, respectively. At baseline 52% of children in the adenoidectomy group and 59% in the watchful waiting group were colonized with multiple pathobionts, at 12 months this was 40% and 56% respectively.

Table 2. Nasopharyngeal colonization per pathobiont for the adenoidectomy and watchful waiting group.

	Baseline			3 months			12 months		
Bacteria type	A (%) (n=54)	WW (%) (n=57)	RD (95% CI)	A (%) (n=51)	WW (%) (n=51)	RD (95% CI)	A (%) (n=45)	WW (%) (n=48)	RD (95% CI)
H. influenzae	34 (63)	38 (67)	-4 (-21 to 14)	31 (61)	28 (55)	6 (-13 to 25)	24 (53)	27 (56)	-3 (-23 to 17)
S. pneumoniae	27 (50)	31 (54)	-4 (-23 to 14)	23 (45)	21 (41)	4 (-15 to 23)	16 (36)	19 (40)	-4 (-24 to 16)
M. catarrhalis	18 (33)	23 (40)	-7 (-25 to 11)	18 (35)	19 (37)	-2 (-21 to 17)	12 (28)	20 (42)	-15 (-34 to 4)
S. aureus	7 (13)	4 (7)	6 (-5 to 17)	4 (8)	5 (10)	-2 (-13 to 9)	10 (22)	4 (8)	14 (-1 to 28)
HSC	1 (2)	0 (0)	1 (n.a.)	1 (2)	0 (0)	2 (n.a.)	1 (2)	2 (4)	-2 (-9 to 5)
GNR	1 (2)	0 (0)	1 (n.a.)	2 (4)	3(6)	-2 (-10 to 6)	2 (4)	1 (2)	2 (-5 to 10)

A = adenoidectomy group; WW = watchful waiting group; RD= rate difference; 95%CI= 95% confidence interval, HSC = Streptococcus hemolyticus, GNR = Gram negative rods (Haemophilus species, Pseudomonas species, Acinetobacter Baumanii, Acinetobacter Calcoaceticus complex, Strenotrophomonas Maltophilia)

Table 3. Number of children with nasopharyngeal colonization of no, one or more pathobionts for the adenoidectomy and watchful waiting group.

	Baseline			3 months			12 months		
No. of different bacteria types	A (%) (n=54)	WW (%) (n=57)	RD (95% CI)	A (%) (n=51)	WW (%) (n=51)	RD (95% CI)	A (%) (n=45)	WW (%) (n=48)	RD (95% CI)
0	5 (9)	6 (11)	-1 (-13 to 10)	8 (16)	9 (18)	-2 (-16 to 13)	6 (13)	7 (15)	-1 (-15 to 13)
1	21 (39)	17 (30)	9 (-59 to 27)	15 (30)	16 (31)	-2 (-20 to 16)	21 (47)	14 (29)	18 (-2 to 40)
2	17 (32)	23 (40)	-9 (-27 to 9)	20 (39)	18 (35)	-4 (-25 to 23)	10 (22)	22 (46)	-24 (-42 to -5)
3	11 (20)	11 (19)	1 (-14 to 16)	8(16)	8 (16)	0 (-14 to 14)	8 (18)	5 (10)	7 (-7 to 21)

Abbreviations: A = adenoidectomy group; WW = watchful waiting group; RD= rate difference; 95%CI= 95% confidence interval

Colonization with a single pathobiont and with multiple pathobionts (1 vs ≥2) at baseline and/or 3 months was not associated with recurrence of URTIs during 12 months follow-up in both groups. For example, children in the adenoidectomy group who were colonized with *Streptococcus pneumoniae* at baseline and/or 3 months had 8.7 URTIs during the first year of follow-up, while this number was 9.0 in the non-colonized children. For the watchful waiting group these numbers were 8.6 and 8.7 respectively. Figures 2 to 5 show this in more detail. The figures show the weekly proportion of children (adenoidectomy and watchful

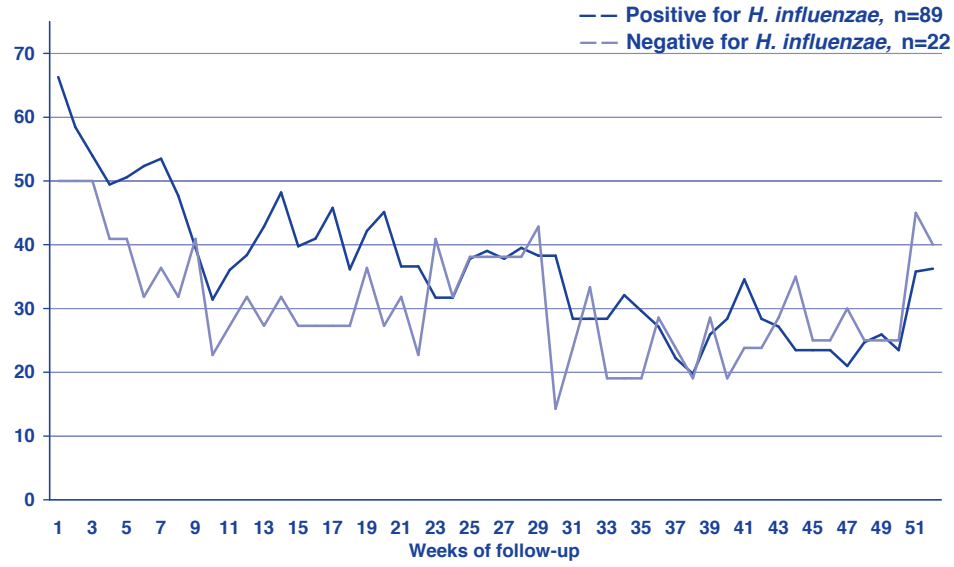

Figure 2. Proportion of children with URTI (prevalence per week) during 12 months follow-up in children with a positive versus a negative nasopharyngeal culture for *Haemophilus influenzae* at baseline and/or 3 months.

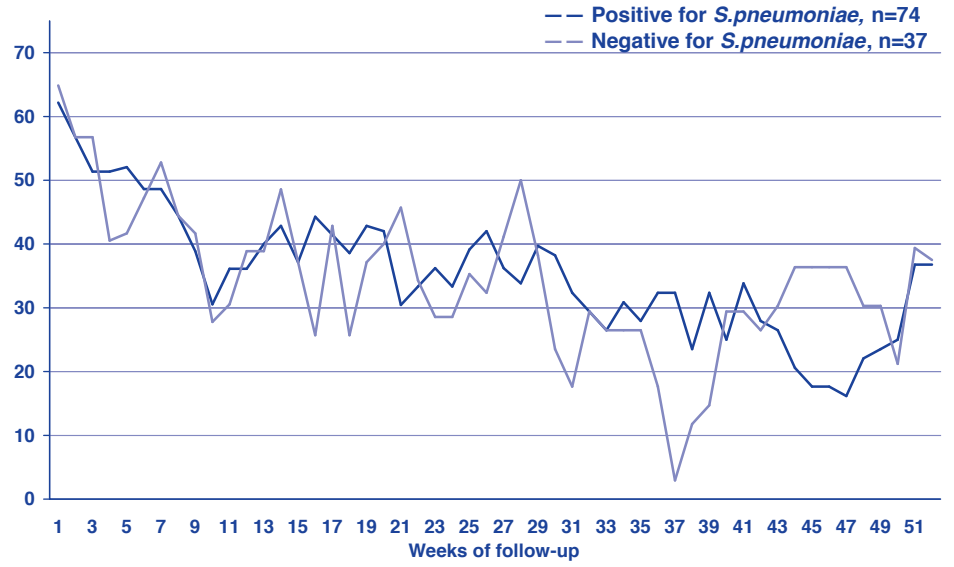

Figure 3. Proportion of children with URTI (prevalence per week) during 12 months follow-up in children with a positive versus a negative nasopharyngeal culture for *S.pneumoniae* at baseline and/or 3 months.

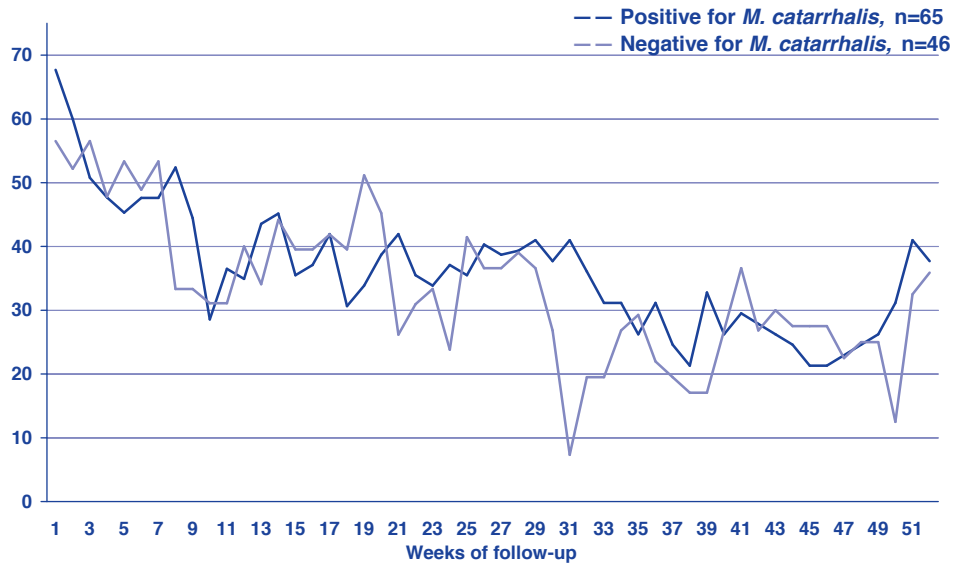

Figure 4. Proportion of children with URTI (prevalence per week) during 12 months follow-up in children with a positive versus a negative nasopharyngeal culture for *M.catarrhalis* at baseline and/or 3 months.

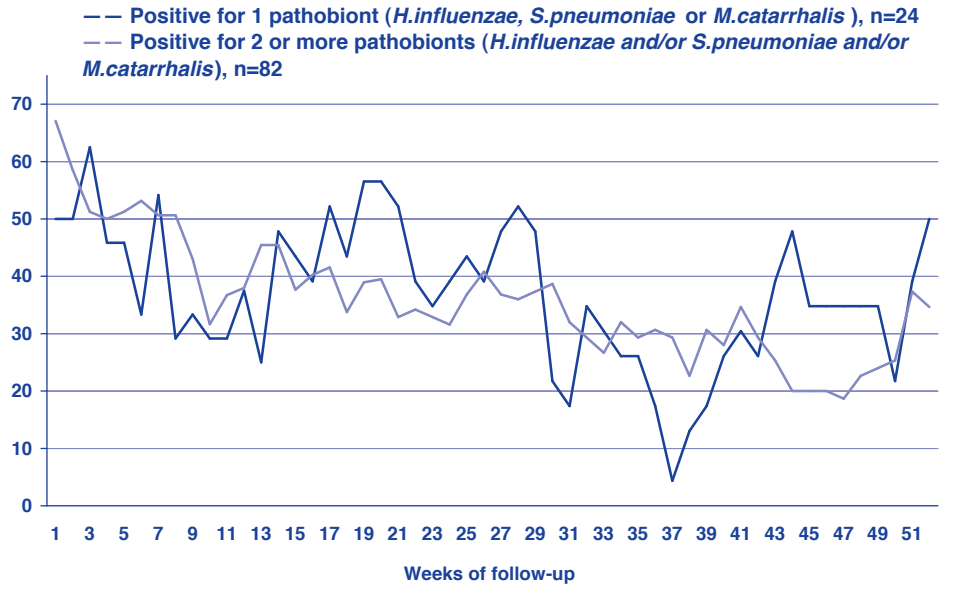

Figure 5. Proportion of children with URTI (prevalence per week) during 12 months follow-up in children with a positive nasopharyngeal culture for one versus two or more pathobionts (*H.influenzae* and/or *S.pneumoniae* and/or *M.catarrhalis*) at baseline and/or 3 months.

waiting group combined) with an upper respiratory tract infection for those who were and were not colonized at baseline and/or 3 months with *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis* and for those with and without multiple colonization of these pathobionts. For example, at 3 months 36% of children who were colonized with *Streptococcus pneumoniae* at baseline and/or 3 months had an URTI, at 12 months this percentage was also 36%. For those who were not colonized with *Streptococcus pneumoniae* at baseline and/or 3 months these percentages were 39% and 37% respectively.
As we found no significant interaction terms for age and adenoid size, we did not further analyse these subgroups of patients.

Discussion

Our RCT shows that adenoidectomy does not affect nasopharyngeal colonization of the most common pathobionts in children with recurrent URTIs. Colonization remained stable over time in both the adenoidectomy and watchful waiting group; e.g. at baseline 50% of children in the adenoidectomy group and 54% in the watchful waiting group were colonized with *Streptococcus pneumoniae*, at 12 months these percentages were 36% and 40% respectively. About half of the children in both groups were colonized with multiple pathobionts. Colonization with these pathobionts at baseline and/or 3 months follow-up was not associated with recurrence of URTIs; e.g. children in the adenoidectomy group who were colonized with *Streptococcus pneumoniae* at baseline and/or 3 months had 8.7 URTIs during the first year of follow-up, this number was 9.0 in the non-colonized children. For the watchful waiting group these numbers were 8.6 and 8.7 respectively.
We recently reviewed the results of previous (cohort) studies on the effect of adenoidectomy on nasopharyngeal colonization. In the short term all studies reported a decrease of nasopharyngeal colonization after adenoidectomy. In the long term results were inconsistent.[6] As none of these studies included a control group of non-adenoidectomy children, it is uncertain whether any changes reflect the effect of the surgical procedure or the natural variation over time. During a recent RCT on the effect of adjuvant adenoidectomy next to tympanostomy tube insertion for otitis media, nasopharyngeal samples were taken at 1, 2 and 3 years follow-up.[4] At 1 year follow-up colonization with *Streptococcus pneumoniae* was higher in the adenoidectomy group than in the non-adenoidectomy group, at 2 and 3 years colonization was the same in the two groups. Colonization with *Haemophilus influenzae* and *Moraxella catarrhalis* was similar in both groups at all time points.
Our study is the first RCT of adenoidectomy in children with recurrent URTIs studying colonization of pathobionts before and after surgery, and relating this to clinical symptoms. Parents documented clinical URTI symptoms in a daily diary: therefore microbiological culture results could be compared to the number of URTIs during follow-up. An additional strength of our study was the high completeness of data: over 90% of the patients completed follow-up and for 82% of children nasopharyngeal swabs were available for all three time-points.
A potential limitation of our study is that 18 children (32%) in the watchful waiting group underwent adenoidectomy during 12 months follow-up. This rate is similar to those in previous RCTs of ENT throat surgery in children.[7-9] We performed an as treated sensitivity analysis including children of the watchful waiting group who had undergone surgery during the first year in the adenoidectomy group. This did not affect our results for

nasopharyngeal colonization nor for recurrence of URTIs. (data not shown)
External validity of our study was addressed by comparing demographic and disease specific characteristics of the 111 children participating in the trial with those of the 165 eligible children referred to the trial who did not participate for various reasons. Mean age, sex and symptoms were similar in both groups. Therefore we believe our results to be generalisable to all children selected for adenoidectomy for recurrent URTIs.

Conclusion

Adenoidectomy has no effect on nasopharyngeal colonization of the most common pathobionts in children with recurrent URTIs, and nasopharyngeal colonization is not associated with recurrence of these infections.

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Chapter 8

Immediate Adenoidectomy vs Initial Watchful Waiting Strategy in Children with Recurrent Upper Respiratory Tract Infections

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Abstract

Objective: To compare the costs associated with 2 clinical strategies in children with recurrent upper respiratory tract infections (URTIs): immediate adenoidectomy vs an initial watchful waiting strategy.

Design: A cost-minimization analysis from a societal perspective including both direct and indirect costs, alongside an open randomized controlled trial with a 2-year follow-up.

Setting: Multicenter study, including 11 general and 2 university hospitals in the Netherlands.

Patients: The study population comprised 111 children aged 1 through 6 years, selected for adenoidectomy for recurrent URTIs according to current clinical practice.

Intervention: A strategy of immediate adenoidectomy with or without myringotomy or a strategy of initial watchful waiting.

Main Outcomes Measures: Difference in median costs during the 2-year follow-up.

Results: The median total of direct and indirect costs in the adenoidectomy and watchful waiting group were €1385 (US $1995) and €844 (US $1216) per patient, respectively. The extra costs in the adenoidectomy group are primarily attributable to surgery and visits to the otorhinolaryngologist. Other costs did not differ significantly between the groups.

Conclusions: In children selected for adenoidectomy for recurrent URTIs, immediate adenoidectomy results in an increase in costs, whereas it confers no clinical benefit over an initial watchful waiting strategy.

Introduction

Adenoidectomy is one of the most commonly performed surgical procedures in children in Western countries. Indications for adenoidectomy include recurrent or chronic nasal discharge, recurrent episodes of acute otitis media, persistent otitis media with effusion, and symptoms of upper airway obstruction. In most cases, children undergo surgery for a combination of nasal and middle ear symptoms. In 2009, in the Netherlands, 15 179 children (16.3 per 1000) aged 0 to 4 years and 5573 children (5.5 per 1000) aged 5 to 9 years underwent adenoidectomy.[1,2] In 60% of these children, recurrent upper respiratory tract infection (URTI) was the indication for surgery.[3] In 2006, in the United States, 129 540 children (1.76 per 1000) up to the age of 18 years underwent adenoidectomy. In 12% of these children, the operation was performed because of chronic infections.[4] In both countries the figures remained stable over the past decade.[4,5] In a recent randomized controlled trial, we compared 2 common clinical strategies in children with recurrent URTIs: immediate adenoidectomy vs initial watchful waiting.[6] We found no relevant differences between both strategies in the incidence of URTIs and middle ear problems or health related quality of life. We concluded that immediate adenoidectomy confers no clinical benefits over an initial watchful waiting strategy.

In clinical practice, the decision for either of these treatment strategies is made by both the physician and parents and is based on careful consideration of anticipated benefits and risks and personal preference. Costs should be part of this decision process as well.[7] So far, no information is available on the costs involved with immediate adenoidectomy or initial watchful waiting in children with recurrent URTIs. This is relevant because in both strategies costs may be considerable. Besides costs related to immediate or delayed surgery, there are those related to physician visits, use of medication for URTIs, and indirect costs, eg, related to parental absence from work. We set out to compare the costs associated with both strategies.

Methods

Study design

A cost-minimization study was carried out alongside an open multicenter randomized controlled trial investigating the effectiveness of adenoidectomy in children with recurrent URTIs. The study was approved by the medical ethics committee of the University Medical Center Utrecht. The design of the study has been reported previously.[6] In short, between April 2007 and October 2010, otolaryngologists from 11 general and 2 academic hospitals in the Netherlands referred children aged 1 through 6 years selected for adenoidectomy for recurrent URTIs to the trial center. Children with previous adenoidectomy or adenotonsillectomy, as well as those with tympanostomy tubes present or an indication for insertion of tympanostomy tubes in combination with adenoidectomy, were excluded from the study. Children with Down syndrome or craniofacial malformation were also excluded. Children, whose parents gave informed consent, were randomly assigned to either (1) adenoidectomy with or without myringotomy within 6 weeks, or (2) an initial watchful waiting strategy. For this purpose we used a computerized minimization strategy, ie, a method of ensuring balance between prognostic factors in small samples. Treatment allocation was concealed until formal informed consent was obtained and the child was included in the trial.

Follow-up

During the 2-year follow-up parents kept a diary, including specific symptoms of URTIs, middle ear complaints, and absence from day care or school because of URTI. They also measured their child's temperature every day with a validated tympanic membrane thermometer.[8] Parallel to these clinical symptoms, parents recorded resources used in the diary, such as physician visits, medication, hospital admissions, and surgical interventions, as well as out-of-pocket expenses for over-the-counter drugs, babysitting, and traveling to medical appointments. Costs reported in the diary were costs made specifically for the participating child because of URTIs. The study physician (MTAvdA) collected the diary data during the scheduled follow-up visits at 3, 6, 12, 18, and 24 months. Where relevant, diary entries were verified by data from the medical records. During follow-up, parents, family physicians, and otorhinolaryngologists of the participating children were encouraged to manage episodes of URTIs according to their regular practice, including antibiotics and ear-nose-throat surgery.

Outcome measures

The primary outcome measure of this cost-minimization study was the difference in median costs between the 2 strategies during the full 2 years of follow-up. To study short-term effects, the secondary outcome was the difference in median costs in the first year of follow-up. These costs included both direct and indirect costs and were estimated at patient level in euros for 2009.

Costs

For out-of-pocket expenses the actual amount of money indicated in the diary was used. For the other expenses, the number of resources used (eg, physician visits) was multiplied by the corresponding cost price. Cost prices were estimated from a societal perspective according to the guidelines for economic evaluation in health care research. Costs of surgery were retrieved from available data from a previous cost study.[9] Costs of diagnostic tests were retrieved from the Dutch diagnostic formulary.[10] Costs of medication were derived from the Dutch Formulary,[10] and a pharmacist's fee was added.[11] Costs of over-the-counter drugs and alternative medicines were based on average retail prices. Costs of consulting a family physician or medical specialist, day case surgery, and other procedures and hospitalizations were based on current Dutch guidelines for pharmacoeconomic evaluation.[11] Indirect costs to society associated with leave or absence from work of the parents were estimated using the friction cost method.[12] Costs associated with absence of professional day care were estimated as the compensation for professional day care as provided by the government. Costs for informal babysitting were estimated using standard rates of the Dutch National Institute for Family Finance Information (NIBUD).[13] According to the guidelines for economic evaluation in health care research, euros were converted to US dollars using the exchange rate of December 31, 2009 (€1 = US $1.4406).[14]

Analysis

We used a short time horizon for all analyses and therefore took no time preference or discount rate into account. Differences in costs were compared between both randomization groups. When relevant, differences were tested by nonparametric Mann-Whitney tests, since costs always have a skewed distribution. Uncertainty was addressed by means of

bootstrapping,[15] for which we replicated the trial 1000 times using random replacement samples. All analyses were performed on an intention to treat basis because we aimed to compare the costs of 2 *strategies* (adenoidectomy vs initial watchful waiting [the latter may include surgery later during follow-up]). Sensitivity analyses were conducted by (1) excluding the children in the initial watchful waiting group who underwent ear-nose-throat surgery during follow-up (per protocol analysis) or (2) by counting these children in the adenoidectomy group (as treated analysis) to analyze if the results were influenced by the crossovers.

Results

Study groups

In total, 111 children were enrolled in the study between April 2007 and April 2009; 54 were allocated to adenoidectomy within 6 weeks and 57 were allocated to an initial watchful waiting strategy. The mean age was 36 months in the adenoidectomy group and 38 months in the watchful waiting group. The median number of episodes of URTIs in the previous year was 10 in the adenoidectomy group and 9 in the watchful waiting group. The median follow-up duration was 24 months in both groups. Overall, 11 children were lost to follow-up for nonmedical reasons (4 from the adenoidectomy group and 7 from the watchful waiting group). All children allocated to adenoidectomy underwent adenoidectomy within 6 weeks: 48 underwent adenoidectomy alone and 6 underwent adenoidectomy combined with myringotomy. During follow-up, 7 children (13%) allocated to adenoidectomy underwent tonsillectomy and revision adenoidectomy and 3 (6%) had tympanostomy tubes inserted. During the course of the trial, of the children allocated to initial watchful waiting, 17 (30%) underwent adenoidectomy (4 children underwent adenoidectomy combined with myringotomy and 2 children underwent adenoidectomy and had tympanostomy tubes inserted; 1 child underwent adenoidectomy in the first year of follow-up and revision adenoidectomy with tympanostomy tubes in the second year of follow-up; and 1 child underwent adenoidectomy in the first 6 months of follow-up and tonsillectomy in the 6 months thereafter) and 6 children (11%) underwent adenotonsillectomy (1 child underwent adenotonsillectomy combined with myringotomy).

Costs

Table 1 gives a detailed overview of the most relevant cost estimates. The median costs per patient during the 2-year follow-up period were €1385 (interquartile range [IQR], €806-€2386) (US $1995; IQR, $1162-$3437) in the adenoidectomy group and €844 (IQR, €416-€1994) (US $1215; IQR, $600-$2873) in the watchful waiting group, ie, an immediate surgical strategy costs €541 (US $779) more than an initial watchful waiting strategy (Table 2). Bootstrapping yielded the same results, which means that there is no uncertainty regarding the median costs. Children in the adenoidectomy group had higher median costs related to surgery (P<.001) and visits to the otorhinolaryngologist (P = .03). Other costs, such as those of visits to the family physician, of (over-the- counter) drugs and parental leave of absence did not differ significantly between the groups. The median costs during the first year of follow-up were €959 (IQR, €632- €1658) (US $1382; IQR, $911-$2388) in the adenoidectomy group and €505 (IQR, €105-€1194) (US $728; IQR, $151-$1720) in the watchful waiting group (Table 2). Again, bootstrapping yielded the same results.

Table 1. Resources used and cost estimates in € and US$ for 2009.

Resources	Cost Estimate, €	Cost Estimate, US$ [a]	Source
Adenoidectomy	336.54	484.82	Cost study
Adenoidectomy and myringotomy	567.39	817.38	Cost study
Adenoidectomy and insertion of tympanostomy tubes	717.02	1032.94	Cost study
Adenotonsillectomy	379.01	546.00	Cost study
Adenotonsillectomy and myringotomy	609.85	878.55	Cost study
Adenotonsillectomy and insertion of tympanostomy tubes	759.48	1094.11	Cost study
Tonsillectomy	357.78	515.42	Cost study
Insertion of tympanostomy tubes	380.47	548.11	Cost study
Diagnostic tests	Several	Several	Guideline
Hospitalization per day	358.68	516.71	Guideline
Consultation ORL / pediatrician	61.40	88.45	Guideline
Consultation family physician	20.79	29.95	Guideline
Consultation other medical professional	25.72	37.05	Guideline
Parental leave of absence (per hour)	35.99	51.85	Guideline
Absence of day-care (per hour)	6.10	8.79	Government
Babysitting (per hour)	5.70	8.21	NIBUD
Pharmacist fee (per prescription)	7.28	10.49	Guideline
Prescribed medication	Several	Several	Dutch formulary
Over-the-counter drugs and CAM	Several	Several	Retail prices

Abbreviations:
Guideline: Dutch guidelines for pharmacoeconomic research[6]
NIBUD: Dutch National Institute for Family Finance Information[8]
ORL: otorhinolaryngologist
CAM: complementary and alternative medication
a Exchange rate 31-12-2009 1 € = 1.4406 US$

Sensitivity analysis

Per protocol analysis resulted in a difference in median cost between the adenoidectomy and initial watchful waiting group of €778 (US $1121) during the 2-year follow-up (P<.001). As treated analysis resulted in a difference in median costs between the 2 groups of €777 (US $1119) during the 2-year follow-up (P< .001) (Table 3).

Table 2. Median costs in € and US$ during the two year follow-up and during the first year of follow-up.

During the two year follow-up		
	Adenoidectomy (n = 54) Median € (IQR)	**Watchful waiting (n = 57) Median € (IQR)**
Surgery and hospitalization	336.54 (336.54 – 599.35)	0.00 (0.00 – 379.01)
Prescribed medication	8.55 (0.72 – 30.35)	6.64 (0.00 – 21.50)
Over-the-counter drugs and CAM	8.36 (2.36 – 28.98)	12.41 (2.03 – 36.78)
Consultations otorhinolaryngologist	61.40 (0.00 – 122.80)	0.00 (0.00 – 107.45)
Consultation other specialist	0.00 (0.00 – 63.53)	0.00 (0.00 – 57.62)
Consultation family physician	72.96 (18.24 – 117.09)	72.96 (20.79 – 172.01)
Absence of day-care	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)
Parental leave of absence	359.90 (53.99 – 899.75)	251.93 (0.00 – 701.81)
Babysitting	0.00 (0.00 – 47.03)	0.00 (0.00 – 45.60)
Other costs (including travel costs)	80.40 (24.58 – 171.45)	80.40 (26.09 – 201.62)
Total	€ 1384.84 (806.48 – 2385.51) US$ 1995.00 (1161.82 – 3436.57)	€ 843.56 (416.40 – 1994.03) US$ 1215.23 (599.87 – 2872.60)

During the first year of follow-up		
	Adenoidectomy (n = 54) Median € (IQR)	**Watchful waiting (n = 57) Median € (IQR)**
Surgery and hospitalization	336.54 (336.54 – 336.54)	0.00 (0.00 – 336.54)
Prescribed medication	6.47 (0.07 – 16.48)	3.36 (0.00 – 13.23)
Over-the-counter drugs and CAM	5.27 (0.97 – 18.17)	8.81 (1.19 – 29.48)
Consultations otorhinolaryngologist	61.40 (0.00 – 69.08)	0.00 (0.00 – 61.40)
Consultation other specialist	0.00 (0.00 – 57.62)	0.00 (0.00 – 47.30)
Consultation family physician	31.38 (0.00 – 62.47)	31.38 (5.30 – 93.95)
Absence of day-care	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)
Parental leave of absence	287.92 (0.00 – 863.76)	0.00 (0.00 – 431.88)
Babysitting	0.00 (0.00 – 45.60)	0.00 (0.00 – 17.10)
Other costs (including travel costs)	47.66 (19.17 – 81.50)	41.58 (7.80 – 121.98)
Total	€ 959.24 (632.12 – 1657.80) US$ 1381.88 (910.63 – 2388.23)	€ 505.40 (104.68 – 1193.66) US$ 728.08 (150.80 – 1719.59)

Abbreviations:
CAM: complementary and alternative medication
IQR: interquartile range
Exchange rate 31-12-2009 1 € = 1.4406 US$

Table 3. Sensitivity analyses on total costs in € and US$ during two year of follow-up.

	Adenoidectomy Median (IQR)	Watchful waiting Median (IQR)	Difference in median costs
Excluding crossovers	€ 1384.84 (806.48 – 2385.51)	€ 606.61 (136.47 – 1478.55)	€ 778.23
	US$ 1995.00 (1161.79 – 3436.57)	US$ 873.88 (196.60 – 2130.00)	US$ 1121.12
Analysing crossovers as treated	€ 1383.54 (756.97 – 2276.46)	€ 606.61 (136.47 – 1478.55)	€ 776.93
	US$ 1993.13 (1090.49 – 3279.47)	US$ 873.88(196.60 – 2130.00)	US$ 1119.25

Abbreviations:
IQR: interquartile range
Exchange rate 31-12-2009 1 € = 1.4406 US$

Discussion

This study shows that in children selected for adenoidectomy for recurrent URTIs, an immediate surgical strategy costs €541 (US $799) more than an initial watchful waiting strategy during 2 years of follow-up. This is an increase of 64%, whereas immediate surgery confers no clinical benefit over an initial watchful waiting strategy. The extra costs are related to surgery and visits to the otorhinolaryngologist. Other costs did not differ significantly between the groups.

The results of our study are in agreement with 3 other studies that reported higher costs for surgical strategies in children with URTIs, ie, adenotonsillectomy in children with mild to moderate throat infections[9] and tympanostomy tubes in children with otitis media with effusion.[16,17] To our knowledge, this is the first economic evaluation of adenoidectomy in children with recurrent URTIs.

The major strength of our study is that we measured costs prospectively alongside a randomized controlled trial and used a societal perspective that included all relevant costs. Some potential limitations should also be taken into consideration. First, 23 children (40%) from the initial watchful waiting group underwent adenoidectomy during the course of the trial. We performed an intention to treat analysis as our primary analysis because our aim was to compare clinical *strategies* and not to compare adenoidectomy vs no adenoidectomy per se. To investigate whether the crossovers influenced our results, we performed 2 sensitivity analyses: a per protocol and an as treated analysis. It should be noted that the sensitivity analyses could suffer from confounding because the baseline comparability of prognosis achieved through randomization, which is the main strength of a randomized controlled trial, may be lost. Interestingly, the per protocol and as treated analyses did not change the clinical results, confirming the lack of benefit following adenoidectomy. However, the differences in costs were substantially higher, €778 (US $1121) and €777 (US $1119) after 1 and 2 years of follow-up, respectively. This larger negative economic effect can be explained by the fact that in the sensitivity analyses children with higher costs (mostly because of surgery) were excluded from the watchful waiting group.

Second, we originally planned this study as a cost- effectiveness study, dividing the difference in costs by the difference in effects. Because our trial showed comparable clinical effectiveness of an immediate surgical strategy and an initial watchful waiting strategy in children with recurrent URTIs, we decided to perform a cost-minimization study, comparing the costs of both strategies.
Third, for those who did not keep the diaries, we could only include the available expense information, ie, physician visits and costs for (additional) surgery. Because the loss to follow-up was very low (10%) and equally distributed over the 2 groups, we do not think that missing cost data would have changed our results.
Fourth, generalizing the results of economic evaluations to other countries might be challenging owing to differences in health care systems and prices. Although the absolute (differences in) costs might indeed not be generalizable, the ratio between the costs in the adenoidectomy and the watchful waiting group will remain applicable to other countries, ie, we expect that in other countries adenoidectomy is also approximately 1.5 times more costly than watchful waiting.
Finally, we indexed costs of surgery from a previous costing study[9] because recent cost figures could not be extracted from the current Dutch 'Diagnosis Treatment Combination' system (DBC-system) introduced in 2005.[18] This system is based on diagnostic classifications rather than on an internationally recognized therapeutic classification system. A DBC can be defined as a predefined average package of care with, in most cases, a fixed price depending on the diagnosis. By using the indexed costs from our previous costing study,[4] instead of a DBC price, our cost prices and final results are comparable to those of previous and future economic evaluations.
In conclusion, in children selected for adenoidectomy for recurrent URTIs, immediate adenoidectomy results in an increase in costs, whereas it confers no clinical benefit over an initial watchful waiting strategy.

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Chapter 9

General discussion

What this thesis adds.

Although adenoidectomy is one of the most common operations in children, evidence on its benefits in children with recurrent upper respiratory tract infections (URTI) was sparse, inconclusive and had significant risk of bias. We therefore initiated a randomised controlled trial (RCT) that showed that a surgical strategy of adenoidectomy is not (cost-) effective as compared to a watchful waiting strategy in children with recurrent URTI. The prevalence of URTI decreased over time, both in children allocated to adenoidectomy as well as in those allocated to a watchful waiting strategy, suggesting that this reflects the natural course of this condition in children rather than the effect of the operation. In contrast to a long-standing belief that adenoidectomy affects the composition of microbial flora of the nasopharynx, our RCT showed no effect of the operation on nasopharyngeal colonisation with the most common potential pathogens. Neither was colonisation associated with recurrence of URTI. These results have raised debate around various aspects of the trial, which we will discuss below.

External validity of our trial and the implications of cross overs to the other treatment arm.

Were the children participating in the trial representative of children undergoing adenoidectomy for recurrent URTI in the Netherlands and were their symptoms serious enough to warrant surgery?

We assessed the external validity of our trial by comparing demographic, disease specific and geographic characteristics of the participating children with those of the children who were eligible for the trial but did not participate for various reasons. The characteristics studied were similar in both groups and therefore the trial participants seem representative of all children selected for adenoidectomy in the Netherlands. This is discussed in more detail on page 129-133.

Whereas young children suffer from an average of 6 URTI episodes per year,[1] our trial participants had an average of 9 to 10 URTI episodes in the year before they entered the trial (parental history). During the first year of the trial children in both arms still had an average of 9 URTI episodes (prospectively monitored). Other than suffering from frequent URTI, the majority of trial participants also had a history of otitis media and sleep disordered breathing. At trial entry 57% of children in the adenoidectomy group and 59% of those in the watchful waiting group had otitis media with effusion (OME), 81% and 73% of children in these groups snored frequently or always and 26% and 27% had obstructive episodes during sleep. This suggests that the trial participants were not only more severely affected by URTI than the average child, but had other upper respiratory symptoms associated with adenoid disease as well.

Are the conclusions based on the trial valid, as 40% of children allocated to watchful waiting crossed over to the surgical arm during the trial?

We emphasise that our trial was designed as a pragmatic trial comparing two management strategies: adenoidectomy versus watchful waiting. An inherent phenomenon of all surgical trials with a non-surgical treatment arm is that some children allocated to the non-surgical

group eventually undergo surgery.[2-4] This reflects everyday practice where the symptomatology can change during follow-up and thus also the balance between the potential benefits of surgery and its potential uncertainties and risks. In some children this balance may change in favour of surgical management.
Children allocated and undergoing surgery however, cannot cross-over to the non-surgical arm and this may introduce bias. Therefore, we explored whether the children allocated to watchful waiting who underwent surgery during the course of the trial were more severely affected by URTI than those who did not undergo surgery. We found this not to be the case: baseline variables and the number of URTI episodes during the first year of follow-up were the same for these two groups. We performed two sensitivity analyses: a per protocol analysis in which we excluded the children in the watchful waiting group who went on to have surgery and an as treated analysis in which we added the children in the watchful waiting group who underwent surgery to the adenoidectomy group. Those analyses yielded similar results as the intention to treat analysis for our primary outcome—that is, URTI episodes during the total follow-up of the trial (table 1).

Table 1. Results of intention to treat, per protocol and as treated analyses for the primary outcome episodes of upper respiratory tract infections during 24 months follow-up.

	Adenoidectomy	Watchful waiting	RD (95% CI)
Intention to treat URTI episodes	7.91	7.84	0.07 (-0.70 to 0.85)
Per protocol URTI episodes	7.91	8.04	-0.13 (-1.02 to 0.77)
As treated URTI episodes	7.81	8.04	-0.23 (-1.08 to 0.62)

Future indications for adenoidectomy.

Do the results of our trial imply that indications for adenoidectomy should be revised?
The trial shows that in children selected for adenoidectomy for *recurrent upper respiratory tract infections*, a strategy of immediate surgery confers no clinical benefits over a strategy of watchful waiting. We therefore suggest to update the recommendations on the indications for adenoidectomy in the relevant Dutch guideline on diseases of the adenoid and tonsils,[5] i.e. in children with recurrent URTI adenoidectomy should not be recommended. Two other Dutch guidelines include recommendations on the use of adenoidectomy in children: 'otitis media in children in secondary care'[6] and 'obstructive sleep apnea syndrome (OSAS) in children'.[7] The results of our Cochrane review on the effectiveness of adenoidectomy in children with otitis media[8] were incorporated in the first guideline i.e. adenoidectomy is not recommended as the primary treatment in children with persistent otitis media with effusion (OME). In children who not only have OME but also have adenoid related symptoms, adjuvant adenoidectomy in combination with tympanostomy tubes may be considered. For recurrent acute otitis media (AOM), adenoidectomy is not recommended. The second guideline recommends adenotonsillectomy as the treatment of choice in children with symptoms suggesting OSAS. These recommendations are similar to those of international guidelines for the same conditions, for example those issued in the UK, US, Finland and Italy.[9-14]

Implications of the trial for everyday practice.

As a practicing ENT surgeon how can I best advise parents of children referred for recurrent URTI?

Based upon the results of our trial we would advise to wait and see. Some parents may struggle to accept this advice, in particular in the Netherlands where there is both a strong tradition of surgical treatment for URTI and belief in its benefits. Given that most children have fewer URTI episodes after adenoidectomy, both parents and physicians have high expectations of adenoidectomy as an effective treatment for recurrent URTI. Our trial shows that rather than the effect of adenoidectomy, this decrease reflects the natural course of the condition. This is best illustrated by figures 1 A and B presenting the prevalence of upper respiratory tract infection in children in the surgical arm and both arms of the trial, respectively for each follow-up week.

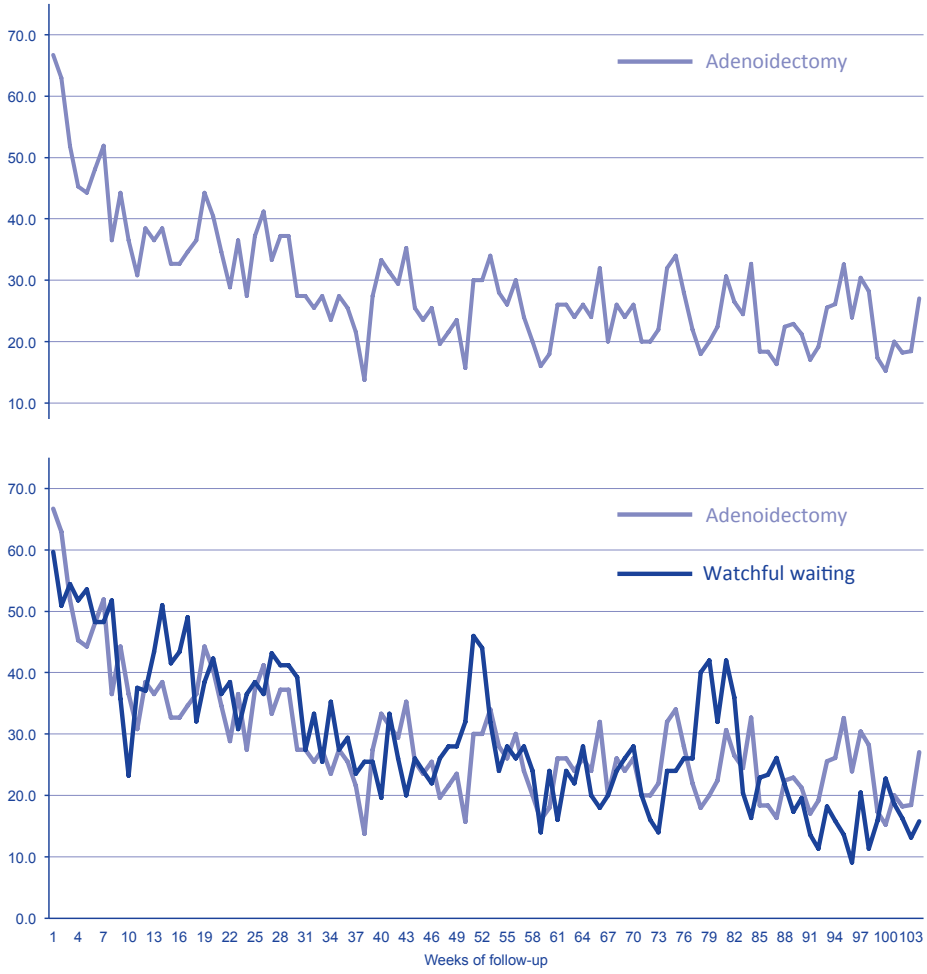

Figure 1 (A and B): Prevalence of URTI in the adenoidectomy group and in both groups per follow-up week. Light blue: adenoidectomy, dark blue: watchful waiting.

This figure may be an effective tool in discussing the pros and cons of various treatment options with the parents. Shared decision-making is an effective strategy for enhancing patient participation in this process: the physician and the patient (or in our case its parents) make a joint decision based on the best available evidence and the patients' values and preferences.[15-18] As such it can help reducing the overuse of treatment options that do not clearly benefit all patients. Hence, we would recommend that the ENT surgeon explores the beliefs and expectations of parents regarding the management of recurrent URTI and informs parents about the benefits, risks and uncertainties of each treatment option. For parents to actively participate in this shared decision-making process it is important that they are familiar with the results of our trial and therefore they should ideally be made available[19] through e-health portals, public sections of the websites of the professional societies involved in the care of these children, magazines aimed at parents of young children, and by means of patient information leaflets. The available clinical decision support system (CDSS or decision aid) www.kiesbeter.nl helps parents making an informed choice on treatment of recurrent throat infections and on otitis media. It empowers parents to 'pull' the evidence generated by clinical trials such as ours into everyday practice. We recommend to add a module on www.kiesbeter.nl on the management of recurrent URTI and the role of adenoidectomy.
Shared decision-making and balancing the pros and cons of various treatment options for recurrent URTI with the parents may take more time than the traditional decision for surgery and lead to fewer operations. Although the latter seems attractive from a health economic perspective, it may also raise issues as in the Dutch health care system insurers pay for a quantity of activities rather than for quality. This method of reimbursement may favour a surgical strategy in children with recurrent URTI, which conflicts with the evidence generated by our trial. Recently, the debate has begun on how to reimburse physicians for quality rather than quantity. It is important that all stakeholders, including physicians, patients, policy makers and the public join this debate, so that changes in the current system aimed at improving the quality of care and patient satisfaction will be widely supported and effectively implemented.

Our trial in perspective.

Are Dutch ENT surgeons frontrunners in evidence-based medicine?

This thesis follows a long tradition of high quality research into paediatric ENT infections in the Netherlands. With their GP colleagues, Dutch ENT surgeons were among the first surgical specialties to embrace the principles of evidence-based medicine and over the past decades they have contributed to surgical and medical trials in this field by recruiting their patients and providing expert advice.[2,20-27] This has built a strong evidence base for the management of children with ENT infections. In the Netherlands the Dutch ENT Society has been instrumental in the implementation of this evidence in everyday practice by initiating the development of multi-disciplinary guidelines on diseases of the adenoid and tonsils, otitis media and OSAS in children.[5-7] Other than treatment recommendations these guidelines also include recommendations for further research.
The way we understand and treat diseases is changing rapidly. As we move away from a one-size fits all approach, healthcare becomes more tailored to the needs and characteristics of the individual patient. Personalised healthcare is a new approach to understanding, classifying,

treating and preventing disease based on information of the individual patient, its disease and environmental characteristics. Individual patient data meta-analysis is one of the available methods that goes beyond the 'grand mean' towards individualised medicine and allows more powerful and reliable estimation of treatment effects across subgroups of patients.
Members of our research group have performed three IPD meta-analyses in the field of ENT diseases in children; the first was on the effectiveness of antibiotics in children with AOM. Individual studies found no benefit of antibiotic treatment in children with AOM at group level and their numbers were too small to identify subgroups. IPD meta-analysis pooling the original datasets of these studies showed that antibiotics were most beneficial in children younger than two years old with bilateral AOM, and in children presenting with acute otorrhoea.[28] The second IPD meta-analysis on the effectiveness of tympanostomy tubes in children with OME identified that typanostomy tubes might be more effective in children attending day care and in older children with a hearing loss of 25dB or greater persisting for at least twelve weeks.[29] Most recently, our IPD meta-analysis on the effectiveness of (adjuvant) adenoidectomy in children with otitis media showed that children with recurrent AOM under two years of age, and children four years and older with persistent OME are most likely to benefit from (adjuvant) adenoidectomy. These IPD meta-analyses thus fine-tune treatment indications.[30]
Evidently, these IPD meta-analyses relied on the fact that numerous high quality RCTs are available in the field of ENT. This contrasts with other surgical fields, for example that of robotic surgery for which too few RCTs are available. ENT surgeons should be acknowledged for initiating and contributing to clinical trials that have provided the necessary evidence to further individualise healthcare.

Recommendations for future research.

Our results provide important new evidence regarding the role of adenoidectomy in children with recurrent URTI. Several challenges still need to be addressed in future research.

First, it is important to properly phenotype children with URTI. When physicians are faced with young children with symptoms of URTI, for example nasal discharge, nasal obstruction, coughs and wheeze they choose one diagnosis from a conglomeration of symptoms which can range from URTI, pharyngitis, tonsillitis, croup, bronchitis, wheezy bronchitis, asthma and allergy. This choice affects how a similar set of symptoms are interpreted, including the probable cause, its course, treatment decisions, and information given to parents. This can introduce practice variation and hampers the reliable estimation of disease burden and its impact on health and health economics.[31] Therefore there is an urgent need for a definition of clear phenotypes within this overall conglomeration of symptoms. Cohort studies can aid us in identifying which (combination of) symptoms are more frequent and more severe for each diagnosis, and help identify which symptoms are most influential for the physician when choosing a certain diagnosis.
Second, we need to know why certain children are more susceptible to *recurrent* URTI than others. So far, most cohort studies on ENT infections have only studied univariate associations or a limited set of factors that may put children at risk for recurrent ENT infections. Many patient specific and environmental factors have been identified,[11,32-37]

however, it is seldom an individual factor or a small set of factors that lead to recurrent disease. In addition there may also be currently unknown risk factors. These factors frequently occur in combination with each other. This is illustrated in the following figure for otitis media.

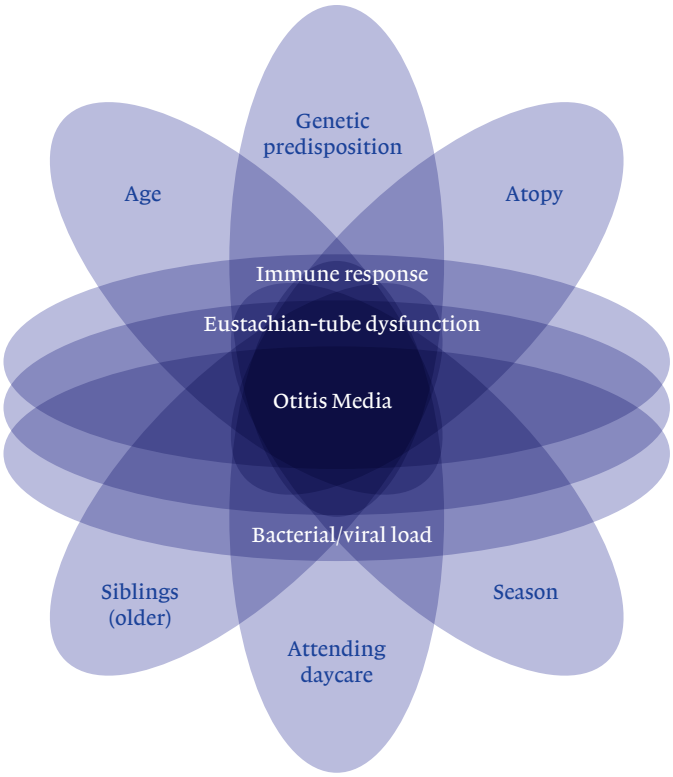

Figure 3. Most important factors involved in pathogenesis of OM. Copied with permission of the author. *Rovers M, Schilder A, Zielhuis G, Rosenfeld R. Otitis media. Lancet 1004;363:465-73 Adapted from: Bluestone CD. Pathogenesis of otitis media: role of Eustachian tube. Pediatr Infect Dis J 1996; 15: 281–91.*

The combination of these known factors differs in each individual child. The question is therefore which combination of factors has a stronger association with suffering from *recurrent* URTI. To answer this question further cohort studies are needed, such as the Leidsche Rijn cohort for which the Utrecht Airway Portal has been set up, Generation-R in Rotterdam or the UK 2014 birth cohort Life study. The first two cohorts have already generated some new evidence on these topics, for example on risk factors for nasopharyngeal bacterial colonisation, asthma, and allergic symptoms.[38-50] These cohort studies will enable us to develop comprehensive and validated prognostic models that discriminate children with a favourable transient course from those children that go on to suffer from chronic or recurrent symptoms. Further study is also needed to better understand the interplay between bacterial and viral carriage in the nasopharynx, including which factors make symptomless carriage of potential pathogens progress to disease.

Third, we need to develop specific management strategies based on the prognostic models developed in the cohort studies. These management strategies should be aimed at those combinations of risk factors that can be altered in children with a high risk of suffering from *recurrent* URTI. A number of the factors that have been associated with an increased risk of suffering from ENT infections cannot be altered such as season, gender or genetic predisposition for example. However, potential factors that can be influenced such as nasopharyngeal colonisation deserve further study. For example, by developing vaccines or pro-biotics that influence the microbiome of the nasopharynx. The aim is to influence the bacterial and viral colonisation of the nasopharynx in such a way that children are either less frequently carrier of potential pathogenic bacteria, or that carriage less frequently leads to disease. Subsequently, we need to study the (cost-) effectiveness of these new management strategies, i.e. by initiating intervention studies aimed at secondary prevention in a high risk population.

Patient and public participation should be actively stimulated in an early phase, as they can play an important role in advising researchers, for example on which subjects have their priority. Their participation can also be valuable for the design of the study, outcomes (Patient Reported Outcomes), recruitment of patients, and implementation of the results (the 'patient pull').

Fourth, since children with special needs such as Down's syndrome or cleft palate have been excluded in all existing systematic reviews and randomised controlled trials, we also need to study the most clinical and cost-effective treatment strategies for children in these special groups.

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Summary

Adenoidectomy is one of the most frequent operations in children. In 2009 in the Netherlands 15 179 children (16.3 per 1000) aged 0-4 and 5573 children (5.5 per 1000) aged 5-9 underwent adenoidectomy. Indications include recurrent upper respiratory tract infections (URTI), otitis media, and upper airway obstruction. Remarkably, the adenoidectomy rate is more than three times higher in the Netherlands than in the US, and the proportion of children operated on for infections varies fivefold across these two countries, suggesting that there is no international consensus as to which children benefit from the operation. Evidence for the effectiveness of adenoidectomy in children with recurrent URTI appeared to be scarce and (inter-) nationally accepted guidelines were lacking. In other words, practice was experience-based rather than evidence-based. The overall aim of this thesis consequently was to study the clinical and cost-effectiveness of adenoidectomy in children with recurrent URTI.

First, we performed an audit of current indications for adenoidectomy used by Dutch ENT surgeons, which is presented in **chapter 2.** During 6 months, ENT surgeons in 1 academic and 7 general hospitals in the Netherlands filled out a questionnaire for children younger than 15 years of age they selected for adenoidectomy either as a single procedure or in combination with myringotomy or tympanostomy tubes. We received questionnaires on 159 children. Their age and gender were comparable to the general population of children undergoing adenoidectomy included in the Dutch Health Care Services. Sixty (38%) of children were selected for adenoidectomy alone, 24 (15%) for adenoidectomy and myringotomy and 75 (47%) for adenoidectomy and tympanostomy tube placement. In children selected for adenoidectomy alone, recurrent URTI was the most frequent indication in 60%, followed by otitis media in 33%. In children selected for adenoidectomy in combination with myringotomy or tympanostomy tubes otitis media was the most frequent indication in 96% and 99%, followed by recurrent URTI in 88% and 59%, respectively. When there was a combination of indications the most common was recurrent URTI and otitis media in 38%. Thus, in daily Dutch ENT practice, almost two-thirds of adenoidectomies are combined with myringotomy or tympanostomy tube placement. The most common indication for adenoidectomy in combination with myringotomy or tympanostomy tubes is middle ear disease, whereas recurrent URTI is the most common indication for adenoidectomy alone.

As no complete literature overview was available on the effectiveness of adenoidectomy in children with recurrent URTI or otitis media we reviewed the available evidence for the Cochrane collaboration in c**hapters 3 and 4.** We performed an extensive literature search for randomised controlled trials comparing adenoidectomy, with or without tympanostomy tubes, versus non-surgical management or tympanostomy tubes alone in children with recurrent or chronic nasal symptoms (**chapter 3**) and in children with otitis media (**chapter 4**). We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT and additional sources for published and unpublished trials. Two authors assessed trial quality and extracted data independently.

In **chapter 3** (effectiveness of adenoidectomy in children with recurrent or chronic nasal symptoms) the main outcomes were the number of episodes, days per episode and per year with nasal symptoms and the proportion of children with recurrent episodes of nasal symptoms.
Only one study included children scheduled for adenoidectomy because of recurrent or chronic nasal symptoms or middle ear disease. The numbers in this study were small (n = 76) and the quality of the study was moderate. The outcome was improvement in episodes of common colds. The risk differences were non-significant, being 2% (95% confidence interval -18% to 22%) and -11% (95% confidence interval -28% to 7%) after 12 and 24 months, respectively. Hence, in this study using a heterogeneous population no beneficial effect of adenoidectomy was found.
A second study included children with recurrent acute otitis media (n = 180). As otitis media is known to be associated with nasal symptoms, the number of days with rhinitis was studied as a secondary outcome measure. The risk difference was non-significant, being -4 days (95% CI -13 to 7 days), i.e. no beneficial effect of adenoidectomy was found for rhinitis in children with otitis media.
We concluded that the current evidence (in 2009) regarding the effect of adenoidectomy on recurrent or chronic nasal symptoms or nasal obstruction alone is sparse, inconclusive and has a significant risk of bias.

In **chapter 4** (effectiveness of adenoidectomy in children with otitis media) the primary outcome studied was the proportion of time with otitis media with effusion (OME). Secondary outcomes were mean number of episodes, mean number of days per episode and per year, and proportion of children with either acute otitis media (AOM) or OME, as well as mean hearing level. Fourteen randomised controlled trials (2712 children) studying the effectiveness of adenoidectomy in children with otitis media were evaluated. Most of these trials were too heterogeneous to pool in a meta-analysis. Loss to follow up varied from 0% to 63% after two years.
Three of these studies studying the effect of adenoidectomy in combination with a unilateral tympanostomy tube for OME could be pooled.
Adenoidectomy had a beneficial effect on the resolution of OME in the non-operated ear; risk difference 22% (95% confidence interval 12% to 32%) and 29% (95% confidence interval 19% to 39%) at 6 and 12 months, respectively. Adenoidectomy with a unilateral tympanostomy tube had a very small (< 5 dB) effect on hearing compared to a unilateral tympanostomy tube only.
The results of studies of adenoidectomy with or without myringotomy versus non-surgical treatment or myringotomy only, and those of adenoidectomy in combination with bilateral tympanostomy tubes versus bilateral tympanostomy tubes only, also showed a small beneficial effect of adenoidectomy on the resolution of the effusion. The latter results could not be pooled due to large heterogeneity of the trials.
As for AOM, none of the trials including this outcome indicate a significant beneficial effect of adenoidectomy, and they were too heterogeneous to pool in a meta-analysis.
Although our review shows a significant benefit of adenoidectomy on the resolution of middle ear effusion in children with OME, the benefit for hearing is small, thus the risks of operating should be weighed against these potential benefits.
The absence of a significant benefit of adenoidectomy on AOM suggests that routine surgery for this indication is not warranted.

The rationale for adenoidectomy in children with recurrent URTI is the longstanding belief that adenoidectomy affects the composition of microbial flora in the nasopharynx. Therefore, we reviewed the literature specifically studying the effects of adenoidectomy on nasopharyngeal flora in children aged less than 18 years (**Chapter 5**). This systematic literature search in Pubmed and Embase yielded 8 eligible studies. All studies were cohort studies and performed nasopharyngeal swabs before and after adenoidectomy in children. Most post-operative nasopharyngeal samples were taken shortly after surgery i.e. 10 days to 1 month post-operatively. In only 2 studies nasopharyngeal swabs were performed in the long-term i.e. 3 to 12 months after surgery. *Streptococcus pneumoniae* and *Haemophilus influenzae* were the most frequently detected pathogens. In the short-term carriage of these bacteria decreased after adenoidectomy in the majority of studies. In contrast, carriage of bacteria belonging to the non-pathogenic nasopharyngeal flora increased after surgery. The two studies with long-term results were inconsistent. The overall quality of the available evidence was low and no relationship with the recurrence of URTI was reported. We concluded that controlled studies were needed into the short- and long-term effect of adenoidectomy on the nasopharyngeal flora and its relationship with recurrence of URTI.

Chapters 6, 7 and 8 describe the results of our open, multi-center randomised controlled trial on the effectiveness of adenoidectomy in children aged 1-6 years with recurrent URTI. In total 111 children from 11 general and 2 academic hospitals selected for adenoidectomy for recurrent URTI participated in the trial. Children with an indication for tympanostomy tubes, Down's syndrome or craniofacial malformations were excluded. After informed consent was signed they were randomised to either adenoidectomy within 6 weeks, or a watchful waiting strategy. During the 24 months follow-up parents kept a symptom diary and measured their child's temperature every day with a validated tympanic thermometer. Follow-up visits took place at 3, 6, 12, 18 and 24 months. Outcome measures were: the number of URTI and otitis media episodes, quality of life, nasopharyngeal flora, and costs.

The clinical outcomes (i.e. episodes and prevalence of URTI, along with otitis media and quality of life) are presented in **chapter 6**. During the median follow-up of 24 months, there were 7.91 episodes of URTI per person year in the adenoidectomy group and 7.84 in the watchful waiting group (difference in incidence rate 0.07, 95% confidence interval −0.70 to 0.85). No relevant differences were found for days of URTI and middle ear complaints with fever in episodes and days, nor for health related quality of life. The prevalence of URTI decreased over time in both groups. Children in the adenoidectomy group had significantly more days with fever than the children in the watchful waiting group. Two children had complications related to surgery. During follow-up 23 (40%) of children allocated to the watchful waiting group underwent further surgery. To assess if this influenced our results we performed additional per protocol and as treated analyses which yielded the same outcome as our intention to treat analysis, namely that adenoidectomy has no clinical benefits over a watchful waiting strategy. We concluded that in children selected for adenoidectomy for recurrent URTI, a strategy of immediate surgery confers no clinical benefits over a strategy of initial watchful waiting.

Chapter 7 shows the results of our microbiological studies that ran in parallel to our RCT. We investigated the effects of adenoidectomy on the nasopharyngeal flora and its relation to

recurrence of URTI. Nasopharyngeal swabs were collected transnasally at baseline, 3 months and 12 months follow-up and cultured for the most common nasopharyngeal potential pathogens *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Streptococcus haemolyticus*, and gram negative rods. The prevalence of each single and multiple potential pathogens were similar in the adenoidectomy and watchful waiting group throughout follow-up. Almost half of the children were colonized with multiple potential pathogens. Colonization of each single and multiple (1 vs ≥2) potential pathogens at baseline and/or 3 months was not associated with recurrence of URTI during 12 months follow-up. Therefore adenoidectomy has no effect on nasopharyngeal colonization with the most common potential pathogens in children with recurrent URTI, and colonization is not associated with recurrence of these infections.

Chapter 8 focused on the cost effectiveness of adenoidectomy in children with recurrent URTI. A cost-minimization analysis from a societal perspective, including both direct and indirect costs, was performed comparing the costs associated with immediate adenoidectomy versus an initial watchful waiting strategy. Our main outcome was the median difference in costs during the 24 months follow-up. The median total of direct and indirect costs in the adenoidectomy group and watchful waiting group were €1385 (US $1995) and €844 (US $1216) per patient, respectively. The extra costs in the adenoidectomy group were primarily attributable to surgery and visits to the ENT surgeon. Other costs did not differ significantly between the groups. We concluded that in children selected for adenoidectomy for recurrent URTI, immediate adenoidectomy results in an increase in costs, whereas it confers no clinical benefit over an initial watchful waiting strategy.

Finally, in **chapter 9** the implications of our trial for clinical practice and recommendations for future research are discussed.
To facilitate the implementation of the results of our study in daily practice we suggest to update the recommendations on the indications for adenoidectomy in the relevant Dutch guideline on diseases of the adenoid and tonsils. In daily practice the ENT surgeon can use this guideline and the figures in this thesis to discuss the pros and cons of various treatment options with parents of children with recurrent URTI.
From our perspective future research should address the urgent need for a definition of clear phenotypes of children with upper respiratory symptoms. Cohort studies can aid us in identifying which (combination of) symptoms are more frequent and more severe in each diagnosis, and can help identify which symptoms are most influential for the physician when choosing a certain diagnosis.
Second, we suggest to investigate why certain children are more susceptible to recurrent URTI than others. It is seldom an individual factor or a small set of factors that lead to recurrent disease. Again, cohort studies can aid us in identifying which combination of factors has a stronger association with suffering from recurrent URTI so that prognostic models can be made. Further study is also needed to better understand the interplay between bacterial and viral carriage in the nasopharynx, including which factors make symptomless carriage of potential pathogens progress to disease. These prognostic models can then be used to develop specific management strategies, for example pro-biotics or vaccines. Subsequently, we advise to study the (cost-) effectiveness of these new management strategies, i.e. by initiating intervention studies aimed at secondary prevention in a high risk

population.
We suggest to actively stimulate patient and public participation in these studies in an early phase. Finally, since children with special needs such as Down's syndrome or cleft palate have been excluded in all existing systematic reviews and randomised controlled trials, we also advise to study the most clinical- and cost-effective treatment strategies for children in these special groups.

Samenvatting

Adenotomie (het knippen van de neusamandel) is één van de meest frequent uitgevoerde operaties bij kinderen; jaarlijks ondergaan in Nederland 15 179 (16.3 per 1000) kinderen van 0 tot 4 jaar en 5573 (5.5 per 1000) kinderen van 5 tot 9 jaar een adenotomie. Indicaties zijn recidiverende bovenste luchtweginfecties (BLWIs), otitis media (middenoorontsteking) en bovenste luchtwegobstructie. Opvallend is dat adenotomie in Nederland meer dan 3 maal vaker wordt uitgevoerd dan in andere westerse landen en dat adenotomie met name vanwege de indicatie recidiverende BLWIs wordt verricht. Een belangrijke reden hiervoor is het ontbreken van wetenschappelijk bewijs omtrent de effectiviteit van adenotomie bij kinderen met BLWIs. Daarom zijn wij het onderzoek gestart dat in dit proefschrift wordt beschreven met als belangrijkste vraagstelling: Wat is de klinische- en kosteneffectiviteit van adenotomie bij kinderen met recidiverende BLWIs?

Allereerst hebben wij de indicaties voor adenotomie geïnventariseerd zoals ze gehanteerd worden door Nederlandse KNO-artsen (**hoofdstuk 2**). In 2004 vulden KNO-artsen uit 1 academisch en 7 perifere ziekenhuizen gedurende een periode van 6 maanden een vragenlijst in voor alle kinderen jonger dan 15 jaar bij wie zij een indicatie voor adenotomie stelden. Wij ontvingen 159 vragenlijsten. De verdeling van leeftijd en geslacht van de kinderen in deze studie kwam overeen met de landelijke verdeling van alle kinderen die een adenotomie ondergingen. Bij 60 kinderen (38%) werd alleen adenotomie verricht, bij 24 (15%) adenotomie in combinatie met paracentese ('doorprikken' van het trommelvlies) en bij 75 (47%) adenotomie in combinatie met het plaatsen van trommelvliesbuisjes. De meest frequente indicatie voor adenotomie was recidiverende BLWI (60% van de kinderen), gevolgd door otitis media (33%). De meest frequente indicatie voor adenotomie in combinatie met paracentese of het plaatsen van trommelvliesbuisjes was otitis media (respectievelijk 96% en 99% van de kinderen), gevolgd door recidiverende BLWI (respectievelijk 88% en 59%). Bij 38% van de kinderen was er zowel sprake van recidiverende BLWI als otitis media.

In **hoofdstuk 3 en 4** hebben wij het beschikbare bewijs in de literatuur over de effectiviteit van adenotomie bij kinderen met recidiverende BLWI en bij kinderen met otitis media systematisch beschreven. We zochten in het Cochrane Ear, Nose and Throat Disorders Group Trials Register; Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; mRCT en aanvullende bronnen naar gepubliceerde en ongepubliceerde studies waarin adenotomie, al dan niet in combinatie met het plaatsen van trommelvliesbuisjes, werd vergeleken met niet opereren of alleen het plaatsen van trommelvliesbuisjes. Twee personen hebben -onafhankelijk van elkaar- de kwaliteit van de studies beoordeeld en de data geëxtraheerd.

In **hoofdstuk 3** waren de belangrijkste uitkomstmaten het aantal BLWIs, het aantal dagen met BLWI en het percentage kinderen met recidiverende BLWI. In slechts één gerandomiseerde studie waren kinderen geïncludeerd die adenotomie ondergingen in verband met recidiverende BLWI; in deze studie deden ook kinderen met middenoorklachten en obstructieve klachten mee. Het aantal deelnemers was klein (n=76) en de kwaliteit van dit onderzoek was matig. Bij zowel de kinderen in de adenotomie groep als in de controle groep nam het aantal BLWIs af; ook oorklachten en obstructieve klachten verbeterden Het risico-verschil tussen beide groepen was echter niet statistisch significant; 2% (95% betrouwbaarheids-interval -18% tot 22%) en -11% (95% BI -28% tot 7%) na respectievelijk 12 en 24 maanden.

Een tweede gerandomiseerde studie includeerde 180 kinderen met recidiverende otitis media acuta (OMA, acute middenoorontsteking). Omdat OMA vaak gepaard gaat met symptomen van een BLWI werden ook het aantal dagen met neusverkoudheidklachten als secundaire uitkomstmaat gemeten. Het risicoverschil tussen de kinderen die een adenotomie ondergingen en de controlegroep was niet statistisch significant; 4 dagen (95% BI -13 tot 7 dagen). Wij concludeerden daarom in 2009 dat het wetenschappelijk bewijs ten aanzien van de effectiviteit van adenotomie bij kinderen met recidiverende BLWI niet eenduidig was en een hoog risico op bias (vertekening) had.

De primaire uitkomstmaat in **hoofdstuk 4** was de proportie van de tijd dat een kind otitis media met effusie (OME; vocht achter het trommelvlies) had. Secundaire uitkomstmaten waren het aantal episoden en dagen met OMA of OME en het percentage kinderen met OMA of OME. Daarnaast analyseerden wij de gemiddelde gehoordrempels.
Veertien gerandomiseerde studies (2712 kinderen) werden geïncludeerd in dit overzicht. De meeste studies waren te heterogeen om een meta-analyse uit te kunnen voeren. Drie studies die het effect van adenotomie in combinatie met een trommelvliesbuisje in één van beide oren bestudeerden konden wel gepoold worden. Adenotomie had een gunstig effect op de resolutie (verdwijnen) van OME in het oor zonder trommelvliesbuisje na 6 en 12 maanden (risicoverschil respectievelijk 22% (95% BI 12% tot 32%) en 29% (95% BI 19% tot 39%; n=3 studies). Het effect op het gehoor was in deze drie studies echter klein (< 5 dB).
De studies die adenotomie met of zonder paracentese vergeleken met een niet-chirurgisch beleid of paracentese en de studies die adenotomie in combinatie met een trommelvliesbuisje in beide oren vergeleken met trommelvliesbuisjes, lieten eveneens een klein maar gunstig effect zien op de resolutie van OME.
De studies die OMA als uitkomstmaat bestudeerden lieten geen gunstig effect van adenotomie op het recidiveren van OMA zien.
Wij concludeerden dat adenotomie een gunstig effect heeft op de *resolutie* van OME, maar omdat de vertaling daarvan naar het gehoor beperkt is, moeten de nadelen van de ingreep goed worden afgewogen tegen de voordelen. Omdat adenotomie geen gunstig effect lijkt te hebben bij kinderen met recidiverende OMA wordt het bij deze kinderen niet aangeraden.

In **hoofdstuk 5** hebben wij de literatuur bestudeerd naar het effect van adenotomie op het dragerschap van bacteriën in de nasofarynx (neus-keelholte) bij kinderen. Onze systematische zoekstrategie in Pubmed en Embase leverde 8 cohort studies op waarin een nasofarynxkweek was afgenomen vóór en na adenotomie. De postoperatieve kweken werden overwegend tussen 10 dagen en 1 maand na de ingreep afgenomen. In 2 studies werden ook kweken tussen 3 en 12 maanden na de ingreep afgenomen. *Streptococcus pneumoniae* en *Haemophilus influenzae* waren de meest frequent voorkomende potentieel pathogene (ziekteverwekkende) bacteriën in de nasofarynx voor adenotomie. In bijna alle studies nam het nasofaryngeaal dragerschap van de potentieel pathogene bacteriën kort na adenotomie af en nam dat van niet pathogene bacteriën juist toe. De resultaten van de 2 studies met lange termijn resultaten waren tegenstrijdig. De kwaliteit van het beschikbare bewijs was matig en de relatie met het recidiveren van BLWI werd niet bestudeerd. Wij concludeerden daarom dat meer onderzoek nodig is naar zowel de korte als lange termijn effecten van adenotomie op het nasofaryngeaal dragerschap van bacteriën, en naar de relatie van dragerschap met het recidiveren van BLWI.

In **hoofdstukken 6, 7 en 8** beschrijven wij de resultaten van onze open, multi-center gerandomiseerde studie naar de effectiviteit van adenotomie bij kinderen van 1 tot en met 6 jaar oud met recidiverende BLWIs. In totaal deden 111 kinderen mee die voor het onderzoek werden aangemeld door KNO-artsen uit 11 perifere en 2 academische ziekenhuizen. Kinderen met een indicatie voor trommelvliesbuisjes, het syndroom van Down, of craniofaciale aandoeningen werden uitgesloten van deelname. Nadat de ouders formeel toestemming hadden gegeven voor deelname, werden de kinderen gerandomiseerd voor adenotomie binnen 6 weken of een afwachtend beleid. De ouders hielden bovenste luchtweg symptomen bij in een dagboek en maten dagelijks de temperatuur van hun kind. De onderzoeksarts bezocht de deelnemers na 3, 6, 12, 18 en 24 maanden thuis om de gegevens te verzamelen. De uitkomsten waren het aantal BLWIs, otitis media episoden, kwaliteit van leven, kosten en nasofaryngeale bacteriële flora.

In **hoofdstuk 6** presenteren wij de klinische uitkomsten. De kinderen in de adenotomie groep hadden 7.91 BLWI episoden per persoonsjaar en de kinderen bij wie een afwachtend beleid werd gevoerd 7.84 BLWI episodes per persoonsjaar (incidentieverschil 0.07, 95% BI −0.70 tot 0.85). De prevalentie van BLWI nam in beide groepen met verloop van de tijd in gelijke mate af. Ook voor wat betreft de andere uitkomstmaten, het aantal dagen met BLWI, otitis media en de kwaliteit van leven, vonden we geen relevante verschillen tussen de groepen. Kinderen in de adenotomie groep hadden meer dagen koorts dan de kinderen in de afwachtend beleid groep. Twee kinderen hadden een complicatie ten gevolge van de ingreep. Gedurende de 2 jaar follow-up ondergingen 10 (19%) van de kinderen in de adenotomie groep nogmaals een KNO-operatie en 23 (40%) in de afwachtend beleid groep alsnog een KNO-operatie.
Om na te gaan of dit van invloed was op onze resultaten hebben wij twee aanvullende sensitiviteitsanalyses uitgevoerd, de zogenoemde 'per protocol' analyse waarin de kinderen in de afwachtend beleid groep die alsnog een operatie ondergingen werden weggelaten uit de analyse en de 'as treated' analyse waarin de kinderen in de afwachtend beleid groep die alsnog een operatie ondergingen werden geanalyseerd in de adenotomie groep. Beide analyses toonden dezelfde resultaten als onze primaire 'intention to treat' analyse, namelijk dat er geen verschil was in het aantal BLWIs tussen de adenotomie en de afwachtend beleid groep. Op basis van deze studie concluderen wij dat adenotomie geen klinisch voordeel biedt boven een afwachtend beleid bij kinderen met recidiverende BLWIs.

In **hoofdstuk 7** beschrijven wij de resultaten van het onderzoek naar de effecten van adenotomie op de bacteriële flora in de nasofarynx, en de relatie tussen dragerschap van bacteriën en het recidiveren van BLWIs. Een nasofarynxkweek werd afgenomen bij inclusie en na 3 en 12 maanden. Wij onderzochten of daarin de meest belangrijkste potentieel pathogene bacteriën *Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus haemolyticus,* en gram negatieve staven aanwezig waren. Op elk tijdstip bleek de prevalentie van elk van deze bacteriën afzonderlijk evenals die van combinaties van deze bacteriën in de nasofarynx niet te verschillen tussen kinderen in de adenotomie en in de afwachtend beleid groep. Ongeveer de helft van de kinderen was drager van meerdere bacteriën. Het nasofaryngeaal dragerschap van deze bacteriën ten tijde van de inclusie en/of na 3 maanden was niet gerelateerd aan het aantal BWLIs gedurende 12 maanden follow-up. Adenotomie lijkt daarmee geen invloed te hebben op het dragerschap

van de meest voorkomende potentieel ziekteverwekkende bacteriën in de nasofarynx, en dit dragerschap lijkt niet gerelateerd aan het terugkeren van BLWIs. Deze bevindingen zijn niet in overeenstemming met de resultaten van ons literatuuronderzoek dat wij in hoofdstuk 5 beschrijven. Mogelijk wordt dit veroorzaakt door de methodologische beperkingen van de andere studies, zoals het ontbreken van een controle groep, de kleine patiëntenaantallen, en het hoge percentage uitval tijdens follow-up. Ook was, in tegenstelling tot onze studie, het tijdstip van kweken bij de eerdere studies zeer kort na de ingreep, waardoor het lastig kan zijn effecten op dragerschap voldoende te analyseren.

In **hoofdstuk 8** beschrijven wij de kosteneffectiviteit van adenotomie bij kinderen met recidiverende BLWI en vergelijken de direct en indirect gemaakte kosten in beide groepen. De totale kosten per patiënt in de adenotomie en de afwachtend beleid groep waren respectievelijk €1385 (US $1995) en €844 (US $1216). De hogere kosten in de adenotomie groep zijn voornamelijk het gevolg van de kosten van de operatie en van controlebezoeken aan de KNO-arts. Andere kosten waren in beide groepen gelijk. Wij concludeerden dat bij kinderen met recidiverende BLWIs adenotomie leidt tot hogere kosten terwijl het geen klinisch voordeel biedt boven een afwachtend beleid.

Het proefschrift eindigt met een beschouwing en enkele adviezen voor toekomstig onderzoek (**hoofdstuk 9**). Om de resultaten van dit onderzoek gemakkelijk toe te kunnen passen in de dagelijkse praktijk, stellen wij voor om onze bevindingen op te nemen in de Nederlandse richtlijn “Ziekten van Adenoïd en Tonsillen in de Tweede lijn” (de ZATT-richtlijn). KNO-artsen kunnen dan de ZATT-richtlijn en de grafieken uit dit proefschrift gebruiken om ouders in de spreekkamer te informeren, zodat zij in goed overleg de beste behandeling voor het kind kunnen kiezen.
Daarnaast pleiten wij voor nader onderzoek naar bovenste luchtwegklachten bij kinderen. Ten eerste is er behoefte aan een betere classificatie van kinderen met klachten van de bovenste luchtwegen. Door middel van cohort onderzoeken kan geanalyseerd worden welke symptomen het meest bijdragend zijn voor het stellen van een diagnose en hoe classificaties daarmee kunnen worden verbeterd. Tevens adviseren wij onderzoek te verrichten naar factoren die bijdragen aan het *recidiveren* van BLWIs. Hierbij dienen (combinaties van) meerdere factoren in ogenschouw te worden genomen omdat er zelden slechts één oorzaak is aan te wijzen voor het recidiveren van BLWIs. Ook hiertoe kunnen cohort onderzoeken bijdragend zijn. Verder is het buitengewoon interessant om te evalueren hoe dragerschap van virussen en van potentieel pathogene bacteriën in de nasofarynx elkaar beïnvloeden en hoe dragerschap over gaat in een BLWI.
Wanneer bekend is welke (combinaties van) factoren een belangrijke rol spelen in het ontstaan van recidiverende BLWIs kunnen daarvoor specifieke behandelingen worden ontwikkeld, zoals bijvoorbeeld pro-biotica of vaccinaties.
Daarnaast worden kinderen met het syndroom van Down of craniofaciale aandoeningen vaak uitgesloten van gerandomiseerd onderzoek. Ook voor hen is onderzoek naar de klinische- en kosteneffectiviteit van de behandeling van bovenste luchtwegklachten noodzakelijk. Tot slot adviseren wij om ouders van kinderen met recidiverende BLWIs in een vroeg stadium bij deze toekomstige onderzoeken te betrekken.

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Curriculum Vitae

Maaike van den Aardweg was born on 20 June 1980 in Leiden, the Netherlands. She lived in Oxford, United Kingdom, from 1984 until 1991. Between 1992 and 2000 she followed the bilingual VWO secondary education programme at the O.S.G. Wolfert van Borselen School in Rotterdam, the Netherlands. She passed the International Baccalaureate English A2 higher level, the VWO exam (comparable to A-levels) and the IGCSE Art and Design exam. During this period she also represented the Netherlands at the final of the "International Public Speaking Competition" in London (1996).

From 2000 until 2006 she studied medicine at Utrecht University, the Netherlands. She completed her internship on ear, nose, throat (ENT) surgery at the Radcliff Infirmary (University of Oxford), United Kingdom, and her internship on general surgery in Hastings, New Zealand. To ensure her training was fully comprehensive she undertook an internship on ENT anatomy at the anatomy department of the University Medical Center Utrecht as well as an additional clinical internship on ENT surgery at the Radboud University Medical Center, Nijmegen, the Netherlands. She performed her research internship under the supervision of Prof. dr. A.G.M. Schilder at the ENT department of the Wilhelmina Children's Hospital, University Medical Center Utrecht. She passed her final medical studies examinations in 2006.

Following this, she started the Ph.D. research that led to this thesis under the supervision of Prof. dr. A.G.M. Schilder and Prof. dr. M.M. Rovers. In 2012 she won the 2nd prize for best junior presentation at the 11th International Congress of the European Society of Pediatric Otorhinolaryngology (ESPO) in Amsterdam. Parallel to her Ph.D. research, she became a resident at the ENT department of the University Medical Center Utrecht in February 2010 (supervisor: Prof. dr. W. Grolman). During her residency she also worked at the St. Antonius Hospital, Nieuwegein (supervisor: Dr. M. Copper) and Gelre Hospital, Apeldoorn (supervisor: Dr. P.P.G. van Benthem).

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