Adenotonsillectomy in Children; Facts and Figures

Emma Henriëtte van den Akker

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Adenotonsillectomy in Children; Facts and Figures

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(met een samenvatting in het Nederlands)

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Emma Henriëtte van den Akker

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Stellingen behorende bij het proefschrift

Adenotonsillectomy in Children;

Facts and Figures

1. Het grote aantal (adeno)tonsillectomieën bij kinderen staat in schril contrast met het wetenschappelijk bewijs voor de effectiviteit van deze ingreep *(dit proefschrift)*.

2. De afname van het aantal (adeno)tonsillectomieën op kinderleeftijd heeft niet geleid tot een evenredige toename van de ingreep bij adolescenten *(dit proefschrift)*.

3. Mede door het ontbreken van duidelijke richtlijnen omtrent de indicaties voor adenotonsillectomie, hanteren Nederlandse artsen in de praktijk meestal minder stringente indicaties dan frequente keelontstekingen of obstructief slaap apnoe syndroom *(dit proefschrift)*.

4. Gezien de beperkte klinische effectiviteit van adenotonsillectomie bij kinderen met milde klachten van recidiverende keelontstekingen of hypertrofie van adenoid en tonsillen, zou bij deze kinderen vaker een niet-chirurgisch beleid overwogen moeten worden *(dit proefschrift)*.

5. Adenotonsillectomie verstoort de ontwikkeling van het humorale immuunsysteem bij kinderen niet *(dit proefschrift)*.

6. Bij een (verhoudingsgewijs) lage inclusie van deelnemers aan een trial, moet niet meteen aan de generaliseerbaarheid van de resultaten getwijfeld worden (*o.a. dit proefschrift*).

7. Het accidenteel doornemen van de chorda tympani bij middenoorchirurgie, leidt slechts bij één derde van de patiënten tot (tijdelijke) klachten van smaakverlies of -verandering.

8. Migraine kan tot hersenschade leiden (*JAMA 2004;291:427-34*).

9. Het uitsterven van het kruid Silphium in de oudheid is een aanwijzing voor de effectiviteit van dit kruid als abortivum (*J.M. Riddle 1992*).

10. Voor een laagste prijs garantie moet je niet op de 'zorgboulevard' zijn.

11. Twee promoties op één kussen, daar staat de computer tussen.

Jet van den Akker
28 september 2004

Voor mijn ouders, Raphaël en Tijmen

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introduction

Background

Tonsillectomy is one of the oldest surgical procedures. The Roman surgeon Celsus published the first report of a tonsillectomy in 30 AD, describing the blunt removal of the tonsils by use of the finger or, where this was not possible, tonsils being picked up with a hook and excised with a scalpel.[1] But it was only in the eighteenth century that tonsillectomies came to be performed on a regular basis. Since then the popularity of this procedure has grown to make it one of the most common operations in children. In the 1920s surgery of tonsils and adenoids accounted for almost one third of all surgical procedures.[2,3] At that time the procedure was considered "a public health measure" to avoid complications of throat infections by ß-haemolytic streptococcus, such as glomerulonephritis, endocarditis and arthritis.[4,5] As antibiotics became available to prevent such complications and as general health improved, indications became stricter. As a result, the number of tonsillectomies decreased considerably in the 1960s and 1970s.[6-9] In spite of this decrease, tonsillectomy (usually combined with adenoidectomy [T&Ads]) was in 2002 still among the 5 most common surgical procedures in children (n=28,433) in The Netherlands, together with grommet insertion (n=35,501), adenoidectomy as a single procedure (n=24,450), circumcision (n=13,295) and inguinal hernia repair (n=4,696).[10]

It is known that surgical rates of T&Ads have not only varied over time, but also across and within countries.[6,8,11,12] This variation can partly be explained by cultural differences such as a preference for medical or surgical therapy for recurrent upper respiratory infections,[13-15] but the lack of (inter)nationally accepted guidelines on indications for adenotonsillectomy also plays an important role. For example, recurrent tonsillitis is considered one of the most important indications for surgery,[16-18] even though there is no consensus as to how "recurrent" should be defined. The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)[16] quantifies 3 or more throat infections per year as "recurrent" and therefore an adequate indication for surgery, whereas the Scottish Intercollegiate Guidelines Network (SIGN)[17] and the Royal College of Pediatrics and Child Health (RCPCH) in Great Britain consider 5 throat infections per year an indication for surgery. An increasingly important indication for T&Ads is sleep-disordered breathing and OSA.[13,19] However, consensus about its definition has not been reached and no clinically available gold standard for its diagnosis exists.[20] Due to the absence of clinical guidelines, rather ill-defined criteria for surgery such as failure to thrive, poor general health and size of tonsils, are used.[21-24] For The Netherlands, it is not known which indications doctors consider important in their decision to list a child for (adeno)tonsillectomy.

The main reason for the lack of generally accepted guidelines is the paucity of scientific evidence for the benefit of T&Ads in children. In 1998 two systematic reviews were published on the effectiveness of (adeno)tonsillectomy (T±Ads) for recurrent throat infections in children.[25,26] Marshall[25] summarised the results of 5 randomised trials[27-31] and concluded that in children severely affected by recurrent throat infections tonsillectomy prevents 2 to 3 throat infections in the following 3 years. In the second review, by the Cochrane group,[26] very stringent criteria for studies to be included in a meta-analysis were used. Only the study by Paradise et al.[31] met these criteria. In this trial, including children with frequent and severe recurrent throat infections (7 or more in the preceding year, or 5 or more in each of the two preceding years, or 3 or more in each of the three preceding years)[31] children in the T±Ads group experienced 2 fewer throat infections in the first year of follow-up and 1 less in the second year as compared to the non-surgical group. In the third year this reduction was smaller and not statistically significant. The natural course of throat infections was found to be favourable, since in each follow-up year most children in the non-surgical group had fewer than 3 throat infections and most of these episodes were mild. The drawback of this trial is that it was conducted in a selected population of children, meeting very strict entry criteria. Consequently, its results are not applicable to the majority of children indicated for T&Ads for milder symptoms of throat infections, or other indications such as recurrent upper respiratory infections or adenotonsillar hypertrophy. For these children, no data regarding the effectiveness of T±Ads are available and so the existing medical literature offers the practising physician little support in deciding which children, might benefit from T±Ads. Therefore, a pragmatic trial on the effectiveness of T&Ads in children indicated for this operation in daily practice is urgently needed.

In the trials and systematic reviews on the effectiveness of T&Ads published so far, investigators have focussed on throat infections and upper respiratory infections as the main outcome measure.[25-31] However, a reduction in number of infections is not the only desired effect of T&Ads; a reduction of sore-throat-related absence from school and an improvement in quality of life are probably equally important to the patient and the practising doctor. Furthermore, in case of reported limited reductions in throat infections following T&Ads,[27-31] assessment of quality of life might clarify why parental and doctor's satisfaction with the procedure is generally high.[32,33] Therefore, health-related quality of life measurements, reflecting the experiences of children and their family with respect to the impact of the child's illness on daily life, need to be included in future trials. In addition, in previous trials, throat infections were documented subjectively, since both parents and doctors knew whether the child had been treated surgically or not. It is likely that in the non-

surgical group, episodes of throat infection or upper respiratory infections were documented more meticulously than in the surgical group. Such information bias artificially increases the effectiveness of the procedure. To avoid such bias, more objective outcome parameters, such as body temperature measured with a thermometer that electronically stores data, are needed.

Traditionally, there has been concern about the effects of adenotonsillectomy on the humoral immune system, especially in young children.[34] Tonsils and adenoids are part of Waldeyer's ring and are important elements in the defence against airborne and alimentary organisms. It has been suggested that removal of such important tissue could result in a depletion of serum immunoglobulins and therefore an increased susceptibility to upper respiratory infections.[35-37] A decline in immunoglobulin levels following adenotonsillectomy has indeed been reported,[38-41] but the question whether such a decline results in an –undesired– higher susceptibility for upper respiratory infections or whether it reflects a –desired– reduction in antigenic stimuli, has not yet been answered satisfactorily. To substantiate or repudiate the suggestion that adenotonsillectomy negatively influences the immune system, it is necessary to measure immunoglobulin levels serially in large controlled studies and relate these levels to the occurrence of upper respiratory infections.

Objective

The first objectives of the studies presented in this thesis are to review the available evidence on the benefits of T&Ads in children and to provide insight into current national and international T&Ads trends and the indications currently used for this operation in The Netherlands. The main goal of this thesis is to establish the effectiveness of adeno-tonsillectomy in children undergoing this procedure according to current medical practice. Apart from the effect on throat infections, the effects on fever episodes, upper respiratory infections, humoral immune system, and health-related quality of life will be studied.

Outline of the thesis

In **Chapter 1** a systematic review of randomised trials and controlled, non-randomised studies on the effectiveness of (adeno)tonsillectomy in children published thus far, is presented. Clinical outcomes include sore throat episodes, days of sore-throat-associated school absence and upper respiratory infections.

Recent surgical rates of tonsillectomy, whether or not combined with adenoidectomy (T±Ads) in children and adolescents across the United States, Canada, Australia and several countries

of the European Union, are presented in **Chapter 2**. In addition, trends in paediatric and adolescent T±Ad rates in The Netherlands and in England over recent decades are presented. In **Chapter 3**, the results of an inventory of current indications for T±Ads in children as practised by Dutch otolaryngologists and general practitioners are presented.
The results of our trial on the effectiveness of adenotonsillectomy in children are presented in **Chapter 4**. During 2 years, 95 otolaryngologists from 24 hospitals co-operated to include 300 children aged 2 to 8 years indicated for T&Ads according to current medical practice. Outcome measures include fever episodes, throat infections, upper respiratory infections and health-related quality of life.
To assess the generalisability of our trial results, we studied the representativeness of children included in this trial with respect to the relevant patient domain (i.e. children currently undergoing adenotonsillectomy in The Netherlands for relatively mild symptoms). We compared demographic and disease-specific characteristics of randomised children with those of eligible but non-randomised children **(Chapter 5)**.
To establish whether children with tonsillar symptoms differ immunologically from healthy children, baseline immunoglobulin levels of our trial population were compared to age-related normal values **(Chapter 6)**. To answer the questions whether serum immunoglobulin levels decrease following T&Ads and, if so, whether this results in an increased susceptibility for upper respiratory infections, we studied changes in immunoglobulin levels during 1 year follow-up in children randomised to the T&Ads or watchful waiting (WW) group and related them to the occurrence of throat infections and upper respiratory infections **(Chapter 7)**.

Finally, implications of the results of the NATAN trial (Nederlands Adenotonsillectomy project; Tonsillectomy and Adenoidectomy in the Netherlands) to the practising otolaryngologists and general practitioners and recommendations for further research are discussed in the **Summary, Discussion and Future Perspectives.**

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chapter 1 Adenotonsillectomy for upper respiratory infections. Evidence-based?

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Abstract

Objectives | Despite high rates of (adeno)tonsillectomy for upper respiratory infections in western countries, the medical literature seems to offers the physician little support in deciding which child might benefit from the operation.

Methods | A literature search was performed to identify randomised trials and non-randomised controlled studies into the effectiveness of tonsillectomy with or without adenoidectomy in children. For the outcomes sore throat episodes, sore throat associated school absence and upper respiratory infections, pooled estimates of the incidence rate ratios and rate differences with 95% confidence intervals were calculated, assuming a Poisson distribution.

Results | Six randomised trials and 7 non-randomised controlled studies on the effectiveness of (adeno)tonsillectomy in children were evaluated. The internal validity of the randomised trials was rather poor (maximum score 6 out of 10). For sore throat episodes data for 2483 person years were available. The pooled risk difference was -1.2 episodes per person year (95% confidence interval -1.3 to -1.1, p-value <0.0001). For sore throat associated school absence 1669 person years were analysed. The pooled risk difference was -2.8 days per person year (95% confidence interval -3.9 to -1.6, p<0.01). For upper respiratory infections 1596 person years were available. The pooled risk difference was -0.5 episodes per person year (95% confidence interval -0.7 to -0.3, p<0.05).

Conclusions | All available randomised trials and non-randomised controlled studies into the effectiveness of (adeno)tonsillectomy had important limitations. The frequency of sore throat episodes and upper respiratory infections reduces with time whether (adeno)tonsillectomy is performed or not. (Adeno)tonsillectomy gives an additional, but small, reduction of sore throat episodes, days of sore throat associated school absence and upper respiratory infections compared to watchful waiting.

Introduction

Tonsillectomy with or without adenoidectomy is one of the most commonly performed surgical procedures in children in western countries.[1] The most common indications are recurrent upper respiratory infections (URIs) and obstructive sleep apnoea. For children with obstructive sleep apnoea due to adenotonsillar hypertrophy, adenotonsillectomy has proven effective.[2-4] Regarding URIs, however, evidence for its effectiveness is limited and no (inter-) nationally accepted guidelines on the indications for this procedure are available.[5,6]

In 1998 two reviews were published on trials on the effectiveness of (adeno)tonsillectomy (T±Ads) for recurrent throat infections in children.[7,8] Both concluded that the available studies were of poor quality. For several reasons, we wondered, whether the current evidence on the effectiveness of (adeno)tonsillectomy is still very limited. First, a literature search from Medline with search term "tonsillectomy" produced 5771 hits. Although most of these were non-randomised studies, they may offer important additional evidence. Second, both the Cochrane reviewers and Marshall focussed on the reduction of sore throat episodes, but for patients and practising physicians outcomes such as sore throat associated school absence and upper respiratory infections are important also.[9-12] Third, the recent report of a second trial by the Pittsburgh group may offer additional evidence.[13]

Therefore, we performed an updated systematic review to provide a quantitative estimate of the effects of (adeno)tonsillectomy on sore throat episodes, upper respiratory infections and sore throat associated school loss, based on available evidence from randomised trials and non-randomised controlled studies.

Methods

Study retrieval and selection

A computerised literature search was done in the Medline (Index Medicus 01/1966-06/2003), OldMedline (Index Medicus 1/1963-12/1965) and Cochrane databases for articles containing original data on the effectiveness of (adeno)tonsillectomy in children (Appendix 1). Reference lists from identified publications were screened to identify pre-1963 studies. Only articles published in English were retrieved.

Eligibility

Studies were included that met the following criteria: a) randomised trial or non-randomised controlled study investigating the effectiveness of (adeno)tonsillectomy; b) the control group underwent either no surgery or adenoidectomy only; c) age at inclusion below 18 years; d) clinically relevant outcome measures were reported, i.e. sore throat episodes and/or upper

respiratory infections and/or sore throat associated school loss and/or fever episodes;
e) results were published before June 2003.

Selection of articles

Two reviewers (BvS, EHvdA) independently assessed eligibility of studies. Randomised trials and non-randomised controlled studies were summarised separately.

Randomised trials

Methods appraisal

The two reviewers performed the quality assessments of the randomised trials independently. The maximum quality score for each study was 10 for internal validity and 8 for external validity (i.e. generalisibility) (see Appendix 2).[14] For each criterion the reviewers assessed the completeness of the information ("yes" 1 point; "no" 0 points, "unclear" ?). Validity scores were used to rank studies.

Data-extraction

Information on patient characteristics (P), interventions (I), the contrast between the interventions (C) and outcomes measured (O) were extracted from all included studies.

Clinical outcomes

The main outcome measures were sore throat episodes, days of sore throat associated school absence, upper respiratory infections, and fever episodes. Results as reported by the authors in the articles were used; no attempt was made to retrieve the original data from the authors as 4 out of 6 trials were performed more than 15 years ago.[15-18] The incidence of upper respiratory infections for the trials by McKee et al.[15,16] was calculated by adding up the episodes of cold, cough, influenzal illness, other respiratory illness and otitis media. For the trial by Mawson et al.[17] the incidence of upper respiratory infections was calculated by adding up the episodes of earache, otitis media and head cold.

Statistical analysis

Effects on the outcome measures were summarised as risk differences and ratios.
For the outcome parameters sore throat episodes, sore throat associated school absence and upper respiratory infections in randomised trials, pooled estimates of the rate ratio and rate difference with 95% confidence intervals were calculated. Poisson regression was used assuming that the number of observed episodes followed a Poisson distribution. Incidence

Table 1. METHODOLOGICAL ASSESSMENT OF THE RANDOMISED TRIALS

First author	Internal validity score	Bias considered likely for validity criteria concerning			Insufficient information for validity criteria concerning			External validity score	Insufficient information for data extraction criteria concerning		
	number of satisfied validity criteria (maximum =10)	population criteria 1-3	intervention criteria 4-7	follow-up criteria 8-10	population criteria 1-3	intervention criteria 4-7	follow-up criteria 8-10	number of satisfied data extraction criteria (maximum=8)	population criterion 1	intervention criteria 2-5	follow-up criteria 6-8
Paradise II, three-way Trial	6		4, 7	8, 9				8			
Paradise II, two-way trial	5		4, 6, 7	8, 9				8			
Mawson I & II	4		4, 6, 7	8, 9		5		5	1	3, 5	
McKee II	4		4, 7	9	1, 3	5		5		4	7, 8
Paradise I	2	3	4, 6, 7	8, 9	1, 2			7			7
McKee I	1	1, 2	4, 6, 7	8, 9	3	5		6			7, 8

rates per person year were calculated to account for differences in duration of follow up between studies. Random effect estimates were reported because the study results were statistically heterogeneous. To test whether the association between (adeno)tonsillectomy and the outcomes was homogenous in the two types of analyses (per protocol versus intention to treat) the significance of the respective interaction term was tested. When a significant difference was found, it was tested whether the difference resulted in different treatment effects.

Non-randomised controlled studies

Data extraction, clinical outcomes and statistical analyses were performed in the same way as in the randomised studies. However, no quality assessment scores were derived and pooled estimates were not calculated.

Results

Study selection

71 studies on the effectiveness of (adeno)tonsillectomy for upper respiratory infections in children were identified. 52 studies were excluded for the following reasons: 19 were uncontrolled studies; 7 included only a before-after treatment comparison; 10 included a control group of healthy controls; and 16 were reviews. Multiple publications were excluded from our analyses.[19-24] Hence, 6 randomised trials[13,15-18] and 7 non-randomised controlled studies[18,25-30] were included.

Validity criteria of the randomised trials

Internal validity of all the randomised trials was rather poor (maximum score 6 out of 10), whereas the external validity (i.e. generalisablity) was generally better (minimum score 5 out of 8); Table 1.

Characteristics of the randomised trials (Table 2)

The inclusion criteria of the trials varied from mild and non-specific to severe and very strict. Marked differences existed between the inclusion periods of the studies and varied from 6 months to as much as 12 years. In 5 trials the control group received watchful waiting or non-surgical management, and in one study adenoidectomy.[16] Mean age at inclusion varied from 6.0 to 8.1 years. In all trials except one,[16] loss-to-follow up was considerable: 8% to 39%. The percentage of switchers from the watchful waiting to the (adeno)tonsillectomy

Table 2. CHARACTERISTICS OF RANDOMISED TRIALS

First author	Inclusion period	Inclusion criteria	Treatment characteristics and group size (n)	Mean age at inclusion (years)	Outcome	Episodes at follow-up (years in T±Ads group)			Episodes at follow-up (years in control group)			Risk difference with 95% confidence interval (episodes/year)	Risk ratio with 95% confidence interval
						1	2	3	1	2	3		
Paradise three-way (2002)	12 years	different criteria for different age groups • *5 or 6 episodes in past year or 4 in past 2 years (age 3-6 years)* • *4-6 episodes in past year or 3 in past 2 years (age 7-15 year)*	T&Ads (n=59) versus tonsillectomy (n=58) versus no surgery (n=60)	T&Ads: 7.4 tonsillectomy: 7.4 no surgery: 7.4	• Sore throat episodes • Sore throat associated days school absence	1.9 3.6	1.7 2.8	1.3 2.7	2.8 5.5	2.9 5.0	2.3 3.7	-1.0 (-1.3 to -0.7) -1.5 (-1.9 to -1.1)	0.62 (0.54 to 0.72) 0.67 (0.60 tp 0.75)
Paradise two-way (2002)	12 years	as Paradise three-way 2003	T&Ads (n=73) versus no surgery (n=78)	T&Ads: 7.4 no surgery: 7.4	• Sore throat episodes • Sore throat associated days school absence	1.9 3.5	1.7 3.2	1.5 2.6	3.6 6.6	2.9 5.4	2.4 4.2	-1.3 (-1.6 to -1.0) -2.3 (-2.8 to -1.9)	0.57 (0.49 to 0.66) 0.57 (0.51 to 0.64)
Mawson (1967)	Not given	children who would be normally placed on the waiting list for T & Ads	T&Ads (n=202) versus no surgery (n=202)	T&Ads: 6.0 no surgery: 5.8	• Sore throat episodes • URI episodes	0.7 4.0	0.6 3.4		2.3 5.2	1.7 3.6		-1.3 (-1.5 to -1.2) -0.6 (-0.9 to -0.3)	0.33 (0.29 to 0.39) 0.85 (0.79 to 0.92)
McKee II (1963)	6 months	≥3 throat infections or URI with cervical adenitis in past 12 months	T&Ads (n=100) versus adenoidectomy (n=100)	T&Ads: 6.7 A: 6.5	• Sore throat episodes • URI episodes • Sore throat associated days school absence	0.3 3.1 0.7			1.5 3.3 4.4			-1.1 (-1.4 to -0.9) -0.2 (-0.7 to 0.3) -3.7 (-4.2 to -3.2)	0.22 (0.15 to 0.32) 0.94 (0.80 to 1.1) 0.16 (0.12 to 0.20)
Paradise (1984)	11 years	≥ 7 throat infections in past year or ≥ 5 throat infections in past two years or ≥ 3 throat infections in past 3 years	T±Ads (n=43) versus no surgery (n=48)	T±Ads: 8.1 no surgery: 8.1	• Sore throat episodes • Sore throat associated days school absence	1.2 3.5	1.6 4.5	1.8 5.1	3.1 6.7	2.7 5.9	2.2 5.9	-1.2 (-1.7 to -0.8) -1.9 (-2.6 to -1.2)	0.55 (0.44 to 0.68) 0.69 (0.60 to 0.80)
McKee I (1963)	11 months	≥ 3 throat infections or URI with cervical adenitis in past 12 months	T&Ads (n=231) versus no surgery (n=182)	T&Ads: 6.7 no surgery: 6.5	• Sore throat episodes • URI episodes • Sore throat associated	0.4 3.0 1.0	0.3 2.5 0.7		2.0 3.4 6.7	1.0 3.0 3.3		-1.2 (-1.3 to -1.0) -0.4 (-0.7 to -0.2) -4.1 (-4.4 to -3.9)	0.23 (0.19 to 0.28) 0.87 (0.80 to 0.94) 0.17 (0.15 to 0.19)

Table 3. *CHARACTERISTICS OF NON-RANDOMISED CONTROLLED STUDIES*

First auteur	Study design	Inclusion criteria (study and comparison group)	Treatment characteristics and group size	Age at inclusion (years)	Outcome assessment	Outcome	T±Ads at follow-up	Control group at follow-up	Risk difference with 95% confidence interval (% improvement or episodes/year)	Risk ratio with 95% confidence interval
Kaiser 1926 (as Kaiser 1924)	Prospective follow-up	T&Ads: Children who had obvious diseased tonsils and adenoids and who underwent T&Ads Control group: parents refused T&Ads	T&Ads: 1200 No surgery: 1200	T&Ads and no surgery: 4 to 7	3 years	Presence of complaints: • Frequent sore throat* • URI= frequent head colds and ear trouble* • Frequent fever attacks*	5% 12% 4%	49% 51% 3%	-44% (-47 to -40%) -39% (-42 to -36%) 2% (0.4 to 3%)	0.11 (0.09 to 0.14) 0.24 (0.20 to 0.28) 1.7 (1.1 to 2.7)
Kaiser 1930 (as Kaiser 1931 and 1940)	Prospective follow-up	As Kaiser 1926	T & Ads: 2200 No surgery: 2200	T&Ads and no surgery: 4 to 7	10 years	Presence of complaints: • Frequent sore throat* • URI= frequent head colds and ear trouble* • Frequent fever attacks*	10% 22% 5%	36% 31% 5%	-25% (-28 to -23%) -9% (-11% to -6%) 0.1% (-1% to 1%)	0.29 (0.25 to 0.33) 0.72 (0.66 to 0.8) 1.0 (0.8 to 1.3)
Monroe 1930	Prospective follow-up	Broad inclusion criteria Author states that TE and control group are comparable	TE: 736 No surgery: 741	TE and no surgery: 4-13	TE group: between 3-18 months Controls: 12 months	Frequent colds and sore throat still present as at inclusion*	14%	58%	-44% (-49% to -40%)	0.24 (0.2-0.29)
Roydhouse 1970	Prospective follow-up	T&Ads: recurrent attacks of tonsillitis and other respiratory infections Control group: hospital waiting list	T&Ads: 252 No surgery: 175	T&Ads and control: 6.1	After 1 and 2 years	• sore throat episodes* • URI episodes* • sore throat associated days school absence*	0.4/year 1.35/year 0.87/year	2.1/year 1.36/year 3.8/year	-1.7 (-1.8 to -1.5) 0.02 (-0.2 to 0.2) -3.0 (-3.2 to -2.7)	0.21 (0.18-0.24) 1.0 (0.89-1.14) 0.23 (0.21-0.26)
Roos 1978 (as Roos 1979)	Retrospective Data from database	T±Ads and control group: one doctor's diagnosis of tonsillitis, peritonsillar abscess or hypertrophy in the year before inclusion	T±Ads 1950 No surgery: 2089	T±Ads and no surgery: < 13	After 1 year	Doctors visit for respiratory diagnosis	0.57	0.76	-0.19**	0.75**
Henteleff 1981	Retrospective Data from database	As Roos 1978	T±Ads: 2233 No surgery: 2670	T±Ads and no surgery: < 13	4 years	Total number of respiratory diagnosis in the 4 follow-up years (from database)	0.45/year	0.52/year	-0.07**	0.87**
Paradise 1984	Prospective follow up. Allocation according to parental preference	Inclusion criteria as RCT Paradise 1984, but children were assigned according to parental preference	T±Ads: 52 No surgery: 44	T±Ads: 7.9 No surgery: 7.6	After 1, 2 and 3 whole years	• sore throat episodes (definition as RCT Paradise 1984) • sore throat associated school absence (definition as RCT Paradise 1984)	1.51/year 5.4/year	2.88/year 6.2/year	-1.4 (-1.8 to -0.9) -1.0 (-1.8 to -0.2)	0.52 (0.42-0.64) 0.84 (0.73-0.96)

* *Outcome was not defined more precisely;* ** *95% CI could not be caluclated*

group varied, except in one trial,[16] from 12% to 28%. None of the studies supplied a power analysis.

Characteristics of non-randomised controlled studies (Table 3)

Four studies were prospective cohort studies and three were retrospective cohort studies. Apart from, of course, the non-randomised allocation to T±Ads, the main methodological limitations included the lack of description of the number of participants lost-to follow-up and the number of children that changed from the watchful waiting to the (adeno)-tonsillectomy group.

Effectiveness

Outcomes of the randomised trials

The outcome sore throat episodes was studied in all trials, sore throat associated days school absence in 5 trials, upper respiratory infections in 3 trials, while no randomised trial reported fever episodes. Outcomes were assessed at 1, 2 and 3 years. Outcomes in all trials were derived from children's experiences in whole-year blocks; incomplete years were excluded from the analyses.

Pooled estimates

For the outcome sore throat episodes, 2483 person years were analysed (54% in intervention groups). The pooled risk difference was -1.2 episodes per year (95% confidence interval -1.3 to -1.1). The heterogeneity between the studies analysed per protocol versus intention to treat was statistically significant ($p < 0.05$), but no significant treatment effect was observed ($p=0.80$). The pooled risk ratio for sore throat episodes was 0.49 (95% confidence interval 0.30 to 0.79).

For the outcome sore throat associated school absence, 1669 person years were available (56% in intervention groups). The pooled risk difference was -2.8 days/year (95% confidence interval -3.9 to -1.6) and the risk ratio for sore throat associated school absence was 0.50 (95% confidence interval 0.26 to 0.97). No significant effect of the different types of analyses (i.e. intention-to-treat or per protocol) was found.

For the outcome upper respiratory infections, 1596 person years could be analysed (54% in the intervention groups). The pooled risk difference was -0.5 (95% confidence interval -0.7 to -0.3). The risk ratio for upper respiratory infections was 0.97 episodes per year (95% confidence interval 0.69 to 1.36). Exclusion of the study by McKee,[16] the only study comparing adenotonsillectomy versus adenoidectomy, yielded similar results.

Outcomes of the non-randomised controlled studies

Except for frequent fever attacks (rate ratio ≥ 1.0), rate ratios for all outcomes (episodes of throat infection, sore throat associated days school absence, upper respiratory infections and doctors visit for respiratory diagnosis) were ≤ 1.0, indicating a beneficial effect of (adeno) tonsillectomy.

Discussion

Our systematic review shows that (adeno)tonsillectomy reduces the incidence of sore throat episodes by 1.2 episodes per year (95% confidence interval 1.1 to 1.3), sore throat associated school absence by 2.8 days per year (95% confidence interval 1.6 to 3.9) and upper respiratory infections by 0.5 episodes per year (95% confidence interval 0.3 to 0.7).

In contrast with the Cochrane reviewers,[7] who excluded all trials in which children of the surgical group were randomised to adenotonsillectomy instead of tonsillectomy alone, all randomised trials studying the effectiveness of (adeno)tonsillectomy were included in the present meta-analysis. In daily practice most children suffering from recurrent throat infections undergo tonsillectomy combined with adenoidectomy and not tonsillectomy alone; in the Netherlands 90% of tonsillectomies in children are combined with adenoidectomy, in the USA this percentage is 84%, in Canada 75% and in England 32%.[1] Our meta-analysis shows that randomised trials comparing adenotonsillectomy versus watchful waiting or tonsillectomy alone versus watchful waiting provide similar results. Our meta-analysis was performed to assess the effects of (adeno)tonsillectomy for upper respiratory infections. The effects of (adeno)tonsillectomy in children with obstructive breathing during sleep were not considered.[2-4]

It is important to realise that all trials had serious methodological limitations, which precludes definite conclusions about the effects of (adeno)tonsillectomy on upper respiratory infections. First, the generalisibility of the results of the trials can be questioned, since only a very small proportion of children undergoing T±Ads was included in the trials. (Adeno)tonsillectomy is one of the most commonly performed surgical procedures in children in western countries; in 1998, for example, 65/10,000 underwent T±Ads in England and 50/10,000 in the United States.[1] Yet the 3 Pittsburg trials[18,19] included only 233 children in the T±Ads group and 186 children in the watchful waiting group with an inclusion period of respectively 11 and 12 years. Second, all studies had significant loss-to-follow up. This can be associated with either good or poor outcome. However, in 4[17-19] out of 6 studies information

about the children who were lost to follow up was provided and in these studies the rates of throat infection during the preceding follow-up period did not differ significantly from the corresponding rates in the respective treatment groups as a whole. Third, three studies were analysed per protocol[15,16,18]. These per protocol analyses underestimate the treatment effect as in surgical trials only children of the watchful waiting group with severe complaints can change treatment group, whereas children of the surgical group, who may experience serious complaints, cannot change treatment group.[15,16,18] Fourth, information bias may be considerable since trials on adenotonsillectomy, as most surgical trials,[31,32] 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 measured daily by a validated thermometer automatically storing data.[33] Fifth, none of the trials provided a power analyses. As all trials, but especially the Paradise trials, included relatively few patients, their power may be too low, leading to a type II error.

The pooled risk difference for recurrent throat infections was -1.2 episodes per year (95% confidence interval -1.3 to -1.1). However in 3 trials the sore throat episode immediately following the operation was not counted.[15-17] Had these been counted, the differences between the groups would have been smaller.
The pooled risk difference for sore throat associated school absence was -2.8 days per year (95% confidence interval -3.9 to -1.6). In none of the trials, however, sore throat associated school absence immediately following surgery were counted. If these days had been included, the rates would probably not have been different. Thus, although (adeno)tonsillectomy reduces the total number of sore throat episodes by a modest 1.2 episodes per year (95% confidence interval 1.1 to 1.3), the reduction in sore throat associated school absence is even more modest. This indicates that the severity of the throat infections in the children of the control group was likely not serious enough to cause substantial school absence.
The pooled risk difference for upper respiratory infections was only -0.5 episodes per year (95% confidence interval -0.7 to -0.3), indicating that (adeno)tonsillectomy has little effect on the incidence of upper respiratory infections. This is important since several recent studies have shown that many ENT-surgeons and general practitioners still regard upper respiratory infections an indication for (adeno)tonsillectomy.[9-12]

In all studies children of the control group had more sore throat episodes and more upper respiratory infections than the children of the surgical group. In all studies, however, the children of the control group experienced fewer episodes during the follow up period than before study entry (Table 2). This natural decrease of the incidence of throat infections is

probably attributable to maturation of the immune system with growing age whether surgery is performed or not. Regression to the mean could also play a role. As a result, surgery induces an additional reduction of sore throat episodes of only 1.2 episodes per year (95% confidence interval 1.1 to 1.3).
It should be emphasised that the results of all trials are indicative of a difference of a strategy involving (adeno)tonsillectomy and a strategy involving initial watchful waiting, knowing that a proportion of the latter will switch to surgery. As in many other surgical trials, the number of switchers was high in most trials. It is very likely that these children have had more throat infections than the children who remained in their original allocated group.

The non-randomised controlled studies, except one,[18] show the classical shortcomings of non-experimental studies: incomparability of the study groups at baseline, which may lead to confounding by indication.[34] In these older studies techniques that can be used to control for these imbalances of known or suspected risk factors such as multivariate adjustment were not used. In their critical article, Selkirk and Mitchell[35] already recognised these problems in 1931. With time, the quality of the non-randomised controlled studies has improved. For example, in the older studies by Kaiser and Monroe[25-27] inclusion criteria and outcomes are ill defined, while in the more recent studies they are more explicitly stated.[18,29,30] Despite these shortcomings the results of the more recent and better non randomised controlled studies[18,28-30] are surprisingly similar to those of the randomised trials and therefore support evidence on the effectiveness of (adeno)tonsillectomy from the trials.

This systematic review shows that all trials and controlled studies have important limitations. Throughout all of the studies the frequency of sore throat infections and upper respiratory infections reduces with time whether (adeno)tonsillectomy was performed or not, highlighting the importance of *controlled* studies. Available evidence from both the randomised trials and non-randomised controlled shows that (adeno)tonsillectomy gives an additional, but small, reduction of sore throat episodes, sore throat associated school absence and upper respiratory infections compared to a non-surgical strategy.

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APPENDIX 1: MEDLINE SEARCH

(("tonsillectomy"[mh] OR tonsillectomy[all fields] OR adenotonsillectomy[all fields] OR "Adenoidectomy"[mh] OR Adenoidectomy[all fields]) AND ((placebo[all fields] OR "drug therapy"[sh] OR "therapeutic use"[sh:noexp] OR "random*"[all fields] OR "randomized controlled trial"[pt] OR "Clinical Trials"[mh] OR "Comparative Study"[mh]) OR ("incidence"[mh] OR "mortality"[mh] OR "follow-up studies"[mh] OR "mortality"[sh] OR prognos*[all fields] OR predict*[all fields] OR course[all fields] OR "Population Surveillance"[mh] OR "Remission, Spontaneous"[mh]) OR ("Review Literature"[MH] OR Meta-Anal* OR "meta-analysis"[pt] OR metaanal*) OR ((quantitativ*[tw] OR systematic*[tw] OR methodologic*[tw]) AND (review*[tw] OR overview*[tw])) OR (("review"[pt] OR review*[tw]) AND ("medline"[tw] OR "cinahl"[tw] OR "embase"[tw] OR "excerpta"[tw] OR "odds ratio"[tw] OR "pooled"[tw] OR "pooling"[tw]))))) NOT (letter[pt] OR editorial[pt] OR comment[pt] OR in vitro[mh] OR ("animal"[mh] NOT ("human"[mh] AND "animal"[mh]))) Field: All Fields, Limits: All Child: 0-18 years.

APPENDIX 2:

Criteria for the assessment of internal validity

(V1) Was the treatment allocation performed in an unpredictable sequence?

(V2) Was the treatment allocation concealed (sealed envelopes, allocation by telephone, etc.)?

(V3) Were the groups similar at baseline regarding prognostic indicators and baseline scores?

(V4) Was the care provider blinded to the treatment (use of a placebo)?

(V5) Were co-treatments avoided or standardised?

(V6) Was the compliance rate (in each group) unlikely to cause bias?

(V7) Was the patient blinded to the allocated treatment?

(V8) Was the crossover / dropouts rate unlikely to cause bias?

(V9) Was the outcome assessor blinded to the treatment?

(V10) Was the timing of the outcome assessment in both groups comparable?

Criteria for external validity

(D1) Were the eligibility criteria specified?

(D2) Were the compared treatments explicitly described?

(D3) Was information about the method of assessment of outcome measures presented?

(D4) Were there a short-term (immediately after treatment) and a long-term follow-up measurement?

(D5) Were adverse effects described?

(D6) Was sample size for each group described, after allocation and at outcome measurement?

(D7) Did the analysis include an intention-to-treat analysis?

(D8) Were point estimates and measures of variability presented for primary outcome measures?

V1 Random (unpredictable) assignments sequence. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

V2 Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.

V3 To receive a "yes", groups must be similar at baseline regarding age, frequency of prior episodes, duration of complaints and severity of complaints.

V4 (attempt for) blinding described in paper.

V5 Co-interventions should either be avoided in the design or comparable between the index and control group (use of antibiotics, ventilation tubes, adenoidectomy, and attention from researchers, etc).

V6 Treatment should be provided as randomised. Non adherence (protocol deviation, cross over) is acceptable if it is < 15% for both groups separate or < 5 % between groups. Qualitative measurement.

V7 (Attempt for) blinding described in paper.

V8 Quantitative measurement.
A yes is scored if "non adherence" and missing data do not lead to substantial bias.

V9 The reviewer determines (per outcome parameter) when enough information about the blinding is given in order to score "yes".

V10 Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.

D1 The reviewer determines if the eligibility criteria are well described.

D2 Adequate description of both the index and control intervention should be given, so that others could replicate the treatment.

D3 Adequate description of the method of assessment of outcome measurements should be given so that others could replicate the study.

D4 Outcome measurements <1 year after the intervention and outcome measurements at the end of the intervention period. Follow-up time and characteristics of effect measurements should be the same in both groups.

D5 Each event should be described and correctly attributed to the allocated treatment (postoperative bleeding, psychological disturbances).

D6 To be presented for each group at randomisation and for the most important outcome assessments.

D7 All randomised patients are reported/analysed for the most important moments of effect measurement (minus missing values) irrespective of non-compliance and co-interventions.

D8 Both point estimates and measures of variability should be presented (to be scored for each important outcome parameter separately). Point estimates are means, medians, modes etc. Measures of variability are: standard deviations, 95% confidence interval, etc.

chapter 2 Large international differences in (adeno)tonsillectomy rates

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Abstract

This article compares recent paediatric and adolescent (adeno)tonsillectomy (T±Ads) rates in several countries of the European Union, The United States, Canada and Australia. Trends in paediatric and adolescent surgical rates in The Netherlands and England from 1974 to 1998 are studied as well. In 1998, the paediatric T±Ad rate varied from 19 per 10,000 children in Canada to 118 per 10,000 in Northern Ireland, while the adolescent rate varied from 19 per 10,000 adolescents in Canada to 76 per 10,000 in Finland. In The Netherlands, the paediatric T±Ad rate decreased rapidly between 1974 and 1985 and remained similar since. Ten years later, between 1985 and 1998, the adolescent T±Ad rate increased. In England, on the other hand, an increase in T±Ads was observed both in children and adolescents. This study shows that paediatric and adolescent T±Ad rates still vary considerably between countries. There is no definitive evidence that decreasing rates of T±Ads in childhood are associated with tonsil related disease, necessitating surgery, in later life.

Introduction

Tonsillectomy with or without adenoidectomy (T±Ads) has long been one of the most frequently performed surgical procedures in children. Nevertheless, several recent publications[1-8] have shown that current indications for T±Ads in children vary considerably between and even within countries. Partly, this variation is explained by cultural differences, such as the use of antibiotics for upper respiratory tract infections,[9,10] but absence of (inter-) nationally accepted guidelines on indications for this common procedure also plays an important role. It is likely that, as opinions regarding the indications for surgery differ from country to country, surgical rates will also differ. So far, this issue has rarely been addressed in a quantitative way.[11] Therefore, we documented the surgical rates of T±Ads in children and adolescents across The United States, Canada, Australia and several countries of the European Union in 1998.

It has been suggested that decreasing paediatric T±Ad rates, known to have occurred over the past 20 years[12-14] may result in more tonsil-related disease in later life and thus an increasing incidence of T±Ad rates in adolescents.[15] To substantiate or repudiate the suggestion that paediatric and adolescent T±Ad rates are related, we studied trends in paediatric and adolescent T±Ads in The Netherlands and in England in recent decades.

Material and Methods

The 1998 surgical rate of paediatric tonsillectomy with or without adenoidectomy (T±Ads) in various countries was calculated as the total number of day-care and inpatient T±Ads, performed in children aged 0-14 years, divided by the 1998 mid-year population estimate of children in the same age range. The 1998 data were used since this was the most recent year for which T±Ad rates were available for the countries included. Data on the number of paediatric T±Ads procedures were obtained from the following institutions: National Medical Register of SIG Health Care Information (now PRISMANT) in The Netherlands, National Institute of Health in the United States, Canadian Institute for Health Information, Australian Institute of Health and Welfare, Department of Health of England, Scotland and Northern Ireland, Ministry of Social Affairs, Public Health and Welfare in Belgium and National Research and Development Centre for Welfare and Health in Finland. Tonsillectomy was coded as 5-281 and tonsillectomy with adenoidectomy as 5-282 in the International Classification of Procedures in Medicine (ICD-9 CM, 1978). Population data were obtained from the national statistical offices: Central Bureau of Statistics in The Netherlands, United States Census Bureau, Statistics Canada, Australian Institute of Health and Welfare, Department of Health, Demographic Statistics Section for England, Scotland and Northern

Ireland, National Statistics Institute in Belgium and National Research and Development Centre for Welfare and Health in Finland.

To calculate the 1998 surgical rate of T±Ads in adolescents, aged 15-19 years, the same procedure was followed: total number of day-care and inpatient T±Ads, divided by the 1998 mid-year population estimate of adolescents in the same age range.

To assess variation in paediatric and adolescent T±Ad rates over time, surgical rates from 1974 to 1998 in The Netherlands and from 1980 to 1998 in England were calculated in a similar fashion. For other countries no data were available over such a long time period. From 1985 to 1990 the Dutch National Health Office has no reliable records on paediatric T±Ad rates. In the same period the English National Health Office has no reliable records on both paediatric and adolescent T±Ad rates. Thus, Figure 2 and 3 show a gap from 1985 to 1990.

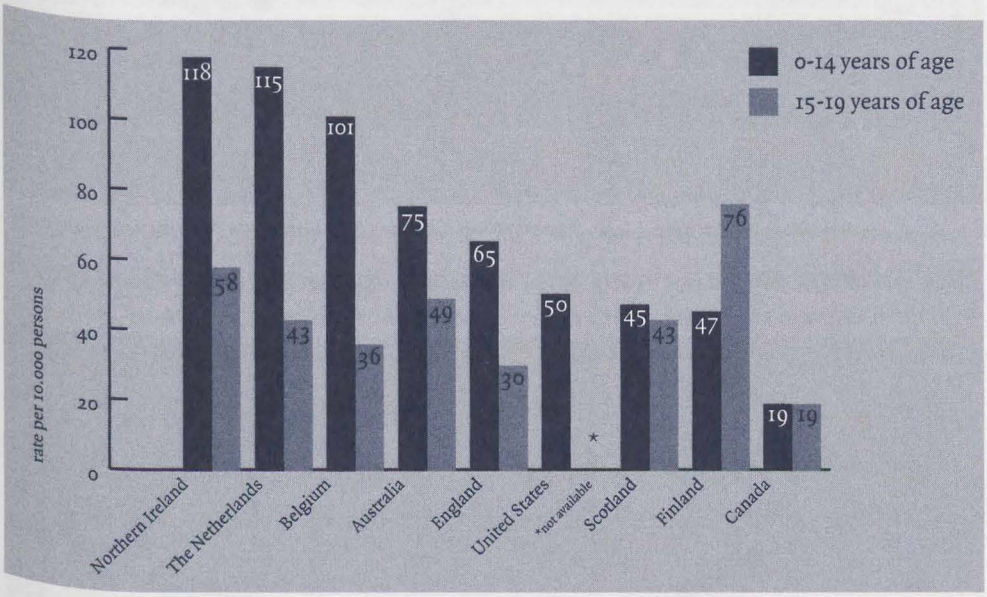
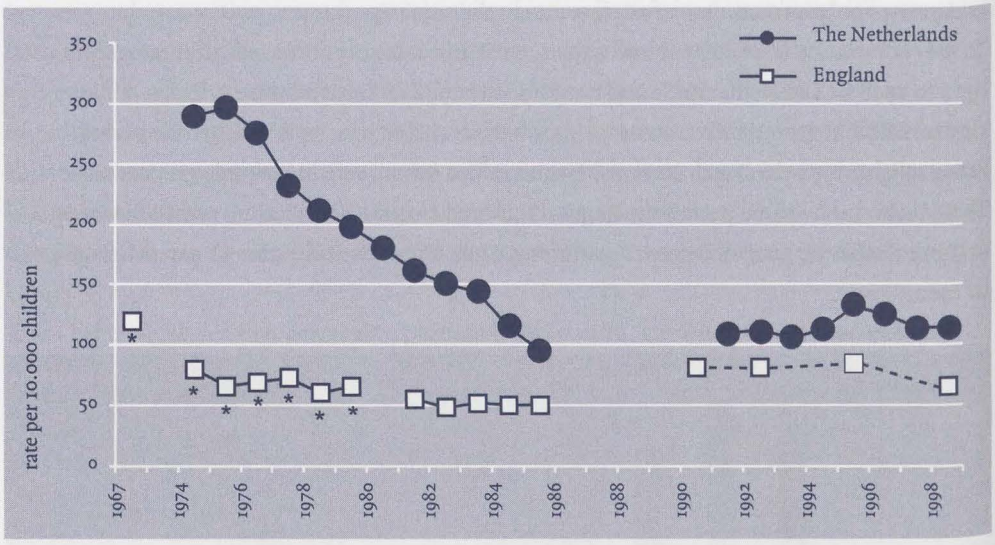


Figure 1. 1998 PAEDIATRIC AND ADOLESCENT T±AD RATES IN DIFFERENT COUNTRIES

Results

The 1998 surgical rate of T±Ads in children, aged 0-14 years, varied from 19 per 10,000 children in Canada to 115 per 10,000 in The Netherlands and 118 per 10,000 in Northern Ireland (Figure 1). Corresponding rates in England and The United States were 65 and 50 per 10,000, respectively. The 1998 T±Ad rates in adolescents, aged 15-19 years, varied from 19 per 10,000 adolescents in Canada to 76 per 10,000 in Finland (Figure 1).

In The Netherlands, a strong decrease in the paediatric T±Ad rate, from 290 to 96 per 10,000, was observed in the period 1974 to 1985 (Figure 2). Since 1991, the surgical rate has remained similar. In England, the stable T±Ad rate of 50 per 10,000 children in the 1980s increased to 80 per 10,000 children in the 1990s.



* data published by Black (1984) - - - dotted lines were used because the T±Ad rates in the intervening years are not known

Figure 2. PAEDIATRIC (0-14 YEARS) T±AD RATES IN THE NETHERLANDS AND ENGLAND BETWEEN 1974 AND 1998

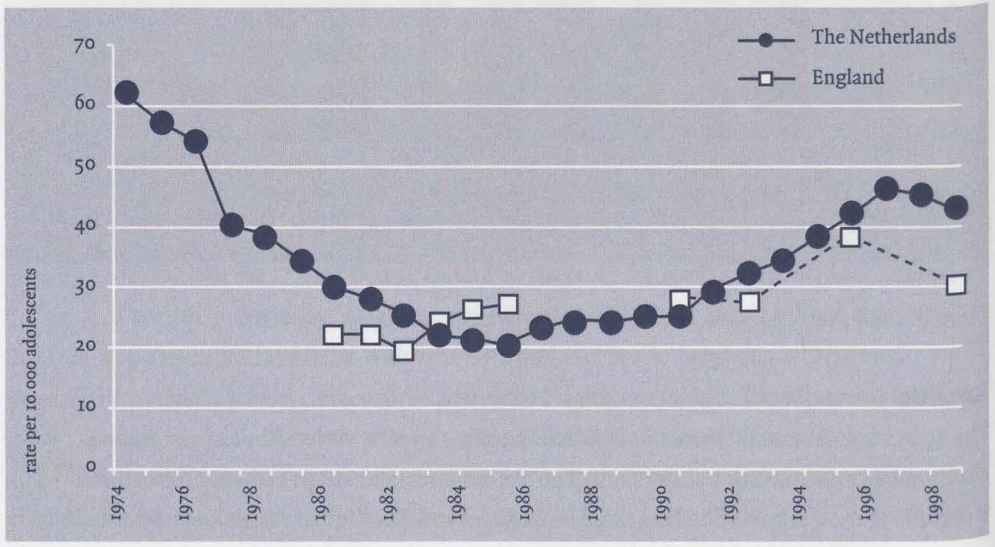


Figure 3. ADOLESCENT (15-19 YEARS) T±AD RATES IN THE NETHERLANDS AND ENGLAND BETWEEN 1974 AND 1998

Since 1985, ten years after the start of the strong decrease in children, the number of T±Ads in adolescents in The Netherlands doubled from 20 to 43 per 10,000 (Figure 3). In England, an increase was seen from 22 to 30 per 10,000 adolescents between 1980 and 1995.

Discussion

The continuing debate about both the proper indications for tonsillectomy with or without adenoidectomy and the value of the surgical procedure are illustrated by the large differences in T±Ad rates between countries. In 1982 McPherson et al.[11] described a similar large variation in T±Ad rates in both children and adults in New England, England and Norway in the 1970s: respectively 29, 6 and 17 per 10,000 inhabitants. They suggested that different attitudes towards alternative therapy and indications for tonsillectomy were related to these differences. Our study illustrates that the incidence rates of T±Ads in children and adolescents still vary strongly between countries. Apparently, no consensus has been reached about the indications for this procedure.

It is known that in the United States as well as in Europe paediatric T±Ad rates dropped considerably since the 1970s. Derkay et al.[12] reported a reduction of 62% in paediatric T±Ads in The United States from 1977 to 1987. In the same period, surgical rates dropped by 63% in The Netherlands.[13] Our finding that in The Netherlands, the rapid decrease in T±Ad rates in children was followed, ten years later, by a considerable increase in the adolescent T±Ad rate suggests a causal relationship. The absolute increase in adolescent T±Ads however is small compared to the absolute decrease in paediatric T±Ads in the preceding decade. In England, such an inverse association was not observed. While in The Netherlands a major decrease in paediatric T±Ad rates occurred in the 1970s and early 1980s, in England this decrease was smaller and occurred mainly in the late 1960s and early 1970s (Figure 2).[14] The tail of this decrease in T±Ad rates from 80 to 65 per 10,000 children in the late 1970s,[14] was followed by stable T±Ad rates of 50 per 10,000 children in the 1980s and 80 per 10,000 children in the 1990s. Thus the observed increase in adolescent T±Ads in England in the nineties can not be directly attributed to a decrease in paediatric T±Ads in the preceding decade. It is more likely that it reflects a different attitude towards performing T±Ads in general.

The coming decade will show whether the Dutch adolescent T±Ad rates will remain similar, as might be expected in view of the almost unchanged incidence in the paediatric rates since 1991. Alternatively, time may show that both paediatric and adolescent tonsillectomy rates are part of a cyclic motion subject to the general attitude towards the use of antibiotics and surgical interventions.[16]

In conclusion, paediatric and adolescent T±Ad rates still vary considerably between countries, most probably as a result of continuing differences in attitudes towards indication for T±Ads and antibiotic therapy. There is no definitive evidence that decreasing rates of T±Ads in childhood are associated with tonsil related disease in later life.

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chapter 3

Current indications for (adeno)tonsillectomy in children; a survey in The Netherlands

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Abstract

Objective | Despite the fact that (adeno)tonsillectomy is one of the most frequently performed procedures in children, studies of current indications are scarce. The purpose of this study is to determine the indications for (adeno)tonsillectomy in children younger than 15 years of age according to Dutch otolaryngologists and general practitioners.

Methods | During a period of 8 months, 18 otolaryngologists in 7 ENT practices and 210 referring general practitioners (GPs) filled out standard questionnaires for 349 children listed for tonsil surgery.

Results | Apart from recurrent tonsillitis (ENT:40%, GP:35%), findings such as enlarged tonsils (ENT:42%, GP:24%) and tonsillar crypt debris (ENT:29%, GP:17%) and non-specific symptoms such as listlessness (ENT:28%, GP:19%) and poor appetite (ENT:28%, GP:16%) were considered important criteria for surgery. Symptoms of obstructive sleep apnoea were present in 25% (ENT) and 6% (GP) of patients but were considered indicative for surgery in only 11% (ENT) and 4% (GP). In contrast to otolaryngologists, general practitioners considered otitis media and hearing loss relatively important indications for (adeno)-tonsillectomy.

Conclusions | Apart from the generally accepted indications such as recurrent tonsillitis and obstructive sleep apnoea, other indications play an equally important role in the decision to perform tonsil surgery in The Netherlands.

Introduction

Indications for (adeno)tonsillectomy in children have been changing over the years. Until the 1950s, tonsil surgery was widely performed to avoid complications of ß-haemolytic Streptococcus infection, such as glomerulonephritis, endocarditis and arthritis.[1,2] As antibiotics to prevent such complications became available, indications were made more strict. As a consequence, the number of tonsillectomies decreased in the 1960s and 1970s. Since 1985 this number has remained more or less constant, at 130 per 10,000 children per year in The Netherlands,[3] 54 per 10,000 per year in Great-Britain[4] and 30 per 10,000 per year in the United States.[5]

The clinical trial by Paradise et al.[6] and the studies by Potsic et al.[7,8] have since led to the recognition that frequent episodes of tonsillitis and obstructive sleep apnoea are the most important indications for (adeno)tonsillectomy. However, studies quantifying the indications currently used in medical practice are scarce. Donnelly et al.[9] established the indications for paediatric (adeno)tonsillectomy in Ireland by means of a questionnaire survey among otolaryngologists and general practitioners. Apart from recurrent tonsillitis and obstructive sleep apnoea, other criteria such as failure to thrive, poor general health, size of tonsils and snoring were reported to be important. In a Scottish audit on tonsillectomy,[10] recurrent tonsillitis was by far the most important indication for surgery in children (approximately 75% of the cases), while obstructive symptoms were the indication for surgery in only 8% of (adeno)tonsillectomies.

Despite high (adeno)tonsillectomy rates in The Netherlands, information on indications currently considered important for surgery is not available. The purpose of the present study is to gather such information.

Material and Methods

During an eight-month period (May–December 1997), 18 otolaryngologists from 7 different hospitals situated in the centre of The Netherlands were asked to fill out a standard questionnaire for all consecutive children younger than 15 years of age listed for adeno-tonsillectomy or tonsillectomy. Children listed for adenoidectomy only were excluded from the study. The questionnaire sought information regarding three categories of potential determinants for surgery: 1/ throat-related symptoms and signs, 2/ nose- and ear-related symptoms and signs and 3/ other possible reasons, such as listlessness and parental pressure. In addition, general information such as age, sex and previous ENT operations was collected. Participating physicians were asked to indicate whether a symptom or sign was present in a specific patient and, if so, to rate its importance for the decision to perform surgery according

to a score ranging from 1 to 3 (1= not important; 2 = moderately important and 3 = very important). As it was the purpose of this study to evaluate common practice, no definitions of the symptoms or signs listed in the questionnaire were provided to the participating physicians. After completing the form, informed consent was obtained from parents to contact the general practitioner with a request to fill out a similar questionnaire on the reasons for referring for surgery.

To assess whether clusters of symptoms and signs were considered important in the decision to perform surgery, a factor analysis was performed. Subgroup analyses were performed to compare indications for adenotonsillectomy and for tonsillectomy. Similar analyses were done to assess whether indications for surgery differed between children up to 5 years of age and children of 5 years and older. Chi-square and Student's T-tests were used to compare categorical and continuous variables, respectively.

Results

In total, otolaryngologists filled out 349 questionnaires. During the study period of 8 months approximately 540 (adeno)tonsillectomies were carried out in participating hospitals, making for a response rate of 65 %. Of the patients referred for surgery by general practitioners (n=302), 210 forms were obtained (210/302, 70%).

The mean age of the children was 5 years (range 1-15 years) with 54% being male. The adenotonsillectomy/tonsillectomy ratio was 90/10. Eighteen percent of the children had had a previous ENT operation: adenoidectomy (13%), myringotomy (6%) and ventilation tubes (7%).

Table 1 shows prevalences of symptoms and signs in children listed for surgery and the indications considered important by the otolaryngologists and general practitioners.

The indications provided by the otolaryngologist did not differ between children for whom a general practitioner's questionnaire was available and those for whom this questionnaire was not returned.

The most prevalent indications for surgery according to otolaryngologists were the presence of enlarged tonsils and a history of recurrent tonsillitis. For general practitioners a history of recurrent tonsillitis was by far the most important reason to refer for surgery. Observations such as tonsillar crypt debris and enlarged cervical lymph nodes were often considered important as well. It is remarkable that, according to the otolaryngologists, only 66% of the children undergoing (adeno)tonsillectomy suffered from recurrent tonsillitis. When present, they considered it a decisive indication for surgery in only two-thirds of the cases. In this particular group, 57% of the children were reported to suffer from 3 to 5 attacks per year and

41% from more than 6 attacks per year. The general practitioners considered recurrent tonsillitis of decisive importance in 35% of all patients; 83% of these children had had 3 to 5 attacks and 3% had had more than 6 attacks per year.

Table 1. PREVALENCE OF SYMPTOMS AND SIGNS PRESENT IN CHILDREN LISTED FOR (ADENO)TONSILLECTOMY AND INDICATIONS CONSIDERED VERY IMPORTANT (SCORE 3) FOR SURGERY BY OTOLARYNGOLOGISTS AND GENERAL PRACTITIONERS

	ENT (n=349 patients)		GP (n=210 patients)	
throat-related symptoms and signs	**prevalence of symptoms or signs**	**very important indications for surgery**	**prevalence of symptoms or signs**	**very important indications for surgery**
enlarged tonsils	90%	42%	84%	24%
recurrent tonsillitis	66%	40%	61%	35%
tonsillar crypt debris	62%	29%	46%	17%
snoring	73%	26%	43%	15%
swallowing difficulties	69%	24%	41%	13%
enlarged cervical lymph-nodes	80%	21%	69%	15%
mouth breathing	70%	20%	65%	21%
obstructive sleep apnoea	25%	11%	6%	4%
drooling	32%	5%	11%	3%
peritonsillar abscess	1%	1%	1%	1%
nose/ear-related symptoms and signs	**prevalence of symptoms or signs**	**very important indications for surgery**	**prevalence of symptoms or signs**	**very important indications for surgery**
recurrent upper respiratory tract infections	69 %	22%	74%	25%
hearing loss	30%	8%	27%	14%
otoscopy OME/AOM*	30%	4%	34%	14%
recurrent otitis media	27%	4%	44%	16%
allergy/asthma	15%	4%	16%	6%
other symptoms and signs	**prevalence of symptoms or signs**	**very important indications for surgery**	**prevalence of symptoms or signs**	**very important indications for surgery**
poor appetite	73%	28%	55%	16%
listlessness	71%	28%	74%	19%
restless sleep	54%	23%	35%	8%
frequent use of antibiotics	40%	10%	30%	10%
request GP to perform surgery	24%	7%	-	-
failure to thrive	20%	7%	8%	2%
T±Ads** in other siblings	29%	6%	17%	4%
parental pressure	31%	5%	31%	6%
school absence	20%	4%	4%	1%

* OME/AOM = otitis media with effusion/acute otitis media

** T±Ads = (adeno)tonsillectomy

The sum of the percentages exceeds 100% because respondents could fill in more than one symptom/indication.

Otolaryngologists reported symptoms of obstructive sleep apnoea to be present in 25% of the children. Interestingly, in only half of these cases was it considered to be of decisive importance. Corresponding figures for the general practitioners were 6% and two-thirds, respectively.

Otolaryngologists reported recurrent upper respiratory tract infections to be present in 69% of the children; in one-third of these children, this was relevant in their decision to operate. Hearing loss and otitis media were less prevalent in this population and not considered important at all by otolaryngologists. General practitioners, however, viewed recurrent upper respiratory tract infections as important for referral for surgery (25%), along with recurrent otitis media (16%) and hearing loss (14%).

Non-specific symptoms such as poor appetite, listlessness and restless sleep were not only frequently present in the children but also often considered important indications for surgery both by otolaryngologists and general practitioners. Parental pressure to perform surgery was reported to be of minor importance.

The results of the factor analysis are shown in Table 2. Three clusters of indications could be identified. Factor 1 consists mainly of indications related to tonsillar hypertrophy. Factor 2 consists of upper respiratory tract and ear-related symptoms and signs. The third factor primarily encompasses non-specific symptoms.

Subgroup analyses revealed no relevant differences between indications for adeno-tonsillectomy and tonsillectomy alone; only peritonsillar abscess (n=2) was more often considered an indication for tonsillectomy than for adenotonsillectomy ($p<0.05$).

A subgroup analysis according to age showed that drooling ($p<0.01$), snoring ($p<0.05$), poor appetite ($p<0.05$) and sleeping difficulties ($p<0.05$) were more often considered important indications in the youngest age group (< 5 years of age).

Discussion

In our study of 349 children undergoing (adeno)tonsillectomy, the most prevalent indications for surgery according to Dutch otolaryngologists were enlarged tonsils (42%) and recurrent tonsillitis (40%). General practitioners considered recurrent tonsillitis (35%) and upper respiratory tract infections (25%) the most important indications for referral.

As age distribution, adenotonsillectomy /tonsillectomy ratio and male/female ratio in this study were similar to those in the national data provided by SIG Health Care Information (now PRISMANT),[3] our population seems representative of Dutch children undergoing (adeno)tonsillectomy.

Table 2. Clusters of symptoms and signs that in combination often are considered very important (score 3) indications for (adeno)tonsillectomy. Results of factor analysis: factor 1 included many tonsillar hypertrophy symptoms; factor 2 nose/ear related symptoms, while factor 3 combined throat-related and non-specific symptoms

Factor 1	Factor 2	Factor 3
mouth breathing	recurrent URTI*	recurrent tonsillitis
snoring	obstructive sleep apnoea	peritonsillar abscess
swallowing difficulties	hearing loss	failure to thrive
enlarged tonsils	recurrent otitis media	parental pressure
tonsillar crypt debris	otoscopy OME/AOM**	T&Ads*** in other siblings
enlarged cervical lymph-nodes	allergy/asthma	school absence
listlessness		frequent use of antibiotics
restless sleep		
poor appetite		
drooling		

* URTI = upper respiratory tract infection, ** OME/AOM = otitis media with effusion/acute otitis media, *** T±Ads = (adeno)tonsillectomy

Table 1 shows that the number of indications reported by general practitioners was lower than that for otolaryngologists; the mean number of indications considered important by general practitioners was 2.5 (SD=2.0) and by otolaryngologists 3.5 (SD=2.4). This may be explained by the fact that general practitioners filled out their questionnaires retrospectively while otolaryngologists gathered information prospectively and therefore could inquire actively after every symptom and sign.

Although several studies[11-13] suggested that the prevalence of physical findings such as enlarged cervical lymphnodes and enlarged tonsils is similar in children with or without recurrent tonsillitis, both Dutch otolaryngologists and general practitioners considered enlarged tonsils, tonsillar crypt debris and enlarged cervical lymph-nodes relevant in their decision to refer for surgery. The cluster analysis showed that these physical findings were often present in children who also suffer from obstructive symptoms such as snoring and drooling. It appears that physicians tend to rely on objective signs and not only on symptoms reported by the parents. Bloor et al.[14] found that otolaryngologists with high (adeno)-tonsillectomy rates tended to consider physical findings more important for surgery than those with low surgical rates. The high (adeno)tonsillectomy rates and the emphasis on physical signs and symptoms in The Netherlands seem to correspond with these findings. Guidelines[1,2,15,16] emphasize the importance of adenotonsillectomy in children with obstructive airway problems. Rosenfeld and Green[17] showed that this indication was responsible for about 19% of the (adeno)tonsillectomies in the United States in 1986.

In our population, symptoms of obstructive sleep apnoea were present in 25% and 6%, respectively, according to otolaryngologists and general practitioners. The difference might be attributed to the fact that general practitioners tend not to inquire after these symptoms because they do not consider them a common problem in children. According to the otolaryngologists, parents more often mentioned symptoms of obstructive sleep apnoea, but in more than half of the cases (11%) this was not considered relevant in the decision to operate. Our findings are remarkably similar to those provided by Donnelly et al.[9] although the methodology of the two studies differs. While in the Irish survey otolaryngologists and general practitioners were asked to indicate which indications they considered important for tonsillectomy in general, our study is based on symptoms and signs present in children actually listed for (adeno)tonsillectomy. Both studies emphasize that non-specific symptoms such as poor appetite, failure to thrive and poor general health are relevant to otolaryngologists and general practitioners. Our finding that general practitioners and otolaryngologists differ in their opinion on the relevance of ear problems for tonsillectomy also accords with the Irish study.

The results of the Scottish Tonsillectomy Audit[10] differ considerably from the survey by Donnelly et al.[9] and the current study. Based on data collected retrospectively from nearly 10,000 hospital records, recurrent tonsillitis was reported to be the only important reason for operation (85%), far more influential than any other indication.

Thus far, scientific evidence for the benefits of (adeno)tonsillectomy has only been documented for a relatively small group of children severely affected by recurrent tonsillitis (7 or more documented episodes of tonsillitis in the preceding year, or 5 or more in each of the two preceding years, or 3 or more in each of the three preceding years)[6] and in those with sleep apnoea due to adenotonsillar hypertrophy.[7,8] In our study only 120 out of 349 children (35%) met either of these strict criteria. As parents tend to overreport the number of tonsillitis episodes, this percentage is possibly even lower.[18]

As the effectiveness of surgery for the majority of prevailing indications has to be established, we are currently preparing a multi-centre trial to determine the effectiveness of adenotonsillectomy including children with such indications.

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chapter 4 Adenotonsillectomy in children: a randomised trial

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Abstract

Objective | While frequent throat infections and obstructive sleep apnoea are generally considered adequate indications for adenotonsillectomy, there is no evidence for the benefits of adenotonsillectomy in the large proportion of children currently undergoing this procedure for milder symptoms. Our study assessed the effectiveness of adenotonsillectomy in these children.

Design | Open randomised controlled trial

Setting | 21 general hospitals and 3 academic centres in The Netherlands

Participants | 300 children, aged 2-8 years, indicated for adenotonsillectomy according to their local otolaryngologist. Excluded were children with very frequent throat infections (7 or more in previous year) or suspected of obstructive sleep apnoea.

Intervention | Adenotonsillectomy versus watchful waiting.

Main outcome measures | Episodes of fever, throat infections, upper respiratory infections and health-related quality of life.

Results | During the median follow-up period of 22 months, children in the adenotonsillectomy group experienced 2.97 fever episodes per person year versus 3.18 in the watchful waiting group (incidence rate difference −0.21; 95% CI −0.54 to 0.12), 0.56 versus 0.77 throat infections per person year (incidence rate difference −0.21; 95% CI −0.36 to −0.06) and 5.47 versus 6.00 upper respiratory infections per person year (incidence rate difference −0.53; 95% CI −0.97 to −0.08). No clinically relevant differences were found regarding health-related quality of life. The effectiveness of adenotonsillectomy was more pronounced in children with a history of 3 to 6 throat infections than in those with 0 to 2 throat infections. Twelve children experienced surgery related complications: primary haemorrhage (n=7), and severe nausea (n=5).

Conclusions | In the children indicated for adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy, the operation had no relevant clinical benefits to offer over a watchful waiting policy.

Introduction

Tonsillectomy with or without adenoidectomy is one of the most commonly performed surgical procedures in children in western countries. Its indications, however, remain uncertain as reflected by the large variation in surgical rates across countries. In 1998, for example, 115/10,000 children underwent (adeno)tonsillectomy in the Netherlands, 65/10,000 in England and 50/10,000 in the United States.[1]

In a previous study,[2] we have shown that in 35% of children currently undergoing adenotonsillectomy in the Netherlands the operation is performed for very frequent throat infections (i.e. 7 or more per year) or obstructive sleep apnoea, whereas 65% are operated for less frequent throat infections and milder symptoms of adenotonsillar hypertrophy, or for other indications such as upper respiratory infections. While frequent throat infections and obstructive sleep apnoea are generally considered adequate indications for adenotonsillectomy in children[3-8], there is no evidence for the benefits of adenotonsillectomy in a large proportion of children currently undergoing this procedure for milder symptoms.[2,9-12] To assess the effectiveness of adenotonsillectomy in these children we initiated a randomised trial.

Material and Methods

Patients

We performed an open multi-centre randomised controlled trial between March 2000 and February 2003. Otolaryngologists in 21 general hospitals and 3 academic centres in The Netherlands (Figure 1) were asked to provide our trial centre with information on every child aged 2 to 8 years indicated for adenotonsillectomy according to current medical practice. For this purpose, they completed a questionnaire including the indication considered most important in their decision to operate: either recurrent throat infections (3 or more episodes per year) or other indications such as obstructive complaints or recurrent upper respiratory infections.

Exclusion criteria

Children with (1) a history of 7 or more throat infections in the preceding year, or 5 or more in each of the two preceding years, or 3 or more in each of the 3 preceding years (Paradise criteria);[3] or (2) high suspicion of obstructive sleep apnoea, i.e. Brouillette's OSA-score[13] of more than 3.5, were excluded. Other exclusion criteria were: Down's syndrome, craniofacial malformation, such as cleft palate, and documented immunodeficiency other than IgA and IgG2 deficiencies.

Randomisation

Children whose parents gave informed consent, were randomly assigned to one of two strategies: adenotonsillectomy within 6 weeks, or watchful waiting. For this purpose a computer generated list of four numbers per block and fixed blocks within each hospital was used.

Inclusion

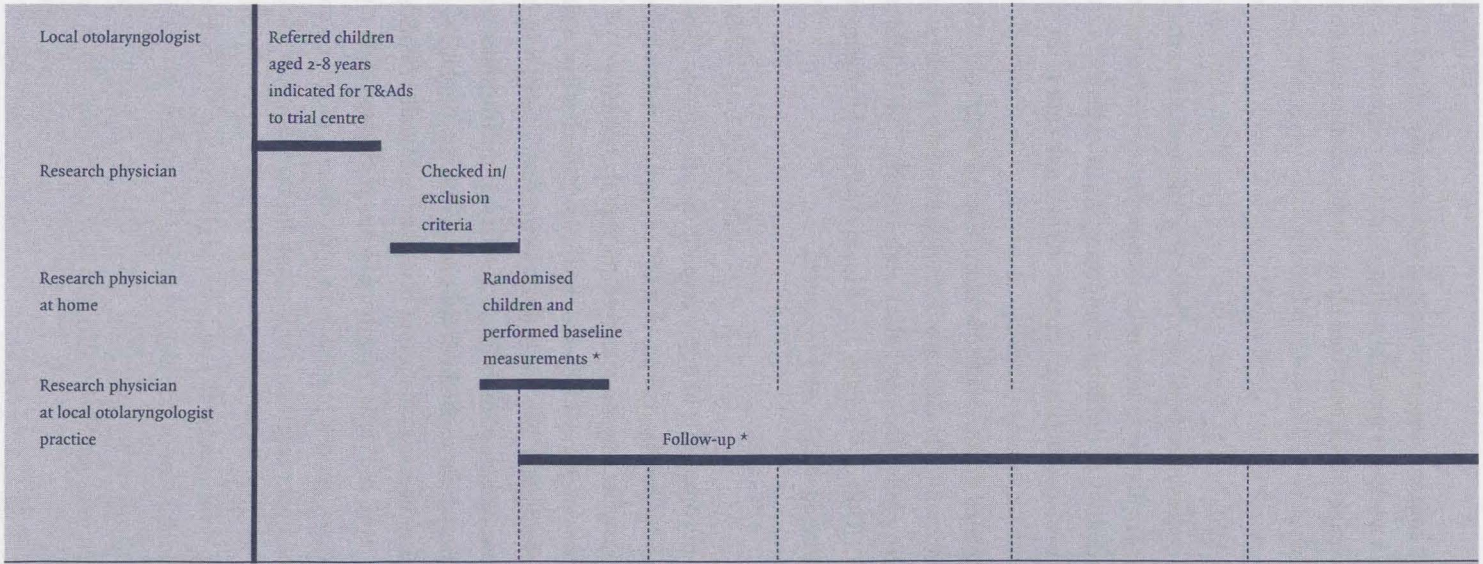
At inclusion, disease-specific questionnaires were filled out, including information on the number of throat infections and upper respiratory infections in the year before trial entry, obstructive symptoms during sleep according to the items composing the Brouillette's OSA-score,[13] eating pattern, previous ear, nose and throat operations and risk factors for upper respiratory infections.

Parents filled out two generic health-related quality of life questionnaires: TAPQoL or TACQoL questionnaire (TNO-AVL Preschool/Child Quality of Life; developed for children from 2 to 5 years of age and for children aged 5 years and older, respectively);[14] and Child Health Questionnaire parental form (CHQpf50).[15] Finally, participants underwent an ear, nose and throat examination and length and weight were measured.

Follow-up

During the study, parents kept a diary of complaints of upper respiratory infections in their child; i.e. sore throat, pain/difficulty at swallowing, cough, rhinorrhea, earache and otorrhea. Absence from day-care or school due to upper respiratory infections was also noted. Furthermore, the child's temperature was measured daily with a validated infrared tympanic membrane thermometer.[16] To avoid information bias, we had an electronic device built in to store date and first temperature measurement of each day. Both diary- and thermometer data were collected by the study physician during scheduled follow-up visits at 3, 6, 12, 18 and 24 months (Figure 1). At these visits, disease-specific and health-related quality of life questionnaires were filled out. An ear, nose and throat examination was performed and length and weight were measured. Parents, general practitioners and otolaryngologists were encouraged to manage sore throats and upper respiratory infections during follow-up according to their regular practice.

Figure 1. SCHEME OF TRIAL MEASUREMENTS



* Baseline and follow-up measurements include:
disease-specific questionnaires; health-related quality of life questionnaires; ENT examination; length and weight measurements

Primary outcome

Incidence of fever episodes was the primary outcome measure. Fever was defined as a body-temperature of 38.0 °C or higher as measured by the infrared tympanic thermometer, for at least one day. Fever was measured in fever episodes and days. An episode ended when children were free from fever (< 38.0 °C) for at least one day. A new episode of fever was recorded after a fever free interval of at least 7 days.

Secondary outcomes

Secondary outcome measures were: throat infections, sore throat days and episodes, upper respiratory infections, absence from day-care or school due to upper respiratory infections, health-related quality of life, sleeping and eating pattern, length and weight. A throat infection was defined as: sore throat and/or pain/difficulty at swallowing as indicated in the diary, in combination with fever measured by the tympanic thermometer. Sore throat was defined as sore throat and/or pain/difficulty at swallowing with or without fever. Upper respiratory infections were defined as having one or more of the following symptoms: sore throat, pain/difficulty at swallowing, cough, rhinorrhea, earache, otorrhea (diary) with or without fever. Throat infections, sore throats and upper respiratory infections were measured in episodes and days. In children undergoing adenotonsillectomy, symptoms of sore throat and upper respiratory infections immediately following surgery were included in the outcomes.

Absence from day-care or school because of upper respiratory infections was calculated on the basis of diary data.

Generic questionnaires (TAPQoL, TACQoL, and CHQpf50) were used to assess health-related quality of life.[14,15]

Sleeping pattern was evaluated by Brouillette's OSA-score[13] and by the percentage of children experiencing snoring, difficulties breathing at night and/or apnoea. Eating pattern was evaluated by asking for difficulties eating solids.

Statistical aspects

Calculations of group size were based on a clinically relevant reduction of fever episodes and throat infections after adenotonsillectomy of 25%. Assuming a mean baseline incidence of 4 (SD2) fever episodes and 4 (SD2) throat infections per year, and taking α=0.05 and a power of 0.80, 104 children were required in each randomisation group. To allow for subgroup analyses, we aimed at including 300 children.

The effects on fever, throat and upper respiratory tract infections were calculated as incidence rate differences and incidence rate ratios per person year with 95% confidence intervals.

Scores of HRQoL instruments were linearly transformed into 0-100 scales and presented per subscale. For the mean number of fever episodes, we calculated a short and a long-term effect, i.e. 0 to 6 and 6 to 24 months follow-up, respectively. Similarly, for health-related quality of life, sleeping and eating patterns, length and weight, short and long term effects were evaluated at 6 and 24 months, respectively. We used Chi-square tests and Student's T-tests to evaluate differences in percentages and mean values between the groups. Bonferroni correction was used to adjust for multiple testing.

Mantel-Haenzel procedures were used to adjust for potential confounding (e.g. indication and gender). Since the effect estimates were not influenced by these adjustments, crude effect estimates are presented.

To detect possible effect modification, subgroup analyses were performed according to burden of upper respiratory symptoms in the year before trial entry and age as pre-specified in the trial protocol. Interactions (subgroups) were analysed with Poisson regression.

All analyses were performed on an intention-to-treat basis.

Results

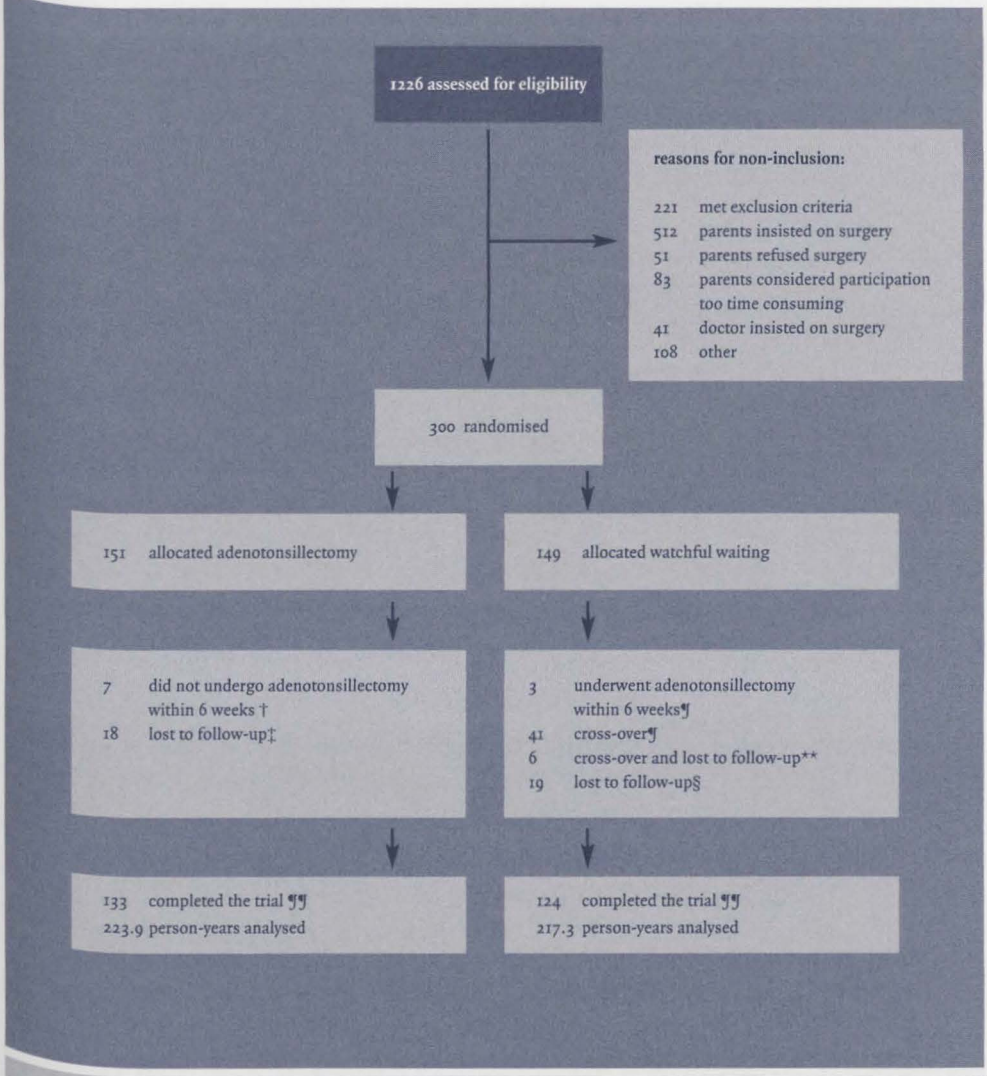
Patients

Between March 2000 and August 2002, 300 children were enrolled; 151 were allocated to adenotonsillectomy and 149 children to the watchful waiting strategy (Figure 2). Baseline characteristics did not differ between the two groups: mean age was 54 months and median number of throat infections in the year before trial entry was 3.0 episodes in both groups (Table 1). During the trial period, 43 children were lost to follow-up: 18 children from the adenotonsillectomy group and 25 from the watchful waiting group. Reasons were non-medical (N=36) (e.g. family moved); serious comorbidity (N=1); or unknown (N=6). Fifty children allocated to the watchful waiting strategy underwent adenotonsillectomy and 7 children allocated to the adenotonsillectomy group did not undergo this operation. Median follow-up was similar in the adenotonsillectomy and watchful waiting group: 22.0 and 22.4 months, respectively.

Primary outcomes

Children in the adenotonsillectomy and watchful waiting group experienced 0.21 fewer fever episodes (95% CI −0.12 to 0.54) per person year (Table 2). During the first 6 months follow-up, the number of fever episodes per person year was lower in children in the adenotonsillectomy than in the watchful waiting group (p=0.03) (Figure 3). From 6 to 24 months, there was no difference between the groups.

Figure 2. FLOW-CHART



* number exceeds 926 because more than one reason could be indicated
† parents declined from surgery after randomisation to surgical group
‡ 16 children for non-medical and 2 for unknown reasons
¶ parents or doctor insisted on surgery because of persistent tonsil-related complaints
** 5 children for non-medical and 1 child for unknown reasons
§ 16 children for non-medical, 2 for unknown reasons and 1 child because of serious co-morbidity diagnosed during follow-up
¶¶ because of a pre-determined end-point of the study in February 2003, not all children completed 2 years follow-up

Table 1. BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF 300 PARTICIPANTS ACCORDING TO TREATMENT ALLOCATION (DATA ARE NUMBERS AND (%) UNLESS OTHERWISE INDICATED)

Characteristic	T&Ads N= 151	watchful waiting N=149
Male sex	81 (53.6)	66 (44.3)
Mean age in months (SD)	54 (17.0)	54 (16.2)
Indication for surgery as indicated by local otolaryngologist		
• recurrent throat infections	76 (50.3)	67 (45.0)
• other indications	73 (48.3)	82 (55.0)
Median number of throat infections (range) in the year before trial entry (only for children indicated for recurrent throat infections; N=143)	3 (0 to 6)	3 (0 to 6)
Median duration of throat infections (range) in months (only for children indicated for recurrent throat infections; N=143)	13 (0 to 50)	12 (0 to 60)
Median number of episodes with rhinorrhoe and/or cough (range) in the year before trial entry	12 (0 to 24)	10 (0 to 24)
Median number of otitis media episodes (range) in the year before trial entry	0 (0 to 12)	0 (1 to 6)
Median OSA-score (range) *	−1.7 (−3.83 to 2.55)	−1.7 (−3.83 to 2.56)
Previous ENT-surgery		
• adenoidectomy	35 (23.2)	33 (22.1)
• tympanostomy tubes	19 (12.7)	17 (11.4)
Enlarged tonsils upon examination†		
• yes	114 (78.1)	114 (77.6)
• no	32 (21.9)	33 (22.4)
Mean weight in kg (SD)	18.6 (4.0)	19.0 (4.4)
Mean height in cm (SD)	108 (10.8)	109 (9.9)
Atopy‡	78 (51.7)	70 (47.0)
Breastfed for more than 1 month	85 (57.4)	92 (61.7)
Tobacco smoke exposure indoors	48 (32.0)	52 (35.1)
Attendance at day-care (only for children less than 4 years of age; N=110)	49 (89.1)	49 (89.1)
Number of siblings		
• 0	32 (21.2)	27 (18.1)
• 1	71 (47.0)	77 (51.7)
• 2 or more	48 (31.8)	45 (30.2)
Educational level mother		
• Low	22 (14.8)	27 (18.6)
• Middle	95 (63.8)	81 (55.9)
• High	32 (21.5)	37 (25.5)
Educational level father		
• Low	34 (22.5)	32 (22.5)
• Middle	73 (48.3)	71 (50.0)
• High	44 (29.1)	39 (27.5)

* Brouillette's OSA-score: 1.42 x difficulty breathing + 1.41 x apnoea + 0.71 x snoring − 3.83.
Range: −3.83 to +3.5. Score >3.5 is highly predictive of OSA; score between −1 and 3.5 indicates possible OSA and score <−1 no OSA.

† enlarged tonsils defined as protruding beyond the pillars but not meeting the uvula, or meeting the uvula and "kissing"

‡ atopy defined as a history of eczema, hay fever, recurrent wheezing or asthma

Table 2. INCIDENCE OF FEVER, THROAT INFECTIONS, SORE THROATS AND UPPER RESPIRATORY INFECTIONS PER PERSON YEAR FOR T&ADS AND WW GROUP, IRR (CI 95%) AND IRD (CI 95%).

	T&Ads Rate per person year	WW Rate per person year	IRR (95% CI)	IRD (95% CI)
Fever episodes	2.97	3.18	0.94 (0.84 to 1.04)	−0.21 (−0.54 to 0.12)
Fever days	5.31	5.93	0.90 (0.83 to 0.97)	−0.62 (−1.06 to −0.18)
Throat infections	0.56	0.77	0.73 (0.58 to 0.92)	−0.21 (−0.36 to −0.06)
Throat infection days	0.83	1.36	0.61 (0.51 to 0.73)	−0.53 (−0.73 to −0.34)
Sore throat episodes	2.25	2.85	0.79 (0.70 to 0.89)	−0.60 (−0.90 to −0.30)
Sore throat days	9.81	15.71	0.62 (0.59 to 0.66)	−5.91 (−6.57 to −5.24)
Upper respiratory infections with fever	1.59	1.88	0.85 (0.73 to 0.98)	−0.29 (−0.53 to −0.04)
Upper respiratory infection days with fever	2.81	3.63	0.77 (0.70 to 0.86)	−0.82 (−1.16 to −0.49)
Upper respiratory infections	5.47	6.00	0.91 (0.84 to 0.99)	−0.53 (−0.97 to −0.08)
Upper respiratory infection days	78.16	89.92	0.87 (0.85 to 0.89)	−11.76 (−13.47 to −10.05)

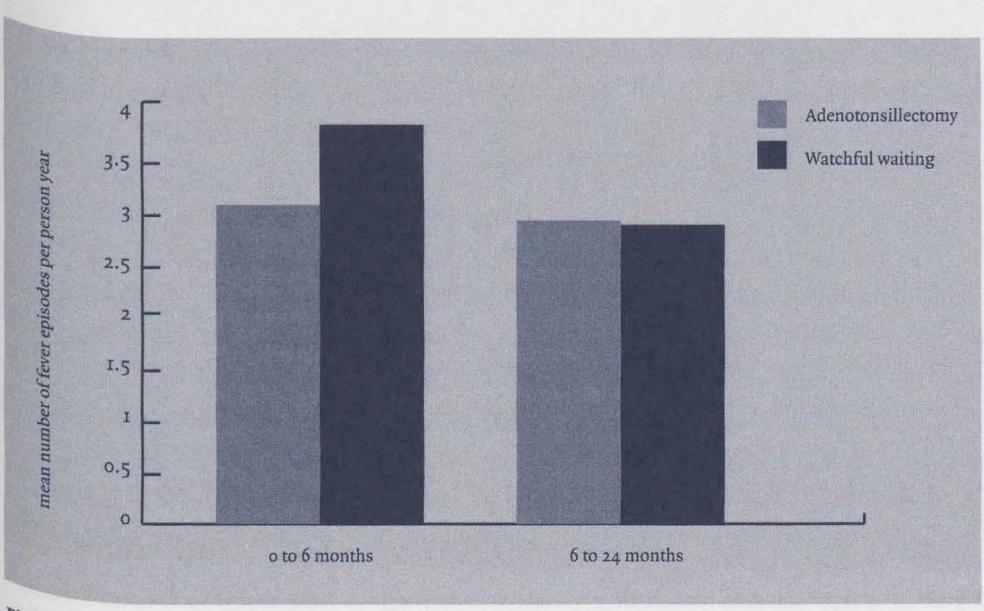


Figure 3. MEAN NUMBER OF FEVER EPISODES PER PERSON YEAR FOR THE ADENOTONSILLECTOMY AND WATCHFUL WAITING GROUP AT 0 TO 6, AND 6 TO 24 MONTHS FOLLOW-UP

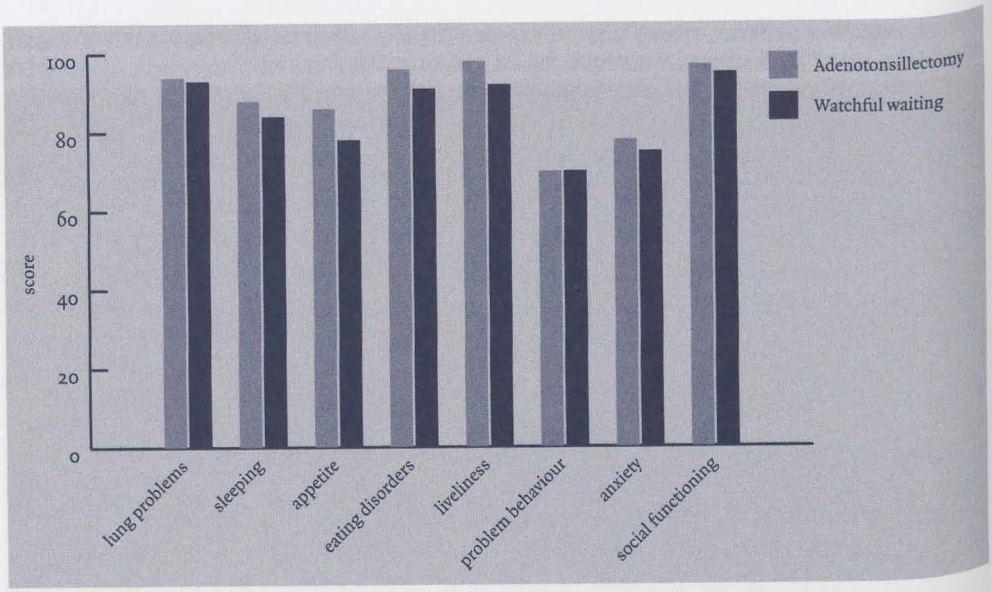


Figure 4A. HEALTH-RELATED QUALITY OF LIFE (TAPQOL) FOR THE ADENOTONSILLECTOMY AND WATCHFUL WAITING GROUP AT 6 MONTHS FOLLOW-UP

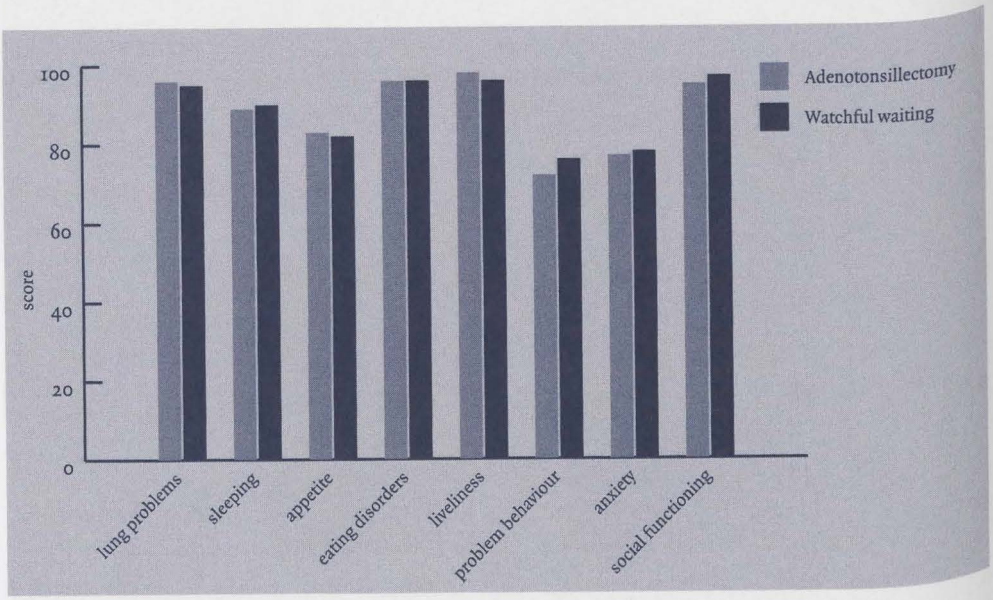


Figure 4B. HEALTH-RELATED QUALITY OF LIFE (TAPQOL) FOR THE ADENOTONSILLECTOMY AND WATCHFUL WAITING GROUP AT 24 MONTHS FOLLOW-UP

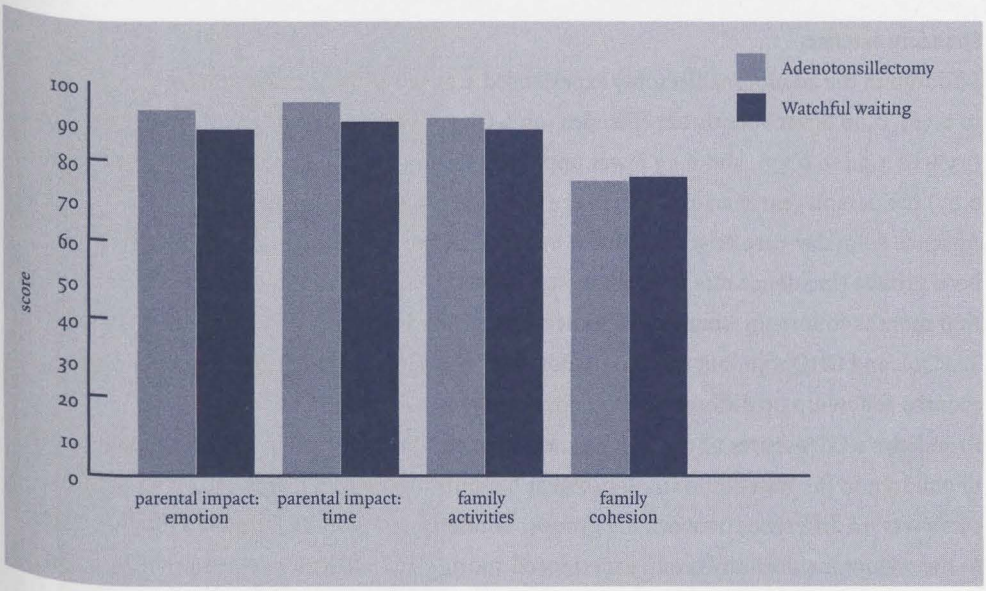


Figure 4C. HEALTH-RELATED QUALITY OF LIFE (CHQ) FOR THE ADENOTONSILLECTOMY AND WATCHFUL WAITING GROUP AT 6 MONTHS FOLLOW-UP

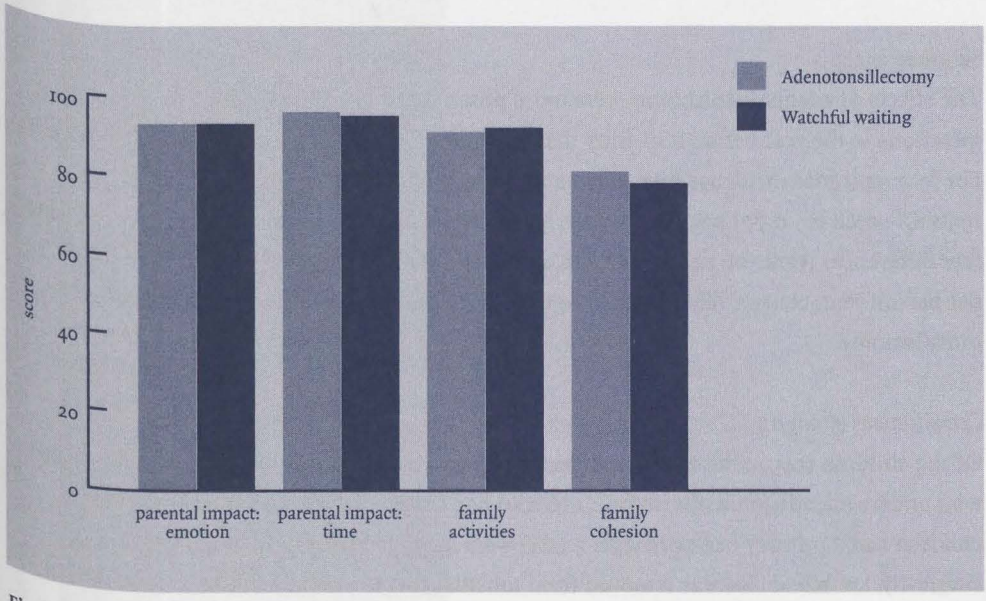


Figure 4D. HEALTH-RELATED QUALITY OF LIFE (CHQ) FOR THE ADENOTONSILLECTOMY AND WATCHFUL WAITING GROUP AT 24 MONTHS FOLLOW-UP

Secondary outcomes

Children in the adenotonsillectomy experienced 0.21 fewer throat infections (95% CI 0.06 to 0.36), 0.60 fewer sore throat episodes (95% CI 0.30 to 0.90), 5.91 fewer sore throat days (95% CI 5.24 to 6.57), and 0.53 fewer upper respiratory infection episodes (95% CI 0.08 to 0.97) per person year than children in the watchful waiting group (Table 2).

Absence from day-care or school due to upper respiratory infections was comparable in both groups (incidence rate difference 0.09 (95% CI –0.27 to 0.44)).

At 6 months follow-up, small significant differences were found for a few domains of the TAPQoL and CHQpf50, but these were not clinically relevant. In other domains and at 24 months follow-up no differences were found (Figure 4A-D).

Brouillette's OSA-scores of children in the adenotonsillectomy group were lower than those of children in the watchful waiting group at 6 months follow-up (Figure 5). At 24 months there was no difference between the groups. Similarly at 6 months follow-up fewer children in the adenotonsillectomy group experienced snoring and difficulties eating solids than in the watchful waiting group, whereas at 24 months follow-up no differences were found (data not shown).

Length and weight of children in both groups remained similar during follow-up (data not shown).

Subgroup analysis

The effects of adenotonsillectomy were more pronounced in children with 3 to 6 throat infections in the year before trial entry than in children with 0 to 2 throat infections (Table 3). For fever episodes incidence rate differences were -1.07 (95% CI –1.59 to -0.56) and 0.34 (95% CI –0.08 to –0.77) per person year, respectively (p=0.01). For sore throat days incidence rate differences were –11.33 (95% CI –12.48 to –10.17) and –2.38 (95% CI –3.19 to –1.60) per person year, respectively (p=0.01). Age did not influence the effectiveness of adenotonsillectomy.

Complications of surgery

Of 195 children (145 in the adenotonsillectomy group and 50 in the watchful waiting group) who underwent adenotonsillectomy, 12 (6.2%) had surgery related complications. Seven children had a primary haemorrhage: 2 (1%) were managed surgically, and 5 (3%) non-surgically, i.e. blood clot was removed from tonsillar fossa; 3 children (2%) were admitted for observation for one night. None of these children needed a blood transfusion. Five children (3%) suffered from postoperative nausea, which was managed by anti-emetic medication and intravenous hydration.

Table 3. *INCIDENCE RATE DIFFERENCES (95% CI) BETWEEN T&ADS AND WW GROUP FOR FEVER-, THROAT INFECTION-, URI EPISODES AND SORE THROAT DAYS IN SUBGROUPS*

	Fever episodes	p-value	Throat infection episodes	p-value	Sore throat days	p-value	URI episodes	p-value
Overall	−0.21 (−0.54 to 0.12)		−0.21 (−0.36 to −0.06)		−5.91 (−6.57 to −5.24)		−0.53 (−0.97 to −0.08)	
Indication								
• Recurrent throat infections	−0.84 (−1.33 to −0.35)		−0.38 (−0.62 to −0.13)		−9.70 (−10.79 to −8.61)		−0.33 (−0.99 to 0.34)	
• Other indications	0.27 (−0.18 to 0.72)	0.10	−0.08 (−0.28 to 0.11)	0.12	−3.19 (−4.04 to −2.35)	0.06	−0.63 (−1.24 to −0.02)	0.79
Number of throat infections in the year before trial entry								
0-2	0.34 (−0.08 to 0.77)		−0.03 (−0.21 to 0.15)		−2.38 (−3.19 to −1.60)		−0.27 (−0.86 to 0.32)	
3-6	−1.07 (−1.59 to −0.56)	0.01	−0.49 (−0.75 to −0.22)	0.05	−11.33 (−12.48 to −10.17)	0.01	−0.92 (−1.61 to −0.23)	0.18

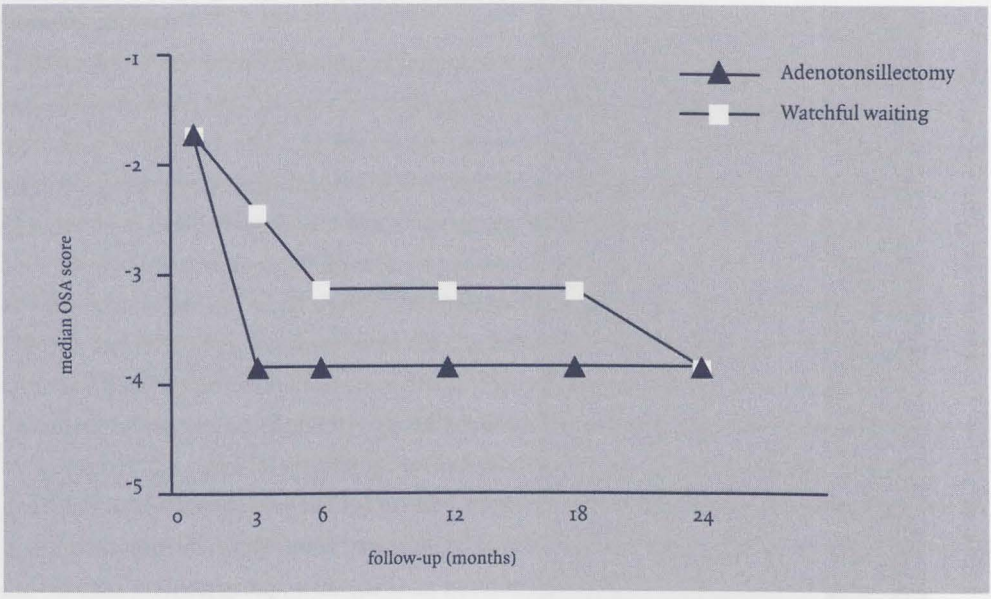


Figure 5. MEDIAN BROUILLETTE OSA-SCORE FOR ADENOTONSILLECTOMY AND WATCHFUL WAITING GROUPS DURING FOLLOW-UP

Discussion

In children undergoing adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy, surgery as compared to watchful waiting reduced the number of fever episodes and throat infections by 0.21, and upper respiratory infections by 0.53 episodes per person year. The effects of adenotonsillectomy were more pronounced in children with 3 to 6 throat infections in the year before trial entry than in those with 0 to 2 throat infections. No clinically relevant differences were found regarding health-related quality of life.

Short-term effect

During the first 6 months of follow-up the incidence of fever episodes was significantly lower in children in the adenotonsillectomy group than in the watchful waiting group. From 6 to 24 months, however, the incidence per person year of fever episodes was the same in both groups. Similarly, sleeping and eating patterns initially improved more in children in the adenotonsillectomy group than in the watchful waiting group, but by 24 months these differences had disappeared. This reduction of complaints in the surgically managed children in the first 6 months following the operation might explain why parents and doctors usually are satisfied with the benefits of the intervention, this being the period

in which routinely postoperative follow-up visits are planned and in which parental satisfaction was measured in most non-controlled studies.[12,17,18]

Possible limitations

To appreciate the results of our trial, several limitations should be mentioned. First, children indicated for adenotonsillectomy for very frequent throat infections or obstructive sleep apnoea were excluded from this trial as these symptoms are generally considered adequate indications for surgery. Our results are therefore generalisable to children with milder symptoms of throat infections or adenotonsillar hypertrophy.

Second, fifty children (34%) changed from watchful waiting to surgery during follow-up. Similar high switch rates have been reported in previous trials of adenotonsillectomy in children.[3,19-22] In surgical trials like ours, only children in the watchful waiting group wishing to change treatment group because of persisting complaints can do this, whereas children in the surgical group, who may experience similar persisting complaints cannot change treatment group. Per protocol analyses excluding children who changed treatment groups will therefore result in an underestimation of the treatment effect. Conversely, analysing children on the basis of the time spent in any treatment arm might result in either an over- or underestimation of the treatment effect. To avoid such bias and taking into account our intention to compare *strategies* including adenotonsillectomy versus initial watchful waiting, we chose for intention-to-treat analysis.

Third, we measured health-related quality of life with generic questionnaires because disease-specific instruments for children with tonsil and adenoid disease were not available when our study was initiated.[23] TAPQoL and TACQoL questionnaires were chosen because they include specific domains thought to be relevant for children with tonsil and adenoid disease, e.g. eating and sleeping pattern.[12] Since the scores of our population at baseline were similar to those of healthy children, large improvement during follow-up was not to be expected.

Fourth, not all eligible children entered the trial, which might influence the generalisability of the results. In an earlier study on the representativeness of our trial population, however, we showed that there were no major differences between included children and eligible children.[24]

Strengths of our study

Because in previous trials[3,19-22,25] an objective outcome measure was not included, all suffer from potential information bias since parents of children in the watchful waiting group may be more likely to report sore throat or upper respiratory infection symptoms than parents of children in the intervention group. This would lead to an overestimation of the intervention

effect.[26,27] The major strength of our study therefore is the inclusion of an objective primary outcome, i.e. fever measured daily by a validated thermometer automatically storing data.[16] Fever is an important physical sign in many childhood diseases; and the majority of fever episodes in children younger than 8 years are caused by upper respiratory infections.[28,29] Our study shows that adenotonsillectomy as compared to watchful waiting did not significantly reduce the objective outcome fever episodes but did have a small but statistically significant effect on the number of throat infections.

Also of importance is that the power of our study was large enough to allow for subgroup analyses, providing a tool for clinicians to identify children that are more or less likely to benefit from adenotonsillectomy.

Conclusion

In the children indicated for adenotonsillectomy for relatively mild symptoms of throat infections or adenotonsillar hypertrophy, the operation had no relevant clinical benefits to offer over a watchful waiting policy.

Ethical approval | The study was undertaken in accordance with the European statement for good clinical practice, which includes the provisions of the declaration of Helsinki of 2000.[30] The medical ethics committees of all participating hospitals approved the study protocol.

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Participating hospitals: Almere, Flevo Hospital; Alphen a/d Rijn, Rijnland Hospital; Amersfoort, Meander Medical Center; Amsterdam, BovenIJ Hospital; Apeldoorn, Gelre Hospital; Baarn, Meander Medical Center; Blaricum, Hospital Gooi-Noord; Gouda, Groene Hart Hospital; 's Hertogenbosch, Jeroen Bosch Hospital; Leiden, University Medical Center Leiden; Leiderdorp, Rijnland Hospital; Lelystad, IJsselmeer Hospital; Nieuwegein, Stichting Sint Antonius Hospital; Rotterdam, Sophia Children's Hospital; Schiedam, Vlietland Hospital; Utrecht, Mesos Medical Center, location Oudenrijn and Overvecht; Utrecht, Wilhelmina Children's Hospital; Vlaardingen, Vlietland Hospital; Voorburg, Reinier de Graaf Hospital; Woerden, Hofpoort Hospital; Zwolle, Isala Clinics, location Weezenlanden and Sophia.

Executive steering committee: AAA Bak, MD PhD; PPG van Benthem, MD PhD; E Buskens, MD PhD; A Fleer, MD PhD; DE Grobbee, MD PhD; JLL Kimpen, MD PhD; EAM Sanders, MD PhD; ThJM Verheij, MD PhD.

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chapter 5 Representativeness of trial populations: an example from a trial on adenotonsillectomy in children

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Abstract

Objective | To compare demographic and disease-specific characteristics of children included in a trial on the effectiveness of adenotonsillectomy with those of children who, although eligible, were not randomised.

Methods | Characteristics were compared between 1) randomised children (n=270); 2) eligible children whose parents immediately decided not to participate (n=243); 3) eligible children whose parents were informed about the trial by a member of the study team, but gave no informed consent (n=406).

Results | Statistically significant but relatively small differences were observed. Notably, breathing difficulties at night and abnormal appearance of the tonsils were more prevalent among eligible children whose parents immediately refused participation than in the other two groups. In contrast, cervical lymphadenopathy and previous ENT surgery were less prevalent among eligible children whose parents immediately refused participation.

Conclusion | Few and relatively small differences were observed between randomised and eligible, but non-randomised children. The trial population appears to be representative of the relevant patient domain, i.e. children currently undergoing adenotonsillectomy in The Netherlands.

Introduction

Randomised controlled trials (RCTs) are widely accepted as the research paradigm for quantifying the magnitude of treatment effects. In well-designed trials, validity is virtually ensured, whereas observational studies are often viewed as having less validity as unrecognized confounding factors may distort the results. A disadvantage of RCTs, however, is that the study population is often a highly selective sample of the clinically relevant domain population,[1-3] i.e. the population to which the study results are meant to be applicable. To facilitate implementation of trial results in daily practice, the results have to be generalisable to the clinically relevant patient domain.

Generalisability can only be assessed adequately when every step in trial recruitment is carefully described and when demographic and disease-specific characteristics are reported not only for the randomised patients, but also for eligible non-randomised patients.[4]

Regarding the effectiveness of adenotonsillectomy in children, 5 trials have been published so far.[5-9] Only the trial performed by Paradise et al.[8,9] is generally considered to be free from methodological flaws. The very strict entry criteria of this trial (children severely affected by throat infections), however, limit generalisability of its results to the much larger population of children undergoing adenotonsillectomy for less severe symptoms. To assess the effectiveness of adenotonsillectomy in children undergoing this operation for less severe symptoms, we initiated an open pragmatic trial including children listed for adenotonsillectomy according to current medical practice in The Netherlands.

This paper documents the representativeness of our trial population by comparing the characteristics of randomised children with those of eligible but non-randomised children.

Methods

This study is part of a multicentre RCT on the effectiveness of adenotonsillectomy in children. Participants were recruited by otolaryngologists in 24 hospitals located predominantly in the West and Centre of the Netherlands (see Figure 1). Participating otolaryngologists were asked to fill out an entry form on every child aged 2-8 years that they considered indicated for adenotonsillectomy. This form included information on the indications for surgery, throat infections, previous ear, nose and throat (ENT) surgery, and physical findings. It also included parental consent for this information to be used for study purposes and for the study team to contact them. Upon receiving this form at the study centre, a member of the study team (physician) contacted the parents by telephone to check the in- and exclusion criteria. Inclusion criteria were: age 2-8 years and indicated for surgery according to current medical practice in The Netherlands. Exclusion criteria were: Down's syndrome, craniofacial

malformation, documented immunodeficiency other than IgA or IgG2 deficiencies, and the indications for which adenotonsillectomy generally is considered to be effective, i.e. a history of 7 or more throat infections in the preceding year, 5 or more in each of the two preceding years, or 3 or more in each of the 3 preceding years[8] and a strong suspicion of obstructive sleep apnoea defined as a Brouillette's OSA-score of 3.5 and higher.[10]

Parents of eligible children were then informed further about the trial. Children for whom informed consent was obtained were randomly allocated to one of two groups. The first group underwent adenotonsillectomy, while in the second group a non-surgical strategy was followed (watchful waiting). Both groups were followed for 2 years. The main outcome measurements were: number of throat infections and fever episodes, and quality of life.

This report concerns the first 270 randomised children. In total, 300 children were included.

Figure 1. MAP OF THE NETHERLANDS SHOWING THE RECRUITMENT OF PARTICIPANTS

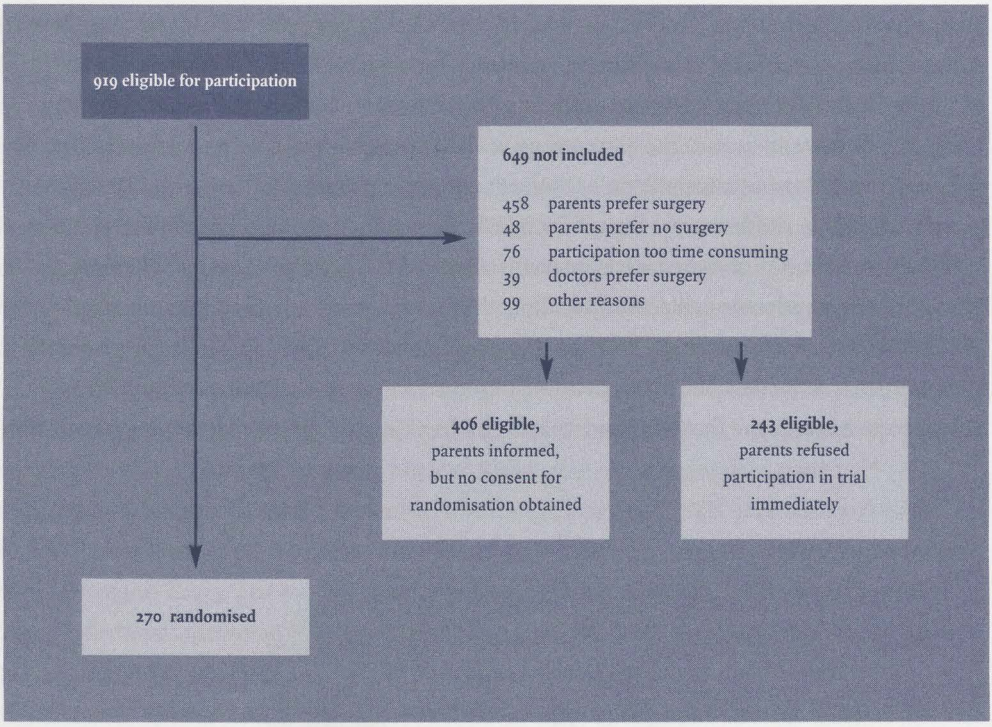

Figure 2. FLOW-CHART OF THE 919 CHILDREN ELIGIBLE TO PARTICIPATE IN THE TRIAL

Patients

Entry forms were received from 1129 children aged 2-8 years, indicated for adenotonsillectomy. Two hundred and ten children met the exclusion criteria, leaving 919 children eligible for participation in the trial. Parents of 270 children gave informed consent for their child to be randomised. Parents of 649 children decided not to participate in the trial for various reasons, see also Figure 2. Within the group of non-randomised children, two groups could be distinguished whose parents decided at different stages in the recruitment process not to participate: 243 parents refused participation immediately when their local otolaryngologist informed them about the trial. These parents did, however, not object to provide further information for study purposes, so that in- and exclusion-criteria could be checked and their reasons for not participating could be documented. The other 406 parents decided against participation in the trial only after they had received detailed information on the trial by a member of the study team.

Comparisons

Demographic and disease-specific characteristics were compared between 3 groups: 1) 270 randomised children; 2) 243 eligible children whose parents immediately decided not to participate; 3) 406 eligible children whose parents were informed by a member of the study team, but did not consent to randomisation. Information on the children was obtained from the entry forms completed by the referring otolaryngologist on every potential participant and from a standard questionnaire completed by a member of the study team during the first contact with the parents by telephone.

The following characteristics were compared: age; gender; previous ENT interventions (myringotomy with/without tympanostomy tubes and adenoidectomy); the indication for adenotonsillectomy, classified as (1) recurrent tonsillitis, (2) obstructive symptoms, (3) other indications such as failure to thrive, otitis media, parental pressure; frequency of tonsillitis episodes in the year before trial entry; total duration of tonsillitis related symptoms; presence of breathing difficulties at night (Brouillette's OSA-score ranging from -1 to 3.5);[10] size of tonsils, with enlarged tonsils defined as enlarged beyond the pillars but not meeting the uvula or "kissing" tonsils; appearance of tonsils, with abnormal defined as the presence of erythema, crypts, or tonsillar exudate; size and number of cervical lymphnodes, with lymphadenopathy defined as multiple palpable lymph nodes smaller than 1 centimeter, or lymph nodes larger than 1 centimeter.

Statistical analysis

Differences between the groups of children were tested using univariate analyses of variance (ANOVA) for mean scores and Chi-square tests for proportions.

Results

Table 1 shows the distribution of the measured demographic and disease-specific characteristics among the randomised (group 1) and non-randomised (group 2 and 3) children. Small but statistically significant differences were found for previous ENT surgery, breathing difficulties at night, abnormal appearance of the tonsils, and presence of cervical lymphadenopathy. A smaller proportion of eligible children whose parents refused participation immediately had had previous ENT-operations (12.7%) as compared to the children included in the trial (22.5%) and the children whose parents did not give informed consent (21.3%). A larger proportion of non-randomised children, especially those whose parents refused participation immediately had breathing difficulties at night (11.7%, 19.6% and 22.1% for groups 1, 2 and 3, respectively). Similarly, abnormal appearance of the tonsils

Table 1. DEMOGRAPHIC AND DISEASE-SPECIFIC CHARACTERISTICS

	Randomised children N=270		Eligible children whose parents did not give informed consent N= 406		Eligible children whose parents refused participation immediately N=243	
	n	% / mean	n	% / mean	n	% / mean
Gender						
• male	136	50.6	229	56.4	120	49.4
• female	133	49.4	177	43.6	123	50.6
Mean age (months)	264	54.1	398	51.9	242	51.7
Indication for surgery						
• recurrent tonsillitis	124	46.3	183	45.8	113	46.9
• obstructive symptoms	56	20.9	81	20.3	48	19.9
• other indications	88	32.8	136	34.0	80	33.2
Mean number of tonsillitis episodes in year before trial entry	149	4.3	225	4.6	133	4.4
Mean duration of tonsillitis related symptoms	162	14.3	260	15.8	159	14.9
Previous ENT-surgery [a]						
• Yes	58	22.5	85	21.3	30	12.7
• No	200	77.5	314	78.7	206	87.3
Breathing difficulties at night [b]						
• Yes	30	11.7	70	19.6	49	22.1
• No	226	88.3	288	80.4	173	77.9
Abnormal appearance of the tonsils [c]						
• Yes	206	79.5	317	81.1	205	88.4
• No	53	20.5	74	18.9	27	11.6
Enlarged tonsils [d]						
• Yes	217	83.1	302	76.1	193	79.4
• No	44	16.9	95	23.9	50	20.6
Cervical lymphadenopathy [e]						
• Yes	185	70.1	300	75.0	159	66.3
• No	79	29.9	100	25.0	81	33.8

For the underlined values statistically significant differences were observed ($p<0.05$)

[a] myringotomy with/without ventilation tubes and/or adenoidectomy;

[b] Brouillette's OSA-score ranging from –1 to 3.5;

[c] presence of tonsillar crypts and/or tonsillar exudate and/or erythema of the tonsils;

[d] tonsils enlarged beyond the pillars but not meeting the uvula or "kissing" at the midline;

[e] presence of several palpable lymph nodes smaller than 1 cm and lymph node(s) larger than 1 cm

was found more often in these children (88.4%) than in those children whose parents were informed in more detail about trial participation (79.5% and 81.1% for group 1 and 2, respectively). Children whose parents did not consent to randomisation where more often diagnosed with cervical lymphadenopathy (75.0%) than the randomised children (70.1%) and the children whose parents refused participation immediately (66.3%).
No differences were observed for gender, mean age, indication for surgery, mean number of tonsillitis episodes in the year before trial entry, mean duration of tonsillitis related symptoms, and size of tonsils.

Discussion

The impact of trial results upon policy and practice depends on the applicability of the results. Therefore, it is important to assess whether the randomised patients are representative of the patients for which the results are meant to be applied, i.e. the clinically relevant patient domain. Only then, a judgement of the generalisability can be formed. We therefore determined the representativity of our trial population and subsequent limitations that there might be in generalizing the results of the trial to current medical practice.
Fewer children whose parents refused participation immediately had had adenoidectomy or tympanostomy tubes placed than children whose parents at least took part in the procedure for informed consent. It is possible that the parents of children who have not been operated upon before prefer adenotonsillectomy over watchful waiting because they expect more from this intervention than parents whose children have been operated upon before. Parents of children with breathing difficulties at night, or abnormal physical findings such as an abnormal appearance of the tonsils were less likely to give informed consent for randomisation.
Loss of representativeness only affects the generalisability of trial results if the included patients differ from the eligible but non-included patients with respect to determinants of the magnitude of treatment effect (i.e. effect modifiers). If for example boys are over-represented in a trial, and the beneficial effect of the intervention is greater for boys than for girls, the treatment effect in the trial would be an overestimate and not generalisable to the population for which the intervention was designed, i.e. all children. On the other hand, if a variable is shown not to influence the treatment effect, any discrepancy in this variable between included and non-included patients does not affect the generalisability of the results. The question therefore remains whether the variables for which we have identified differences modify treatment effect.
The most important variables that might modify treatment effect are indication for surgery, mean number of tonsillitis episodes in the year before trial entry, and mean duration of

tonsillitis related symptoms. All these factors will be related to the severity and might also have the greatest impact on effect magnitude.[8] In this study, however, only small differences between the randomised and non-randomised children were found for these characteristics. Moreover, the trial is large enough to study the effects in subgroups.

A limitation of our study is that information on some potential effect modifiers, such as day-care attendance, number of siblings, and socio-economic status, was not available in the non-randomised children, and thus comparison with the included children was not possible. However, it seems unlikely that large differences in these variables existed, since they would have resulted in differences in some of the disease specific variables, e.g. in the mean number of tonsillitis episodes or the duration of symptoms.

This study showed, in agreement with others,[4,11,12] that the implication of the trial results should not be evaded by suggestions that patients participating in a trial differ importantly from patients in a particular local practice or part of the healthcare system. However, to overcome this often heard criticism it is important to build up knowledge enabling generalisation.

In summary, given the similarity between children who were randomised and eligible children who were not, it seems justified to conclude that the children included in our trial are representative of children of the clinically relevant patient domain, i.e. children not meeting the so called "Paradise criteria"[8] and undergoing adenotonsillectomy according to current medical practice in the Netherlands.

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chapter 6 Immunological evaluation in children with tonsillar disease

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Submitted for publication

Abstract

Objective | The aim of the present study is to evaluate the humoral immune status of children with tonsillar disease as compared to that of healthy age-matched controls.

Design | Serum immunoglobulins IgM, IgG and IgA and IgG subclasses were determined in 218 children indicated for adenotonsillectomy and compared to normal age-matched control values. Immunoglobulins IgM, IgG and IgA were determined by rate nephelometry, IgG subclass concentrations were measured by radial immunodiffusion. To investigate the relation between number of tonsillitis episodes and immunoglobulin levels, children were divided in two groups: children with 0 to 2 episodes of tonsillitis in the year before trial entry (indicated for adenotonsillectomy predominantly because of tonsillar hypertrophy) versus children with 3 to 6 episodes of tonsillitis in the year before trial entry (indicated for adenotonsillectomy because of recurrent tonsillitis).

Results | For the overall group of 218 children, IgM, IgG, IgA and IgG1 levels were in the high normal range or higher than 2 SD above the age-specific mean. In contrast, IgG2 levels were in the low normal range. No significant differences in immunoglobulin levels were found between children with tonsillar hypertrophy and children with recurrent tonsillitis.

Conclusions | In children with tonsillar disease no overall immunodeficiency was found. Variation in immunoglobulin levels does not seem to play an essential role in the predisposition of children to tonsillar disease.

Introduction

Tonsils and adenoids are part of Waldeyer's ring and as such involved in the defence against airborne and alimentary microorganisms.

Little is known about the immune status of children with tonsillar disease, such as recurrent tonsillitis and tonsillar hypertrophy, as compared to that of healthy age-matched controls. Immunoglobulin levels may be elevated due to repeated antigenic stimulation caused by recurrent infections, or may be reduced reflecting an immunological dysfunction, resulting in tonsillar disease. Previous studies have shown immunoglobulin levels of children with recurrent tonsillitis and tonsillar hypertrophy to be elevated.[1-9] These studies, however, were based on small groups of children. Only three studies[2,4,5] have associated immunoglobulin levels with clinical symptoms.

In children with recurrent acute otitis media (rAOM)[10] and recurrent respiratory infections (rRI)[11] on the other hand, low levels of IgG2 have been found, indicating a partial immunodeficiency resulting in increased susceptibility to infections. This has not been demonstrated for children with tonsillar disease.

The purpose of the present study is to study humoral immunity (IgM, IgG, IgA and IgG subclasses) in a large group of 218 children with a well documented clinical history of tonsillar disease, participating in a multicentre randomised controlled trial on the effectiveness of adenotonsillectomy. To study the relationship between the number of tonsillitis episodes and immunoglobulin levels, children are divided in two groups: children with 0 to 2 episodes of tonsillitis in the year before trial entry (indicated for adenotonsillectomy predominantly because of tonsillar hypertrophy) versus children with 3 to 6 episodes of tonsillitis in the year before trial entry (indicated for adenotonsillectomy because of recurrent tonsillitis). With the results we hope to be able to answer the question whether variation in immunoglobulin levels predisposes children to tonsillar disease.

Material and Methods

The present study is part of a multicentre randomised controlled trial on the effectiveness of adenotonsillectomy in children in The Netherlands. Inclusion criteria for the trial were: (1) Adenotonsillectomy, indicated according to current Dutch guidelines,[12] i.e. 3 or more episodes of tonsillitis per year, or symptoms of tonsillar hypertrophy such as difficulty swallowing, snoring and disturbed sleep; (2) age between 2 and 8 years. Not included in the study because for these indications the effectiveness of adenotonsillectomy has previously been established, were children with: (1) a history of 7 or more throat infections in the preceding year, or 5 or more in each of the two preceding years, or 3 or more in each of the

3 preceding years (Paradise criteria)[13]; (2) high suspicion of obstructive sleep apnoea syndrome (Brouillette's OSA score ≥ 3.5).[14] Other exclusion criteria were: (1) Down's syndrome; (2) craniofacial malformation; (3) documented immunodeficiency, other than IgA or IgG2 deficiencies.

Baseline measurements comprised disease-specific questionnaires including number of tonsillitis episodes in the year before trial entry and obstructive symptoms during the night according to the Brouillette's OSA-score (this score combines the degree of snoring, difficulty breathing during sleep and apnoea as observed by the parents)[14] Serum samples for immunological evaluations were obtained at the first visit. Informed consent was obtained from the caregivers / parents of all children before participation in the study. The Medical Ethics Committee of all participating hospitals had approved the study protocol.

Total serum immunoglobulin concentrations of IgM, IgG and IgA were determined by rate nephelometry. The IgG subclass concentrations were measured by radial immunodiffusion (Behring Werke,Mannheim, Germany and Central Laboratory of the Red Cross Blood Transfusion Service, Amsterdam, The Netherlands). A serum immunoglobulin level within the range of two standard deviations below or above the age-specific mean was considered normal.[15] Total deficiency of IgA was defined as a serum level of ≤0.05 g/l. Total deficiency of IgG2 was defined as a serum level of ≤0.02 g/l.

To investigate the relationship between clinical recurrent tonsillitis episodes in the year before trial entry and the immunoglobulin levels, the children were divided in two groups: children with 0 to 2 episodes of tonsillitis in the year before trial entry (indicated for adenotonsillectomy predominantly because of obstructive symptoms due to tonsillar hypertrophy) versus children with 3 to 6 episodes of tonsillitis (indicated for surgery because of recurrent tonsillitis).

Differences in percentages between children with tonsillar hypertrophy and children with recurrent tonsillitis were analysed with Chi-square test or Fisher's Exact test when appropriate. Differences in means were analysed with Student's t-test for independent samples and a difference in median OSA score was analysed with ANOVA. Differences in mean immunoglobulin levels between children with tonsillar hypertrophy and children with recurrent tonsillitis were analysed with Student's t-test for independent samples. Group differences were considered statistically different at $p<0.05$.

Table 1. PATIENT CHARACTERISTICS OF 218 CHILDREN INDICATED FOR ADENOTONSILLECTOMY.

	Indications for surgery		
	Tonsillar hypertrophy (0-2 episodes of tonsillitis in the year before trial entry) (N=129)	Recurrent tonsillitis (3-6 episodesof tonsillitis in the year before trial entry) (N=89)	P-value
Mean age in months (SD)	57 (± 15.0)	56 (± 19.0)	0.84
Mean number of tonsillitis episodes in the year before trial entry (SD)	0.73 (± 0.83)	4.03 (± 1.04)	<0.001
Median Brouillette's OSA score (range)*	-1.7 (-3.83 to 2.56)	-2.4 (-3.83 to 2.55)	0.006
Male sex N (%)	65 (52.0%)	46 (51.7%)	0.96
Nasal allergy N (%)	39 (31.2%)	25 (28.1%)	0.85
Recurrent wheezing N (%)	10 (8.0%)	9 (10.1%)	0.52
Breastfed for more than 1 month N (%)	82 (66.1%)	49 (55.7%)	0.12
Attendance at day-care (only for children younger than 4 years of age) N (%)	34 (29.1%)	33 (39.8%)	0.11
Previous ENT surgery (myringotomy, tympanostomy tubes and/or adenoidectomy) N(%)	35 (28.0%)	22 (24.7%)	0.59

* Brouillette's OSA-score: 1.42 x difficulty breathing + 1.41 x apnoea + 0.71 x snoring – 3.83.

Table 2. MEAN (SEM) SERUM IMMUNOGLOBULIN CONCENTRATIONS ACCORDING TO THE NUMBER OF TONSILLITIS EPISODES IN THE YEAR BEFORE TRIAL ENTRY

Immunoglobulin	0-2 episodes of tonsillitis per year (n=129)	3-6 episodes of tonsillitis per year (n=89)	P-value
IgA g/l	1.14 (0.04)	1.21 (0.06)	0.40
IgG g/l	10.67 (0.21)	10.69 (0.24)	0.94
IgM g/l	1.47 (0.05)	1.54 (0.06)	0.33
IgG1 g/l	8.62 (0.20)	8.53 (0.19)	0.74
IgG2 g/l	1.53 (0.05)	1.46 (0.07)	0.48

Results

Between March 2000 and August 2002, 301 children were included in the trial. Serum samples for immunological evaluation were available for 218 children. The 218 children in the present study were comparable to 83 children from whom we did not obtain serum samples, concerning sex, number of tonsillitis episodes in the year before trial entry and Brouillette's OSA score. Because of difficulties in obtaining serum samples in young children, the mean age of the children from whom no serum samples were obtained was 49.4 months and that of the children in the present study population was 56.4 months (P< 0.001).

Patient characteristics of the children with few versus frequent episodes of tonsillitis are

provided in Table 1. Other than the expected difference in the Brouillette's OSA score (-1.7 for children with few and −2.4 for children with frequent episodes of tonsillitis; p=0.006), the two groups did not differ significantly.

IgM, IgG, IgA and IgG1 values of the total group of children were significantly higher than 2 SD above the mean normal value (IgM: t=6.171, p<0.001; IgG: t=9.084, p<0.001; IgA: t=3.771, p<0.001 and IgG1: t=-2.484, p<0.05). The IgG2 levels were mostly in the low normal range (Figure 1). IgG3 and IgG4 levels were also found to be in the low normal range. Since latter IgG subclasses have a limited clinical relation with upper respiratory tract infections, they are not included in further analyses. Two children were detected with total IgA deficiency. Neither of them had suffered from episodes of tonsillitis in the preceding year. One child was detected with IgG2 deficiency. He had had 3 episodes of tonsillitis in the year before trial entry.

Table 2 shows the mean total serum levels of IgM, IgG, IgA, IgG1 and IgG2, according to number of tonsillitis episodes in the year before trial entry. No significant differences between the group with 0 to 2 episodes of tonsillitis and that with 3 to 6 episodes of tonsillitis were found.

Discussion

The present study of a large group of children with symptoms of tonsillar disease shows that IgM, IgA, total IgG and IgG1 levels range from normal to high compared to age-matched normal control values, whereas IgG2 subclass levels are in the low normal range. No relation was found between the frequency of tonsillitis episodes and serum immunoglobulin levels. Several authors[1-9] have compared immunoglobulin levels in children with recurrent tonsillitis to those of healthy age-matched controls. Their results are not equivocal. Jung et al.[8] found significantly higher IgA levels in children with diseased tonsils than in those with healthy tonsils. They suggested that the presence of Haemophilus Influenzae and beta-Haemolytic Streptococci stimulate both serum- and saliva IgA levels. On the other hand, Donovan et al.,[2] Østergaard,[3] and Kerr et al.[4] reported that immunoglobulin IgA levels are significantly lower in children with tonsillar disease compared to those in a healthy control population. They suggest that these low levels are part of a delayed immunological maturation. Veltri et al.[1] described elevated levels of both immunoglobulins IgA and IgG in children referred for adenotonsillectomy compared to healthy age-matched controls. Surjan et al.[5] found elevated immunoglobulin IgG levels. The results of the studies by Lal et al. and Zielnik-Jurkiewicz et al.[6,9] are comparable to ours: stimulated levels of IgM, IgG and IgA in children with tonsillar symptoms compared to normal age-matched immunoglobulin levels. Apparently, persistent

or repeated exposure to pathogens (viral or bacterial) causes elevation of serum immunoglobulin levels. It will be interesting to follow whether the stimulated immunoglobulin levels of the present group of children will change after adenotonsillectomy compared to children from whom surgery is withheld.

Veenhoven et al.[16] have shown a relation between immunoglobulinlevels and the number of AOM episodes. IgG, IgA, IgM, IgG1 and IgG2 levels were significantly lower in children with a history of more than 4 episodes of AOM per year than in those with 2-3 episodes per year, indicating a general humoral hyporesponsiveness to repeated antigenic stimulation in otitis-prone (>4 episodes of AOM) children. In children with recurrent tonsillitis this has only been demonstrated in young children. Yokoyama et al.[17] found that serum immunoglobulin levels IgA and IgG in children indicated for adenotonsillectomy correlated positively to episodes of tonsillitis in children aged 2-5 years but not in children aged 6-15 years. In our population no relation between the incidence of tonsillitis and serum immunoglobulin levels was found. However, by excluding children with very frequent episodes of tonsillitis (Paradise criteria),[13] we may have missed such relationship.

The finding of low-normal levels of IgG2, while total IgG level is high in this study, is remarkable. Similar, but more outspoken reduction of IgG2 levels (> 2 SD below the normal value) have been found by Freijd et al.[10] in children with rAOM and by Shackelford et al.,[11] Stanley et al.,[18] and Umetsu et al.[19] in children with rRI. They suggested that low levels of IgG2 in children might be part of a discrete immunodeficiency associated with increased susceptibility to respiratory infections. In children with tonsillar disease however, such a minor immunodeficiency could not be demonstrated.

In conclusion, in children with tonsillar disease no overall immunodeficiency was found. Variation in immunoglobulin levels does not seem to play an essential role in the predisposition of children to tonsillar disease.

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chapter 7

Long-term effects of paediatric adenotonsillectomy on serum immunoglobulin levels: results of a randomised controlled trial

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Abstract

Background | It remains controversial whether paediatric adenotonsillectomy ultimately results in decreased serum immunoglobulin levels, and if so whether such a decrease is associated with increased susceptibility to upper respiratory infections (URIs).

Objective | To evaluate changes in serum immunoglobulin levels in relation to occurrence of URIs in children participating in a randomised controlled trial on the effectiveness of adenotonsillectomy.

Methods | 300 children aged 2 to 8 years, with symptoms of recurrent throat infections or tonsillar hypertrophy, were randomly assigned to either adenotonsillectomy (T&Ads) or a watchful waiting strategy (WW). Serum samples were collected at baseline and at 1 year follow-up. Serum IgM and IgA were measured by rate nephelometry, IgG1 and IgG2 by radial immunodiffusion. Occurrence of throat infections and other upper respiratory infections during first-year follow-up were recorded in a diary by the child's parents.

Results | Paired serum samples were available for 123 children (T&Ads: 63 and WW: 60). IgG1 and IgG2 levels decreased but remained within normal range for age in both study arms. IgM and IgA levels decreased as well, but remained elevated. IgA in the T&Ads group decreased in significantly greater degree compared to the WW group, but this difference disappeared in cases where children suffered from frequent URIs. In general, no relation between immunoglobulin levels and the number of throat infections or URIs at 1 year follow-up was found.

Conclusions | Immunoglobulin levels of children indicated for T&Ads decreased from elevated to slightly elevated or normal values for age during 1 year follow-up irrespective of treatment (T&Ads or WW). IgA showed a greater decrease in the T&Ads group, but rose to levels comparable with the WW group in case of frequent URIs. This indicates that the remaining mucosa associated lymphoid tissue (MALT) can compensate for the loss of tonsil and adenoid tissue.

Introduction

Tonsils and adenoid are part of Waldeyer's ring and are important elements in the defence against airborne and alimentary organisms. They play an important immune-inductive role as components of mucosa-associated lymphoid tissue (MALT).[1] Tonsils contain B-cells that, in response to antigens, differentiate to plasma cells and generate polymeric IgA (pIgA), resulting in systemic immunity as well as mucosal immunity.[2]

Adenotonsillectomy (T&Ads) is one of the most frequently performed surgical procedures in children. Nevertheless, there is still uncertainty about the ultimate effects of the procedure.[3-5] It has been hypothesized that the removal of tonsils and adenoid in young children may cause a delay in development, and a limited and less differentiated immune response.[1,6] This, in turn, might increase children's susceptibility to respiratory infections rather than lead to the intended decrease of infections, by surgical removal of the infection focus. With respect to humoral immunity, several studies have reported a decrease in serum immunoglobulin levels following adenotonsillectomy.[7-15] The relevance of these findings is however questionable since most of these studies did not include a randomly allocated non-surgical control group and no associated occurrence of respiratory infections could be found.[7,9,11,12]

The present study aims to answer the following questions: 1) Do immunoglobulin levels change following adenotonsillectomy in children and, if so, are these changes different from those in children managed non-surgically for the same tonsillar complaints? 2) Are changes in serum immunoglobulin levels related to the occurrence of throat infections and other upper respiratory infections? To answer these questions we evaluated changes in immunoglobulin levels and the occurrence of upper respiratory infections in a large population of children participating in a multicentre randomised controlled trial on the effectiveness of adenotonsillectomy.

Material and Methods

Patients

The present study is part of an open multicentre randomised controlled trial (RCT) on the effectiveness of adenotonsillectomy in children in The Netherlands.[16] Between March 2000 and August 2002, otolaryngologists in 21 general hospitals and 3 academic centres in The Netherlands recruited participants and provided information for every child aged 2 to 8 years indicated for adenotonsillectomy (T&Ads) according to current medical practice. For this purpose, participating otolaryngologists completed a questionnaire including the indication considered most important in their decision to perform surgery: either recurrent

throat infections (3 or more episodes per year) or other indications such as obstructive complaints or recurrent upper respiratory infections.

Exclusion criteria

Children with either (1) a history of 7 or more throat infections in the preceding year, or 5 or more in each of the two preceding years, or 3 or more in each of the 3 preceding years,[17] or (2) with a high suspicion of obstructive sleep apnoea syndrome, i.e. Brouillette's OSA score of more than 3.5,[18] were excluded from this trial because consensus already exists as to the benefit of the procedure for these indications. Other exclusion criteria were: (1) Down's syndrome; (2) craniofacial malformation; (3) documented immunodeficiency, other than IgA and IgG2 subclass deficiency.

Randomisation

Children whose parents gave informed consent were randomly assigned to one of two trial arms: 1) adenotonsillectomy (T&Ads) within 6 weeks, or 2) a non-surgical or watchful waiting (WW) strategy. For this purpose computer generated fixed blocks of four were used within hospitals. The study was undertaken in accordance with the European statement for good clinical practice, which includes the provisions of the declaration of Helsinki of 2000.[19] The medical ethics committees of all participating hospitals approved the study protocol.

Inclusion

At inclusion, disease-specific questionnaires were filled out, including information on number of throat infections and upper respiratory infections (URIs) in the year before trial entry, previous ENT operations and risk factors for URIs such as atopic symptoms and attendance at day-care. A venous serum sample for immunoglobulin evaluation was collected.

Follow-up

During the study, parents kept a diary of complaints of upper respiratory infections in their child, such as sore throat, pain/difficulty at swallowing, cough, rhinorrhea, earache and otorrhea. The child's temperature was measured daily with a validated infrared tympanic membrane thermometer.[20] Both diary- and thermometer data were collected by the study physician during the scheduled follow-up visits at 3, 6, 12, 18 and 24 months. At 12 months a second serum sample for immunoglobulin evaluation was collected.

Immunological measurements

Total serum immunoglobulin concentrations of IgM and IgA were determined by rate nephelometry. The IgG subclass concentrations were measured by radial immunodiffusion (Behring Werke, Mannheim, Germany and Central Laboratory of the Red Cross Blood Transfusion Service, Amsterdam, The Netherlands). Serum immunoglobulin levels within the range of two standard deviations (2 SD) below or above the age-specific mean were considered normal.[21] Complete deficiency of IgA was defined as a serum level of ≤0.05 g/l. Complete deficiency of IgG2 was defined as a serum level of ≤0.02 g/l.

Subgroups

To address the question whether children with few throat infections during follow-up differ immunologically from children with frequent throat infections, children were divided in two subgroups; 103 children with 0 or 1 throat infection during the first year of follow-up versus 20 children with 2 or more episodes. Similar subgroups were formed for children with 0 to 3 upper respiratory infections (n=105) versus 4 or more episodes (n=18) during the first year of follow-up.

Throat infections were defined as sore throat and/or pain/difficulty at swallowing combined with fever (≥ 38.0 °C as measured by the infrared tympanic thermometer)[20] for at least one day. Upper respiratory infections were defined as sore throat and/or pain/difficulty at swallowing and/or cough and/or rhinorrhea and/or earache and/or otorrhea combined with fever (≥ 38.0 °C as measured by the infrared tympanic thermometer) for at least one day.

A throat infection or URI episode ended when patients were symptom-free for at least one day. A new episode of throat infection or URI was registered after a minimum 7-day interval free of symptoms.

Since age plays a role in susceptibility to infections, the children were divided into two age groups: 2 to 4 years and 4 to 8 years.

Data analysis

Chi-square tests and Student's T-tests were used to evaluate possible differences in respectively categorical and continuous characteristics between the T&Ads and the WW group, at baseline. Paired T-tests were used to compare the immunoglobulin levels at To and T12. Fold decrease of immunoglobulins were calculated by dividing the mean immunoglobulin level at To by the mean level at T12. Student's T-tests were used in subgroup analyses.

Table 1. DEMOGRAPHIC AND DISEASE-SPECIFIC CHARACTERISTICS OF 123 TRIAL PARTICIPANTS, ACCORDING TO TREATMENT GROUP (DATA ARE NUMBERS (%) UNLESS INDICATED OTHERWISE)

	T&Ads (N=63)		WW (N=60)	
male sex	38	(60.3%)	32	(53.3%)
mean age in months (SD)	59	(16.9)	57	(13.9)
mean number of tonsillitis episodes in the year before trial entry (SD)	2.69	(1.60)	2.70	(1.68)
previous ENT-surgery				
• adenoidectomy	12	(19.0%)	12	(20.0%)
• tympanostomy tubes	4	(6.3%)	6	(10.0%)
atopy *	32	(50.8%)	32	(52.5%)
breastfed for more than 1 month	37	(59.7%)	39	(65.0%)
attendance at day-care (only for children younger than 4 years of age; N=31)	14	(93.3%)	16	(100%)

T&Ads = adenotonsillectomy; WW = watchful waiting

* Atopy defined as having eczema, hay fever, recurrent wheezing or asthma

Results

Patients

Between March 2000 and February 2003, 300 children participated in the trial. At baseline (T0), 218 venous serum samples were collected for immunological evaluation; at one year follow-up (T12), 165 samples. For 123 children, paired samples were available; 63 children in the adenotonsillectomy group and 60 children in the watchful waiting group. Patient characteristics did not differ between groups; e.g. mean ages at inclusion were 59 months (SD 16.9) and 57 months (SD 13.9), respectively (Table 1).

Changes in immunoglobulin levels during follow-up

Table 2 shows the changes in immunoglobulin levels from baseline to 12 months follow-up, according to randomisation- and age group. In children aged 2 to 4 years, mean IgA and IgM levels decreased both in the T&Ads and WW group, but remained elevated, i.e. mean concentrations at T12 were above 2 SD of the age-related mean. In children aged 4 to 8 years, mean IgA and IgM levels decreased from elevated to values within the normal range. Mean IgG1 and IgG2 levels in both randomisation groups, regardless of age, were within the normal range at baseline and although they decreased during follow-up, the levels remained within the normal range for age. Differences between the T&Ads group and the WW group were only noted for IgA levels; mean serum IgA decreased more in children aged 4 to 8 years in

Table 2. MEAN SERUM IMMUNOGLOBULIN LEVELS IN G/L AT BASELINE AND 12 MONTHS FOLLOW-UP, ACCORDING TO TREATMENT- AND AGE GROUP

		Immunoglobulin (g/l)	To	T12	Difference (SD)	Paired T-test	Normal range
T&Ads	2-4 years of age	IgA	1.08	1.04	-0.04 (0.44)	0.72	0.31-0.87
		IgM	1.54	1.33	-0.21 (0.48)	0.11	0.56-1.22
		IgG1	8.42	7.35	-0.96 (2.09)	0.11	2.25-8.50
		IgG2	1.47	1.22	-0.21 (0.24)	0.005	0.50-2.80
	4-8 years of age	IgA	1.24	0.94	-0.30 (0.35)	<0.001	0.48-1.22
		IgM	1.54	1.33	-0.20 (0.28)	<0.001	0.60-1.34
		IgG1	9.16	7.70	-1.48 (2.35)	<0.001	3.50-10.00
		IgG2	1.64	1.43	-0.19 (0.43)	0.005	0.50-3.50
WW	2-4 years of age	IgA	0.96	1.08	0.11 (0.43)	0.31	0.31-0.87
		IgM	1.34	1.29	-0.05 (0.41)	0.63	0.56-1.22
		IgG1	8.04	7.60	-0.44 (1.54)	0.27	2.25-8.50
		IgG2	1.12	1.14	0.03 (0.37)	0.77	0.50-2.80
	4-8 years of age	IgA	1.22	1.18	-0.05 (0.37)	0.43	0.48-1.22
		IgM	1.44	1.25	-0.19 (0.33)	<0.001	0.60-1.34
		IgG1	8.77	8.03	-0.79 (1.76)	0.005	3.50-10.00
		IgG2	1.62	1.50	-0.10 (0.47)	0.18	0.50-3.50

T&Ads vs. WW at T12; 2-4 years of age:	IgA p=0.88	T&Ads vs. WW at T12; 4-8 years of age:	IgA p= 0.01
	IgM p=0.85		IgM p= 0.30
	IgG1 p=0.61		IgG1 p= 0.42
	IgG2 p=0.64		IgG2 p= 0.49

T&Ads = adenotonsillectomy
WW = watchful waiting

Table 3. FOLD DECREASE (To / T12) OF MEAN IMMUNOGLOBULIN LEVELS, ACCORDING TO TREATMENT GROUP

	To / T12 (SD)		
Immunoglobulins (g/l)	T&Ads (N=63)	WW (N=60)	p
IgA	1.30 (0.35)	1.06 (0.33)	<0.001
IgM	1.16 (0.25)	1.16 (0.27)	0.90
IgG1	1.22 (0.34)	1.10 (0.22)	0.02
IgG2	1.17 (0.34)	1.10 (0.41)	0.31

T&Ads = adenotonsillectomy
WW = watchful waiting

Table 4. MEAN IMMUNOGLOBULIN LEVELS AT 12 MONTHS FOLLOW-UP BY NUMBER OF THROAT INFECTIONS DURING THE FIRST YEAR OF FOLLOW-UP, ACCORDING TO TREATMENT GROUP (SD)

Throat infections	Immunoglobulins (g/l)	T&Ads	WW	p
0-1 episode	IgA	0.96 (0.46)	1.18 (0.56)	0.03
	IgM	1.35 (0.40)	1.30 (0.51)	0.53
	IgG1	7.83 (1.85)	7.97 (1.85)	0.71
	IgG2	1.39 (0.45)	1.44 (0.58)	0.59
≥ 2 episodes	IgA	1.02 (0.53)	1.03 (0.41)	0.97
	IgM	1.20 (0.25)	1.09 (0.41)	0.47
	IgG1	6.32 (1.52)	7.69 (1.46)	0.06
	IgG2	1.31 (0.71)	1.24 (0.40)	0.79

Table 5. MEAN IMMUNOGLOBULIN LEVELS AT 12 MONTHS FOLLOW-UP BY NUMBER OF UPPER RESPIRATORY INFECTIONS DURING FOLLOW-UP, ACCORDING TO TREATMENT GROUP (SD)

Upper respiratory infections	Immunoglobulins (g/l)	T&Ads	WW	p
0-3 episodes	IgA	0.95 (0.45)	1.18 (0.57)	0.02
	IgM	1.34 (0.39)	1.30 (0.50)	0.69
	IgG1	7.66 (1.92)	7.87 (1.71)	0.57
	IgG2	1.37 (0.45)	1.43 (0.57)	0.54
≥ 4 episodes	IgA	1.14 (0.65)	1.05 (0.37)	0.69
	IgM	1.30 (0.25)	1.09 (0.45)	0.32
	IgG1	7.18 (1.39)	8.11 (2.08)	0.34
	IgG2	1.43 (0.67)	1.30 (0.49)	0.70

the T&Ads group than in the WW group (p=0.01). Overall, mean serum immunoglobulin levels at 1 year follow-up did not differ significantly between both randomisation groups. None of the children developed hypogammaglobulinemia or IgA deficiency.
Fold decreases (To/T12) of IgA, IgM, IgG1 and IgG2 levels are presented in Table 3. Fold decreases of IgA and IgG1 are more pronounced in the T&Ads group than the WW group: 1.30 vs. 1.06 for IgA (p<0.001) and 1.22 vs. 1.10 for IgG1 (p=0.02), respectively. For IgM and IgG2 the differences between both randomisation groups are smaller and not statistically significant.

Association between immunoglobulin levels at 1 year follow-up and occurrence of throat infections and upper respiratory infections

In the present study, no significant difference was found between children in the T&Ads and the WW group in the mean number of throat infections and URIs in the first year of follow-up: 0.71 (SD 0.87) vs. 0.68 (SD 0.93) throat infections and 1.73 (SD 2.26) vs. 1.92 (SD 1.90) URIs, respectively. Children from the T&Ads group with 0 or 1 throat infection during the first year of follow-up had a lower serum IgA level at 1 year follow-up than children from the WW group with the same number of throat infections: 0.96 g/l (SD 0.46) vs. 1.18 g/l (SD 0.56) (p=0.03) (Table 4), while other immunoglobulin levels did not differ. In children with 2 or more throat infections during the first follow-up year, however, serum IgA levels at 1 year follow-up were the same for T&Ads and WW group: 1.02 g/l (SD 0.53) vs. 1.03 g/l (SD 0.41) (p=0.97). Again, serum IgG1, serum IgG2 and IgM at 1 year follow-up were not statistically different between the children in the two randomisation groups. In Table 5 a similar analysis is shown for number of URIs categorized as 0-3 and 4 or more episodes during the first year of follow-up, with comparable findings.

Discussion

In this large group of children participating in a RCT comparing the effectiveness of adenotonsillectomy and a non-surgical watchful waiting strategy, serum IgG1 and IgG2 immunoglobulin levels decreased during 1 year follow-up, but remained within normal ranges for age, irrespective of treatment (T&Ads versus WW). IgA and IgM levels in both randomisation groups were above the normal range for age at baseline, decreased after 1 year follow-up but remained higher than 2SD above the mean value for age, irrespective of treatment. A greater decrease of serum IgA was observed in children aged 4 to 8 years in the T&Ads group compared with those of the same age in the WW group. For children with few throat infections (0 or 1 episode) we found significantly lower IgA levels in the T&Ads

group, but as soon as children had experienced 2 or more throat infections, IgA levels became comparable in both randomisation groups. In general, no relation was found between immunoglobulin levels and occurrence of throat infections and URIs during the first year of follow-up.

In a previous study (unpublished data), we showed serum IgG1, IgM and IgA levels in children with tonsillar disease, both recurrent tonsillitis and tonsillar hypertrophy, to be above normal values for age, probably due to repeated antigenic stimulation. Similar results were obtained in other populations of children with tonsillar disease.[7,8,10,13,22] Regarding changes in pre- and post-tonsillectomy serum immunoglobulin levels in children with tonsillar disease, however, study results were inconsistent.[7-15,23,24] Some found only a decline in IgG levels following adenotonsillectomy,[8,9] while others only found low IgA levels[7,11,23,24] or a decline of all immunoglobulin levels.[10,12-15] In these studies, the magnitude of the decrease in immunoglobulin levels differed as well. A possible explanation for the different results of immunoglobulin changes following adenotonsillectomy is the moment of serum collection: samples taken within 1 to 4 months postoperatively show a larger decrease in immunoglobulin levels of most isotypes than samples collected after 1 year. Apparently, immunoglobulin levels tend to normalize over time.[15]

The only significant difference we found between both randomisation groups was a greater decrease in IgA levels after 1 year in the T&Ads group than in the WW group, especially in children aged 4 to 8 years (Tables 2 and 3). It has been suggested that low IgA levels are associated with an increased susceptibility to upper respiratory infections.[25,26] In our population, however, no associated occurrence of throat infections or upper respiratory infections during follow-up was found. These results are in agreement with those of others who found (transitory) serum IgA decreases following tonsillectomy but without an associated increase in respiratory infections.[7,11,13,23] Interestingly, we observed this difference in IgA levels between the T&Ads and WW groups confined to the children with few infections (0 or 1 throat infection and 0-3 URIs during follow-up), thus not in children with 2 or more throat infections or 4 or more URIs. Apparently, in children who experience frequent upper respiratory infections in the T&Ads group the remaining MALT compensates for the loss of IgA production by the tonsil and adenoid, similar to children who were managed non-surgically.

We can compare our study only to that of Friday et al.[9] who studied immunoglobulin changes in children participating in a RCT on the effectiveness of adenotonsillectomy. They found a significantly lower IgG level in the T&Ads group than in the WW group, but also no relation between immunoglobulin level changes and the occurrence of throat infections during follow-up. Thus, although some effect of T&Ads on the different isotype serum levels have been

observed, one may conclude that it does not result in a higher susceptibility to respiratory infections.

To appreciate the results of this study, strengths and limitations should be considered. First, by excluding children with very frequent throat infections from our trial, the relationship between these infections and serum immunoglobulin levels may be underestimated. Friday et al.,[9] however, included children with very frequent recurrent throat infections, and neither did they find an association between immunoglobulin levels and number of throat infections. Second, paired serum samples were available for only 41% of the trial participants (123/300). The only significant differences between children included in the present study and the 177 other children in the trial were gender (male sex: 56.9% vs. 43.8% respectively; p=0.03) and attendance at day-care (96.8% vs. 76.8% respectively; p=0.02). Subgroup analyses for gender and day-care attendance, however, showed no differences in immunoglobulin levels.

Third, we did not measure salivary IgA (sIgA). Decreases in salivary IgA (sIgA) following T&Ads have been reported,[27,28] and have been suggested to be correlated with the occurrence of upper respiratory infections.[29] Nevertheless, several other studies have shown that after 1 month the salivary IgA levels were comparable to age-matched controls, suggesting that such decreases are transitory.[12,23]

The strength of our study is that our results are based on a large population of children participating in a RCT in which throat infections and upper respiratory infections have been carefully documented in diaries and fever associated with these infections has been measured objectively with a validated infrared tympanic membrane thermometer.[20] By including a randomly allocated non-surgical comparison group, possible changes in immunoglobulin levels in the T&Ads group can be put in perspective. Since the study by Friday et al. published in 1992,[9] this is the first prospective controlled study on immunoglobulin levels in association with occurrence of throat infections and URIs. The number of participants in our study was larger than in the previous one: 123 versus 75 children in the study by Friday et al.[9] We not only evaluated the relation of immunoglobulins to throat infections but also to upper respiratory infections, since currently used indications for T&Ads also include recurrent upper respiratory infections.[30-33] However, no such relation was found.

In conclusion, immunoglobulin levels of children indicated for T&Ads decreased to levels within or slightly above the normal range for age after 1 year follow-up irrespective of treatment (T&Ads or WW). This decline did not result in an increased susceptibility to throat infections or upper respiratory infections. Most likely, the observed decrease is compatible with a natural reduction of antigenic stimulation with age. In children with persisting recurrent infections during follow-up, IgA levels are similar in children of the T&Ads and the WW group, indicating that the remaining mucosa associated lymphoid tissue (MALT)

compensates for the loss of tonsil and adenoid tissue in children with frequent upper respiratory infections.

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Summary, Discussion and Future Perspectives

Summary

The social and medical importance of assessing the effectiveness of adenotonsillectomy (T&Ads) in children is obvious when considering that in The Netherlands approximately 13% of children have had their tonsils removed by the age of 8 years. By the age of 15 years this percentage is 17%.[1] With 28,000 to 34,000 procedures per year in the last decade, T&Ads is, after tympanostomy tube insertion (n=35,501), the second most frequently performed operation in children in The Netherlands.[1]

In **Chapter 1** of this thesis the current evidence regarding the effectiveness of (adeno)-tonsillectomy (T±Ads) in children is presented. A meta-analysis of the existing 6 trials of T±Ads shows that the operation reduces the incidence of sore throat episodes by 1.2 episodes per person year (95% CI 1.1 to 1.3), sore throat associated school absence by 2.8 days per person year (95% CI 1.6 to 3.9) and upper respiratory infections by 0.5 episodes per person year (95% CI 0.3 to 0.7) compared to no surgery. Additional evidence from 7 non-randomised studies confirms these findings. This review shows that (adeno)tonsillectomy provides only a small additional reduction in sore throat episodes and upper respiratory infections compared to a watchful waiting strategy. Apparently, the frequency of these infections reduces with age, irrespective of whether (adeno)tonsillectomy is being performed or not.

In **Chapter 2** we demonstrate that current (adeno)tonsillectomy rates in children and adolescents vary considerably across countries. In 1998, the rate of paediatric tonsillectomy with or without adenoidectomy (T±Ads) varied from 19 per 10,000 children in Canada to 115 per 10,000 in The Netherlands and 118 per 10,000 in Northern Ireland. The surgical rate in adolescents varied from 19 per 10,000 adolescents in Canada to 43 per 10,000 in The Netherlands and 76 per 10,000 in Finland. To substantiate or repudiate the suggestion that decreasing paediatric T±Ad rates result in more tonsil-related disease in later life and thus in increasing T±Ad rates in adolescents, we studied trends in adenotonsillectomy rates in children and adolescents in recent decades. In The Netherlands, the paediatric T±Ad rate decreased 3-fold, from 290 to 96 per 10,000, over the period 1974 to 1985. Since 1991, the surgical rate remained the same with approximately 115 per 10,000 children per year. Over the period 1985 to 1998, about ten to fifteen years after the T±Ad rates in children started to fall, the surgical rate in adolescents in The Netherlands doubled from 20 to 43 per 10,000. Although at first sight this finding suggests a causal relationship, the absolute increase in adolescent T±Ads is small compared to the absolute decrease in paediatric T±Ads in the preceding decade. We therefore conclude that there is no definitive evidence that decreasing rates of (adeno)tonsillectomy in childhood are associated with more tonsil-related disease in later life.

In **Chapter 3**, we investigated the current indications for (adeno)tonsillectomy (T±Ads) in children younger than 15 years of age in The Netherlands. Otolaryngologists prospectively filled out standard questionnaires for 349 consecutive children they listed for tonsillectomy or adenotonsillectomy. General practitioners (GPs) were asked to retrospectively fill out a similar questionnaire on the same children including information on their reasons for referral to the otolaryngologist. Participating physicians were asked to indicate whether a symptom or sign was present in a specific patient and, if so, to rate its importance for the decision to refer for or perform surgery according to a score ranging from 1 to 3 (1= not important; 2 = moderately important and 3 = very important). Apart from recurrent tonsillitis (40% and 35% of children according to otolaryngologists and GPs, respectively), recurrent upper respiratory infections (22% and 25% of children), physical findings such as enlarged tonsils (42% and 24% of children) and tonsillar crypt debris (29% and 17% of children), non-specific symptoms such as listlessness (28% and 19% of children) and poor appetite (28% and 16% of children) were considered important criteria for surgery (score 3). Symptoms of obstructive sleep apnoea were an important indication for surgery in only 11% (otolaryngologists) and 4% (GPs) of children. Apparently, besides the generally accepted indications for T±Ads (i.e. frequent recurrent tonsillitis and obstructive sleep apnoea), indications such as recurrent upper respiratory tract infections and the presence of enlarged tonsils or tonsillar crypt debris play an equally important role in the decision of physicians to perform or refer for tonsil surgery. We estimated that for approximately 65% of the children currently undergoing adenotonsillectomy in The Netherlands, such indications are decisive in the decision to perform surgery. Since the effectiveness of T±Ads in these cases has not been established yet, we initiated a randomised controlled trial including children with relatively mild symptoms of recurrent throat infections, upper respiratory infections or adenotonsillar hypertrophy.

In **Chapter 4**, the results of our NATAN trial (Nederlands Adenotonsillectomy project; Tonsillectomy and Adenoidectomy in the Netherlands) on the effectiveness of adenotonsillectomy in 300 Dutch children aged 2 to 8 years, indicated for adenotonsillectomy according to current medical practice, are reported. Excluded from this trial were children with frequent recurrent tonsillitis (7 or more throat infections in the preceding year, or 5 or more in each of the two preceding years, or 3 or more in each of the 3 preceding years) or a high suspicion of obstructive sleep apnoea, i.e. Brouillette's OSA-score of more than 3.5, because there is general agreement among doctors that for these indications adenotonsillectomy is beneficial. Other exclusion criteria were: Down's syndrome, craniofacial malformation and documented immunodeficiency other than IgA or IgG2 deficiencies. During the median follow-up period of 22 months, children allocated to

adenotonsillectomy, experienced 2.97 fever episodes per person year versus 3.18 in children allocated to a watchful waiting strategy (incidence rate difference (IRD) −0.21; 95% CI −0.54 to 0.12), 0.56 versus 0.77 throat infections per person year (IRD −0.21; 95% CI −0.36 to −0.06) and 5.47 versus 6.0 upper respiratory infections per person year (IRD −0.53; 95% CI −0.97 to −0.08). No clinically relevant differences were found regarding health-related quality of life. Subgroup analyses showed that the effectiveness of T&Ads was more pronounced in children with 3 to 6 throat infections in the year before trial entry than in those with 0 to 2 throat infections: children with 3 to 6 throat infections allocated to T&Ads experienced 1.07 (95% CI 0.56 to 1.59) fewer fever episodes per year and 0.49 (95% CI 0.22 to 0.75) fewer throat infections per year than those allocated to watchful waiting.

For children with 0 to 2 throat infections in the year before trial entry, these differences were +0.34 (95% CI 0.08 to 0.77) and -0.03 (95% CI -0.21 to 0.15) for fever episodes and throat infections, respectively.

These results indicate that in children with relatively mild symptoms of recurrent throat infection, upper respiratory infections or obstructive symptoms due to adenotonsillar hypertrophy, T&Ads had no relevant clinical benefits to offer over a watchful waiting strategy.

In **Chapter 5** the representativeness of children participating in our trial for the relevant clinical domain; i.e. children currently indicated for T&Ads in The Netherlands, is assessed. Demographic and disease-specific characteristics were compared between 1) randomised children (n=270); 2) eligible children whose parents immediately decided not to participate (n=243) and 3) eligible children whose parents were informed in detail about the trial by a member of the study team, but gave no informed consent (n=406). Important characteristics that might modify the effect of T&Ads, were the same for randomised and eligible but non-randomised children: 46.3%, 45.8% and 46.9% of children in group 1, 2 and 3 respectively were indicated for surgery for symptoms of recurrent tonsillitis; 20.9%, 20.3% and 19.9%, respectively suffered from obstructive symptoms; the mean number of throat infections in the year before trial entry was 4.3, 4.6 and 4.4 episodes for group 1, 2 and 3, respectively; and the mean duration of tonsillitis related symptoms was 14.3 months, 15.8 and 14.9 months, respectively. Small differences were found regarding previous ENT surgery (22.5%, 21.3% and 12.7%, respectively), breathing difficulties at night (11.7%, 19.6% and 22.1%, respectively) and abnormal appearance of tonsils (79.5%, 81.1% and 88.4%, respectively). These findings indicate that our trial population is representative of the relevant patient domain; i.e. children currently undergoing T&Ads in The Netherlands for relatively mild symptoms of recurrent throat infection or adenotonsillar hypertrophy.

In **Chapter 6 and 7** baseline and follow-up immunoglobulin levels of the children participating in the trial are presented. At baseline, children indicated for T&Ads had immunoglobulin levels that were within or above the normal age-specific range, suggesting that variation in immunoglobulin levels does not seem to play an essential role in the predisposition of children to tonsillar disease. After 1 year follow-up in the randomised trial mean immunoglobulin levels had declined, but were still within or above the normal range for age, irrespective of treatment (T&Ads vs. WW). Only the IgA level decreased significantly more in the T&Ads group than in the WW group. No association between immunoglobulin levels at 1 year follow-up and the number of throat infections or other upper respiratory infections during the first year of follow-up was observed. Therefore, the observed decline in immunoglobulin levels reflects a natural reduction of antigenic stimulation with age and the mucosa-associated lymphoid tissue (MALT) remaining after T&Ads can compensate for the loss of tonsil and adenoid tissue.

Critical issues

To appreciate the results of the studies presented in this thesis, several additional questions will be addressed.

Are the results of the NATAN trial applicable to children consulting the otolaryngologist in every-day practice for symptoms of tonsillar disease?

We believe that our trial results are indeed applicable to the group of children indicated for relatively mild symptoms of tonsillar disease.

Evidently, the participating otolaryngologists did not refer all children indicated for T&Ads to our trial centre. In theory they may have operated upon the more severely affected children and only referred the children with the mildest symptoms for participation in the trial, thereby limiting the generalisability of the trial results. To address this issue, we compared demographic and disease specific characteristics of children referred to the trial with those of children who were not referred. For this reason, patient charts of all children who were eligible for participation in the NATAN trial, i.e. indicated for T&Ads in the year 2000 (n=282), of one of the participating hospitals were studied. During the inclusion period of our trial only for 63 of these 282 children (22%), information was sent to the trial centre, and of these 63 children, 8 (8/282= 3%) were randomised. Differences between referred and non-referred children were small and not clinically relevant. For example, the mean age was 54 months vs. 53 months in the referred and non-referred children, respectively; 50% vs. 46% was male; the mean number of episodes of tonsillitis in the last year was 4.1 vs. 4.3,

respectively; 87% vs. 88% snored; 24% vs. 15% had undergone previous ENT surgery; and 99% vs. 94% had enlarged tonsils (protruding beyond the pillars).

In addition, we estimated how many children with relatively severe tonsillar symptoms were included in the trial. Thirty-nine children (23 in the T&Ads and 16 in the WW group; 15% and 11%, respectively) had suffered from 5 or 6 episodes of throat infection in the year before trial entry, and 37 children (18 in the T&Ads and 19 in the WW group; 12% and 13%, respectively) had a Brouillette score between –1 and 3.5 at baseline, indicating possible obstructive sleep apnoea (OSA).[2] These figures indicate that children with substantial tonsillar symptoms are sufficiently represented in our trial.

Furthermore, in Chapter 5 we showed that the 300 children included in the trial did not differ appreciably from the 1005 children who were eligible for the trial but who for various reasons did not participate, regarding the most important variables that could modify treatment outcome, most notably indications for surgery. Subgroup analyses that were performed after completion of the NATAN trial showed that the variables that did differ between participants and non-participants; i.e. previous ENT surgery, breathing difficulties at night and abnormal appearance of tonsils, did not modify the treatment effect regarding the primary outcome fever episodes, or the secondary outcomes, i.e. throat infections, upper respiratory infections and health-related quality of life.

We conclude that the results of our trial are generalisable to children currently undergoing T&Ads in The Netherlands for relatively mild symptoms of throat infections or obstructive symptoms due to adenotonsillar hypertrophy.

Did the relatively high proportion of children randomised to the watchful waiting group that underwent adenotonsillectomy during follow-up, bias the trial results?

Ideally, all participants in a trial complete the study and remain in the treatment group they are randomly allocated to. In reality, however, patients switch treatment groups. In our trial, 50 children (34%) of the WW group underwent adenotonsillectomy during follow-up. Inappropriate handling of these data can lead to bias. For instance, per protocol analysis excluding children who changed treatment groups will result in an underestimation of the treatment effect, because in surgical trials such as ours, only children of the watchful waiting group can change treatment group due to persisting complaints, whereas children in the surgical group, who may experience similar persisting complaints cannot change treatment group. Analysing children on the basis of the time spent in any treatment arm might result in either an over- or an underestimation of the treatment effect. Furthermore, the value of randomisation is that it prevents imbalance between the intervention and control group in

Table 1. Baseline demographic and disease-specific characteristics of 300 subjects. The watchful waiting group is divided in true watchful waiting (i.e. switchers excluded) and switchers to T&Ads (data are numbers (%) unless indicated otherwise)

Characteristic	T&Ads N= 151	watchful waiting, switchers excluded N=99	switchers from the WW group N=50
Mean age in months (SD)	54 (17.0)	56 (16.3)	50 (15.3)
Indication for surgery as indicated by the local otolaryngologist			
• recurrent tonsillitis	76 (50.3%)	47 (47.5%)	20 (40%)
• other indications	75 (49.7%)	52 (52.5%)	30 (60%)
Median number of throat infections in the year before trial entry in children with the indication recurrent tonsillitis; N=143 (range)	3 (0 to 6)	3 (0 to 6)	3 (0 to 6)
Median duration of throat infections in months in children with the indication recurrent tonsillitis; N=143 (range)	13(0 to 50)	12(0 to 60)	12 (0 to 36)
Median number of episodes with rhinorrhoe and/or cough in the year before trial entry (range)	12 (0 to 24)	12 (0 to 24)	8 (0 to 24)
Median number of otitis media episodes in the year before trial entry (range)	0 (0 to 12)	1 (1 to 4)	1 (1 to 6)
Median OSA score (range) *	-1.7 (-3.83 to 2.55)	-1.7 (-3.83 to 2.55)	-1.7 (-3.83 to 2.55)
Previous ENT-surgery			
• adenoidectomy	35 (23.2%)	21 (21.2%)	12 (24%)
• tympanostomy tubes	19 (12.7%)	11 (11.1%)	6 (12%)

* Brouillette's OSA score: 1.42 x difficulty breathing + 1.41 x apnoea + 0.71 x snoring – 3.83 (range: –3.83 to +3.5)

(known and unknown) important factors that could influence the clinical course of the condition studied. By analysing the switchers from WW to T&Ads as treated or by omitting these switchers from the analyses, one might introduce imbalance between the intervention and control group. It will then be difficult to differentiate between the effects of T&Ads on the outcome parameters from that of other factors (e.g. age, indication for T&Ads).

Only if all participants of a surgical trial adhere to the treatment group they were allocated to during the whole follow-up period, the real effect of a surgical procedure (e.g. T&Ads) can be evaluated. As this is infeasible in clinical practice and unethical in most trials, randomised controlled trials studying the effect of a surgical intervention can only be used to compare strategies, i.e. T&Ads versus *initial* watchful waiting.

The data-analytic strategy that can confidently be assumed to eliminate the above mentioned bias includes two components. The first is the "intention-to-treat analysis". This implies that all study participants are included in the analysis as part of the group to which they were randomised, regardless of whether they switched or not. The second component includes a comparison of the switchers with the children remaining in the watchful waiting group and those in the T&Ads group with respect to baseline variables that might influence the clinical course and thus the outcome of the trial (see also Table 1). We found no clinically relevant differences between the switchers and children remaining in the WW and T&Ads group regarding these baseline characteristics.

In conclusion, the children who switched from the watchful waiting group to the T&Ads group do not represent a highly selective sample of children with severe complaints at baseline.

How can otolaryngologists treat children with tonsillar disease "evidence-based"?

In children with very **frequent throat infections** (i.e. 7 or more physician diagnosed throat infections in the preceding year, or 5 or more in each of the two preceding years, or 3 or more in each of the 3 preceding years) T&Ads should be considered. Surgery adds a benefit of 1.5 fewer throat infection episodes per year over a period of 2 years over non-surgical management.[3] However, in the decision to list such children for T&Ads, the otolaryngologist should inform parents about the fact that even in these children the natural course of throat infections is favourable.

Children with a **(high suspicion of) obstructive sleep apnoea (OSA)** due to adenotonsillar hypertrophy also benefit from T&Ads. Although the effectiveness of adenotonsillectomy for obstructive sleep apnoea has not been ascertained by randomised controlled trials, several uncontrolled studies in children with objectively diagnosed OSA, have shown considerable improvement of objective sleep parameters and obstructive complaints during sleep, school

performance and quality of life after surgery.[4-9] Therefore, randomised controlled trials are generally considered unethical in these children.

It is important for practising clinicians to distinguish simple snoring or mild sleep disordered breathing from OSA. Based on the clinical history alone, it is not possible to make this distinction.[2,10,11] Currently, overnight hospital-based polysomnography (PSG) is generally accepted as the "gold standard" in the diagnosis of OSA, but this evaluation is expensive, time-consuming, and not uniformly available.[12-14] In a substudy among NATAN participants,[15] we showed that the results of single-night unattended home cardiorespiratory recordings with a a portable device, the Embletta ®PDS, set-up by the parents, were disappointing and of limited use in every day practice in the assessment of OSA. Overnight pulse oximetry could be more useful as a first screening modality in children with symptoms of snoring and mild sleep disordered breathing.[15-17]

In Chapter 3, we showed that children with very frequent throat infections or a high suspicion of OSAS constitute approximately 35% of the children currently undergoing T&Ads in The Netherlands. But how should the otolaryngologist treat the 65% of children with **relatively mild symptoms of recurrent throat infection, upper respiratory infections or obstructive symptoms due to adenotonsillar hypertrophy**?

Our trial results suggest that Dutch otolaryngologists could be more restrictive with surgery in these children (Chapter 4), as the benefits of operation for the entire group were small. To identify subgroups, in which the effect of T&Ads might be larger, we performed several subgroup analyses. Children with **3-6 episodes of tonsillitis** in the year before trial entry allocated to T&Ads experienced 1.07 (95% CI 0.56 to 1.59) fewer fever episodes per person year and 0.49 (95% CI 0.22 to 0.75) fewer throat infection episodes per person year than those allocated to watchful waiting. For children with **0-2 episodes of tonsillitis** in the year before trial entry, these differences were + 0.34 (95% CI –0.08 to 0.77) and -0.03 (95% CI –0.15 to 0.21) per person year for fever episodes and throat infections, respectively. Thus, the effect of T&Ads was larger in the subgroup of children with a history of frequent throat infections. This finding corresponds with our expectation that when the indications for surgery approach the exclusion criteria of our trial (for which T&Ads is generally considered to be effective),[3] the effect of T&Ads increases. The additional benefit of T&Ads in the subgroup with 3 to 6 episodes of throat infection in the year before trial entry however, remains relatively small. This effect is similar to that found by Paradise et al.[18] in their study published in 2002 in children moderately affected with recurrent throat infection. They concluded that the benefit of the operation does not justify its risks, morbidity and costs. We therefore believe that –in otherwise healthy children– with recurrent throat infections, one could be restrictive with surgery.

In the subgroup of children with **possible obstructive sleep apnoea** (Brouillette's OSA score between –1 and 3.5), allocated to T&Ads, fewer children had obstructive symptoms during sleep as compared to those allocated to watchful waiting: at 3 months, 0.9% and 11.8% of the T&Ads and WW group had obstructive symptoms during sleep, respectively; at 6 months these percentages were 0% and 8.9%, respectively; at 12 months 1.1% and 5.2%, respectively; and at 24 months 1.7% and 1.5%, respectively. For the subgroup of children **without any symptoms of sleep disordered breathing** at baseline (Brouillette score of less than –1), none of the children in the T&Ads or WW group experienced obstructive symptoms during sleep at 3, 6, 12 and 24 months of follow-up. We believe that in children with possible OSA, surgery should be considered. However, in the light of the favourable natural course, a watchful waiting policy is a reasonable alternative.
In children with fewer throat infections, upper respiratory infections or mild sleeping and eating difficulties, we suggest, in the light of our trial results, that other options besides surgery should be considered first.

What are the alternative treatments, other than T&Ads, for children with tonsillar disease?
Children with tonsillar disease do need and deserve our care since many of them suffer considerably.[19] Currently available alternatives for surgery are antibiotics and watchful waiting including counselling of the parents regarding the natural course of the complaints, adequate pain management, monitoring for an irregular course of infection or obstructive disease and control of risk factors. Other potentially interesting alternatives include vaccines and other immunomodulatory interventions such as probiotics and bacterial replacement therapy, aiming at prevention of infections.

Antibiotics
Should we consider the use of antibiotics in children with sore throats now that we have shown that the benefits of T&Ads are limited in a large proportion of children? Dutch physicians have always been more restrictive in their prescribing of antibiotics for upper respiratory infections and tonsillitis compared to physicians in most other countries.[20] This attitude is justified, since many infections are of viral origin[21,22] and the effect of antibiotics is limited. A recent systematic review on the use of antibiotics for sore throats in adults and children[23] showed that antbiotics provided only modest benefit in the treatment of sore throat compared to placebo; overall the duration of symptoms was shortened by 16 hours. The recent study by Zwart et al.[24] in 156 children with sore throat presented to a primary care physician showed that penicillin treatment had no beneficial effect on the average duration of symptoms. Penicillin may, however, reduce streptococcal sequelae.

About the effectiveness of antibiotics for recurrent throat infections in children referred to the otolaryngologist, no scientific evidence is available. Thus it seems justified to conclude that currently antibiotics cannot be considered an evidence-based alternative to surgery.

Vaccination

Preventive measures such as vaccination, might become important in the management of upper respiratory infections and adenotonsillar hypertrophy resulting from chronic antigenic stimulation. So far, influenza vaccine is the only available vaccine against viral pathogens involved in URIs.[25,26] Since Influenza A virus is the causative pathogen in only 3-5% of tonsillitis episodes,[21,27] this vaccine adds little benefit in the management of tonsillar disease. The most important bacterial pathogens in acute tonsillopharyngitis are Haemolytic Streptococcus (group A, B, C), (non-typable) Haemophilus Influenzae, Moraxella Cattharalis and Streptococcus pneumoniae.[28,29] The only commercially available vaccine against these pathogens are pneumococcal vaccines. In 1985, Christensen et al.[30] showed in a non-randomised, but double blind prospective study in 405 children, that a 14-valent streptococcal pneumoniae polysaccharide vaccine reduced the number of doctors visits due to upper respiratory tract infections (including acute pharyngitis and tonsillitis) by 30% ($p<0.01$). No randomised trials have been performed on the effectiveness of the newly developed pneumococcal conjugate vaccines in children with recurrent upper respiratory tract infections or sore throats. Studies on otitis media have shown that replacement of vaccine serotypes with non-vaccine serotypes at the nasopharyngeal level reduces the effectiveness of these vaccines regarding mucosal infections.[31,32] Vaccines against non-typable haemophilus influenzae (NTHi) have proven to be effective in adults with recurrent acute bronchitis when given in autumn and winter.[33] No studies on its effectiveness in children with upper respiratory infections have been performed.[34] Vaccines against M. Cattharalis are still under development.[35,36] Since group A Streptococcus consists of many serotypes, developing a single vaccine against group A Streptococcus remains difficult.[37] So far, no randomised trials have been performed with such a vaccine.

Probiotics and bacterial replacement therapy

Interesting and promising preventive measures include probiotics and bacterial replacement therapy. Probiotics are a dietary supplement of living microorganisms found in the normal flora with low or no pathogenicity but with positive effects on the health of the host. They improve balance of the gut flora by bacterial interference, in which the presence of a micro-organism limits the pathogenic potential of another microorganism.[38] A recent study[39] on the effect of probiotics (Lactobacillus GG) on upper respiratory infections in children

attending day-care, showed that probiotic milk reduced respiratory infections by 17% and antibiotic prescription because of upper respiratory infections by 19%. Further clinical studies are underway. Bacterial replacement therapy includes the introduction of a-virulent bacteria that can competitively prevent outgrowth of potentially disease-causing bacteria, without disturbing the microbial ecosystem.[40] A small prospective study in 130 patients using a alpha-Streptococci spray following antibiotic treatment to prevent recurrence of tonsillo-pharyngitis,[41] showed that the spray lowered the recurrence rate of GAS tonsillopharyngitis from 23% to 2% compared to a placebo spray. However, since the safety of such interventions remains to be established, no studies in children have been performed.

Watchful waiting

Finally, the most important alternative is watchful waiting with careful counselling of the parents and children.[42,43] This strategy seems reasonable since the NATAN trial confirmed that the natural course of recurrent throat infections and obstructive symptoms in children is favourable in many children and surgery provides little additional benefit. Such a strategy can only be implemented when GPs and otolaryngologists accept its value[44] and are willing to explain to parents and their children the ratio behind this policy.[45,46] First, it is important that the GPs and otolaryngologists not only inform the parents about the favourable natural course of the complaints, but also on possible complications and their signs. They should ensure an adequate follow-up with clear instructions on when parents should return to their physician. In case of a sore throat, supportive medication, i.e. analgesics/anti-inflammatory drugs should be given.[43,47] They should also advice parents about reducing risk factors for URIs such as parental smoking and, if possible, day-care outside the home.

Recommendations for future research

Evaluation of the implementation of the trial results

It is notoriously difficult, to implement results of randomised controlled trials to everyday clinical practice.[48,49] Several barriers are known to influence the implementation of trial results, i.e. lack of awareness or familiarity with trial results, lack of agreement on the implications of these results, lack of motivation, and external barriers.[49] First, it is important that we study how the published results of our NATAN trial relate to clinical practice.[50-52] We already evaluated the current medical policy of both otolaryngologists and GPs regarding 3 specific case histories of children with tonsillar disease and estimated the prior beliefs regarding the benefit of surgery in these 3 individual cases. After dissemination of our trial results, we shall assess their posterior beliefs as well. The results of this enquiry will clarify

whether otolaryngologists and or GPs are familiar with the results of the NATAN trial and whether they are willing to implement our trial results in daily practice.

IPD meta-analysis

It is important to identify subgroups that might benefit more from T&Ads; e.g. children from certain age groups, with specific indications for surgery, or with specific characteristics related to the risk of upper respiratory infections such as atopy, positive family history or attending group day-care. Although our study was powered to perform several subgroup analyses, the power of the individual trials on adenotonsillectomy is too limited to identify these subgroups in detail. To enable identification of these clinically relevant patient subgroups, an individual patient data (IPD) meta-analysis with original data from the available adenotonsillectomy trials and our current NATAN trial, could be performed.
It would be advisable to also include data from the NESTAC trial (North of England Study of Tonsillectomy and Adenotonsillectomy in Children),[53] which is currently in its recruitment phase.
By performing an IPD meta-analysis, the evidential value of effectiveness of T&Ads in children is raised to the highest level of evidence, from individual trial results (A2) to the best evidence possible (A1). This will eventually facilitate the development of (inter)national guidelines.

Etiological research

Upper respiratory infections are known to be a complex, multifactorial disease resulting from the interplay between host factors such as age, genetic predisposition, immunological response, and the viral or bacterial load, which is influenced by environmental factors such as number of siblings, attending day-care and season.[54,55] The interaction between the various etiological factors is still poorly understood. More insight in the pathogenesis of upper respiratory infections is urgently needed to be able to understand why some children are more susceptible to recurrent or persistent infections than others. When the mechanisms underlying such susceptibility are understood, the targeting of existing therapies and the development of new preventive strategies could be improved.

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Samenvatting, conclusies en toekomstig onderzoek

Samenvatting

Adenotonsillectomie (ATE) is een van de meest frequent uitgevoerde operaties bij kinderen: momenteel worden er in Nederland zo'n 30.000 ingrepen per jaar uitgevoerd. Bij ongeveer 13% van de Nederlandse acht-jarigen zijn de neus- en keelamandelen operatief verwijderd. Opvallend is dat dit percentage in Nederland veel hoger ligt dan in andere Europese landen. Deze variatie wordt behalve door culturele verschillen, zoals voorkeur voor een chirurgische dan wel antibiotische behandeling van bovenste luchtweginfecties, ook bepaald door het ontbreken van richtlijnen omtrent de indicatie voor deze ingreep.

De belangrijkste oorzaak voor het ontbreken van algemeen geaccepteerde richtlijnen is de slechte kwaliteit van wetenschappelijk onderzoek naar de effectiviteit van tonsillectomie al dan niet gecombineerd met adenotomie ((A)TE) bij kinderen. Artsen zijn het er over eens dat (A)TE effectief is bij kinderen met zeer frequente keelontstekingen en bij kinderen met obstructief slaap-apnoesyndroom (OSAS). De effectiviteit van (A)TE ten aanzien van keelonstekingen is echter alleen betrouwbaar in een gerandomiseerde trial onderzocht in de Verenigde Staten bij een streng geselecteerde groep kinderen met zeer frequente keelontstekingen. Ten aanzien van OSAS is de effectiviteit van (A)TE onderzocht in verschillende voor-en-na studies, die aanzienlijke postoperatieve verbetering laten zien van subjectieve en objectieve parameters. Nader gerandomiseerd onderzoek naar de effecten van (A)TE bij deze kinderen wordt daarom algemeen als onnodig en niet-ethisch beschouwd.

Er is echter geen bewijs dat (A)TE effectief is voor de meerderheid (ongeveer 65%) van de kinderen die momenteel in Nederland geopereerd worden voor andere indicaties. Deze indicaties betreffen met name minder frequente keelontstekingen, mildere klachten van tonsil- en adenoidhypertrofie en recidiverende bovenste luchtweginfecties.

In dit proefschrift wordt een overzicht gegeven van het huidige bewijs ten aanzien van de effectiviteit van (adeno)tonsillectomie bij kinderen. Nationale en internationale trends in het aantal (A)TE's worden beschreven, evenals de huidige indicaties voor (A)TE bij kinderen in Nederland. Tenslotte worden de resultaten van het NATAN project (Nederlands Adenotonsillectomie project; Tonsillectomy and Adenoidectomy in the Netherlands) naar de effectiviteit van ATE bij kinderen beschreven, met extra aandacht voor de effecten van ATE op de humorale immuniteit.

In **Hoofdstuk 1** worden de beschikbare onderzoekingen naar het huidige bewijs voor de effectiviteit van (adeno)tonsillectomie bij kinderen kritisch beschouwd. Een meta-analyse van de zes gepubliceerde trials toont bij kinderen in de (adeno)tonsillectomie groep in vergelijking met een afwachtend beleid een afname van keelontstekingen met 1,2 episoden per persoonsjaar (95% betrouwbaarheidsinterval (BI) 1,1 tot 1,3), een afname van keelpijn-gerelateerd

schoolverzuim met 2,8 dagen per persoonsjaar (95% BI 1,6 tot 3,9) en een afname van bovenste luchtweginfecties met 0,5 episoden per persoonsjaar (95% BI 0,3 tot 0,7). Aanvullende informatie uit niet-gerandomiseerde studies bevestigt deze bevindingen. Hoewel de methodologie alsmede de omvang van de beschikbare onderzoekingen veel beperkingen kent, maakt dit review aannemelijk dat (adeno)tonsillectomie in vergelijking met een afwachtend beleid hoogstens een beperkte winst oplevert betreffende keelontstekingen en bovenste luchtweginfecties. Grotere en kwalitatief betere trials zijn nodig om te onderzoeken bij welke (subgroepen) kinderen ATE het meest effectief is.

In **Hoofdstuk 2** tonen we aan dat het aantal (A)TE's bij kinderen en adolescenten aanzienlijk verschilt per land. In 1998 varieerde de frequentie van (A)TE bij kinderen van 19 per 10.000 in Canada tot ongeveer 115 per 10.000 in Nederland en Noord-Ierland. De frequentie van (A)TE bij adolescenten varieerde van 19 per 10.000 in Canada tot 43 per 10.000 in Nederland en 76 per 10.000 in Finland. Vaak wordt gesuggereerd dat de afname van het aantal (A)TE's op kinderleeftijd leidt tot een toename in tonsil-gerelateerde aandoeningen op latere leeftijd. In de periode van 1974 tot 1985 is in Nederland het aantal (A)TE's bij kinderen afgenomen van 290 tot 96 per 10.000 kinderen per jaar en vanaf 1991 min of meer stabiel gebleven: 115 per 10.000 kinderen per jaar. Van 1985 tot 1998, ongeveer 10 tot 15 jaar na de initiële afname van (A)TE's bij kinderen, verdubbelde het aantal (A)TE's bij adolescenten van 20 to 43 per 10.000 per jaar. Alhoewel deze bevinding in eerste instantie een causaal verband doet vermoeden, is de absolute toename van het aantal (A)TE's bij adolescenten klein in vergelijking met de absolute afname van (A)TE's bij kinderen in de voorafgaande decade. Er is derhalve geen onomstotelijk bewijs dat de afname van (A)TE's op kinderleeftijd geassocieerd moet worden met een toename van tonsil-gerelateerde aandoeningen op latere leeftijd.

In **Hoofdstuk 3** worden de huidige indicaties voor (adeno)tonsillectomie bij kinderen jonger dan 15 jaar in Nederland geïnventariseerd. Hiertoe hebben KNO-artsen prospectief een standaard vragenlijst ingevuld voor 349 opeenvolgende kinderen die zij op de lijst hebben gezet voor tonsillectomie of adenotonsillectomie. Daarna werd huisartsen gevraagd om retrospectief een soortgelijke vragenlijst in te vullen voor dezelfde kinderen met daarin hun redenen voor verwijzing naar de KNO-arts. Participerende artsen werd gevraagd om aan te geven of een symptoom of afwijking aanwezig was in een specifieke patiënt en zo ja, om aan te geven hoe belangrijk deze informatie was in hun besluit tot verwijzing of operatie. Behalve recidiverende tonsillitiden (40% van de kinderen volgens KNO-artsen en 35% van de kinderen volgens huisartsen), werden recidiverende bovenste luchtweginfecties (22% en 24% van de kinderen), afwijkende bevindingen bij KNO-onderzoek zoals vergrote tonsillen (42% en 24% van de kinderen) en beslagen en crypteuze tonsillen (29% en 17% van de kinderen), niet-specifieke symptomen zoals lusteloosheid (28% en 19% van de kinderen) en slechte eetlust

(28% en 16% van de kinderen) als belangrijke redenen voor de operatie beschouwd. Obstructieve klachten tijdens de slaap waren bij slechts 11% (KNO-artsen) en 4% (huisartsen) van de kinderen belangrijk in de beslissing tot operatie. Hieruit blijkt dat naast de algemeen geaccepteerde indicaties voor (A)TE (frequent recidiverende tonsillitiden en obstructief slaap apnoesyndroom), indicaties als recidiverende bovenste luchtweginfecties en de bevinding van vergrote- of onrustige tonsillen net zo belangrijk zijn in het besluit van artsen om te verwijzen voor een (A)TE of om een (A)TE te verrichten. We hebben berekend dat voor ongeveer 65% van de kinderen die momenteel in Nederland een (A)TE ondergaan dergelijke indicaties doorslaggevend zijn. Omdat de effectiviteit van adenotonsillectomie voor deze indicaties nog niet is vastgesteld, zal bij deze groep kinderen een gerandomiseerde trial worden uitgevoerd. In Hoofdstuk 4 wordt verslag gedaan van de resultaten van het NATAN onderzoek naar de effectiviteit van adenotonsillectomie bij 300 Nederlandse kinderen van 2 tot 8 jaar die volgens de huidige klinische praktijk in aanmerking kwamen voor ATE. Uitgesloten werden kinderen met frequent recidiverende keelontstekingen (7 of meer keelontstekingen in het voorafgaande jaar; of 5 of meer in elk van de voorafgaande 2 jaren; of 3 of meer in elk van de voorafgaande 3 jaren) of een sterke verdenking op het obstructief slaap-apnoesyndroom (Brouillette score van meer dan 3,5), omdat er onder artsen overeenstemming bestaat dat voor deze indicaties adenotonsillectomie zinvol is. Overige uitsluitingscriteria waren: syndroom van Down, craniofaciale malformatie en gedocumenteerde immunodeficiëntie anders dan IgA- en IgG2-deficiëntie. Bij de randomisatie werden 151 kinderen toegewezen aan de ATE groep en 149 aan de niet-chirurgische (afwachtend beleid) groep. Gedurende de mediane follow-up periode van 22 maanden, hadden kinderen in de ATE groep 2,97 koortsepisoden per persoonsjaar versus 3,18 bij kinderen in de niet-chirurgische groep. Dit betekent dat adenotonsillectomie in vergelijking met een afwachtend beleid het aantal koortsepisoden met 0,21 (95% BI −0,12 tot 0,54) per persoonsjaar verminderde. Kinderen in de adenotonsillectomie groep hadden respectievelijk 0,56 keelontstekingen en 5,47 bovenste luchtweginfecties per persoonsjaar, versus respectievelijk 0,77 keelontstekingen en 6,0 bovenste luchtweginfecties in de niet-chirurgische groep. Dit betekent dat adenotonsillectomie in vergelijking met een afwachtend beleid het aantal keelontstekingen met 0,21 (95% BI 0,06 tot 0,36) per persoonsjaar verminderde en het aantal bovenste luchtweginfecties met 0,53 (95% BI 0,08 tot 0,97) per persoonsjaar. Er werden geen klinisch relevante verschillen gevonden voor gezondheids-gerelateerde kwaliteit van leven. Subgroepanalyses toonden aan dat adenotonsillectomie in vergelijking met een afwachtend beleid iets effectiever was in de subgroep van kinderen met 3 tot 6 keelontstekingen in het jaar voorafgaand aan de studie dan bij kinderen met 0 tot 2 keelontstekingen: kinderen met een voorgeschiedenis van 3 tot 6 keelontstekingen die een ATE ondergingen hadden respectievelijk 1,07 (95% BI 0,56 tot 1,59) koortsepisoden per persoons-

jaar minder en 0,49 (95% BI 0,22 tot 0,75) keelontstekingen per persoonsjaar minder dan kinderen in de niet-chirurgische groep. Voor kinderen met 0 tot 2 keelontstekingen in het jaar voorafgaand aan de trial waren deze verschillen respectievelijk +0,34 (95% BI 0,08 tot 0,77) en –0,03 (95% BI –0,21 tot 0,15) voor koortsepisoden en keelontstekingen per persoonsjaar. Deze resultaten geven aan dat bij kinderen met relatief milde klachten van recidiverende tonsillitiden en/of tonsil- en adenoidhypertrofie en/of recidiverende bovenste luchtweginfecties, de voordelen van een ATE gering zijn in vergelijking met een afwachtend beleid.

In **Hoofdstuk 5** wordt besproken in hoeverre de kinderen die deelnamen aan de trial representatief waren ten opzichte van het relevante klinische domein: dat wil zeggen kinderen die in Nederland een ATE ondergaan. Demografische en ziekte-specifieke karakteristieken werden vergeleken tussen 1) gerandomiseerde kinderen (n=270); 2) kinderen die in aanmerking kwamen voor deelname, maar wier ouders direct al besloten niet deel te nemen aan de trial (n=243), en 3) kinderen die in aanmerking kwamen en wier ouders uitgebreid geïnformeerd waren over de trial door een medewerker van het onderzoek, maar waarbij diezelfde ouders uiteindelijk geen toestemming voor deelname gaven (n=406). Belangrijke karakteristieken die het effect van ATE zouden kunnen beïnvloeden bleken vergelijkbaar: respectievelijk 46,3%, 45% en 46,9% van de kinderen in groep 1, 2 en 3 waren aangemeld voor ATE vanwege recidiverende keelontstekingen; respectievelijk 20,9%, 20,3% en 19,9% had klachten van bovenste luchtwegobstructie; het gemiddelde aantal keelontstekingen in het jaar voorafgaand aan de trial was respectievelijk 4,3, 4,6 en 4,4 episoden voor groep 1, 2 en 3; en de gemiddelde duur van recidiverende keelontstekingen was respectievelijk 14,3, 15,8 en 14,9 maanden. Er werden kleine verschillen gevonden wat betreft eerdere KNO-ingrepen (respectievelijk 22,5%, 21,3% en 12,7%), ademhalingsproblemen gedurende de nacht (respectievelijk 11,7%, 19,6% en 22,1%) en onrustige tonsillen (respectievelijk 79,5%, 81,1% en 88,4%). Deze bevindingen geven aan dat onze trialpopulatie representatief is voor de grote groep kinderen die momenteel een ATE ondergaat in Nederland vanwege relatief milde klachten van recidiverende keelontstekingen of tonsil- en adenoidhypertrofie.

In **Hoofdstuk 6 en 7** worden baseline en follow-up immunoglobulinewaarden gepresenteerd van kinderen die deelnamen aan de trial. Bij de start van het onderzoek waren de immunoglobuline IgA-, IgM-, IgG1- en IgG2- waarden conform aan de leeftijds-gecorrigeerde normaalwaarden bij Nederlandse kinderen of iets verhoogd ten opzichte daarvan. Dit suggereert dat variatie in immunoglobuline gehalten geen belangrijke rol speelt bij de predispositie van kinderen voor keelklachten. Na één jaar follow-up waren de gemiddelde immunoglobulinewaarden afgenomen, maar bleven gelijk aan of hoger dan de normaalwaarden voor de leeftijd, onafhankelijk van de behandeling (ATE versus afwachtend beleid). Slechts IgA daalde statistisch significant meer in de ATE groep dan in de niet-chirurgische groep. Er werd geen

relatie gevonden tussen de immunoglobulinewaarden na 1 jaar follow-up en het aantal keelontstekingen of bovenste luchtweginfecties tijdens het eerste follow-up jaar. Ook bij kinderen die frequent bovenste luchtweginfecties doormaken na een ATE, zijn de immunoglobulinewaarden gelijk aan die van kinderen in de niet-chirurgische groep. Deze gegevens maken aannemelijk dat afname van immunoglobuline gehalte in beide randomisatiegroepen een natuurlijke afname van antigene stimulatie met de leeftijd weerspiegelt. Na een adenotonsillectomie lijkt het resterende mucosa-geassocieerde lymfoïde weefsel (MALT) in staat om de functie van het ontbrekende tonsil- en adenoidweefsel te compenseren.

Hoe kan een KNO-arts bij een kind met keelklachten 'evidence-based' handelen?
In Nederland ondergaat ongeveer 35% van de kinderen een (A)TE vanwege zeer frequente keelontstekingen of een sterke verdenking op OSAS. Dit betekent dat 65% van de kinderen in Nederland de ingreep ondergaat vanwege niet-evidence-based indicaties, zoals minder frequente keelontstekingen of mildere symptomen van adenoid- en tonsilhypertrofie.
De resultaten van onze trial tonen aan dat de voordelen van de ingreep in vergelijking met afwachtend beleid voor deze groep als geheel gering zijn. Er zullen echter zeker kinderen zijn, bij wie de ingreep effectiever is. Zo hebben onze subgroepanalyses aangetoond dat de ingreep effectiever is bij kinderen met 3 tot 6 keelontstekingen in het jaar voorafgaand aan de trial dan bij kinderen met minder frequente keelontstekingen. Niettemin, de voordelen van adenotonsillectomie vergeleken met een afwachtend beleid waren ook in deze eerste groep beperkt.

Het moet worden benadrukt dat de kinderen die momenteel in aanmerking komen voor een ATE, serieuze klachten hebben en dus adequate zorg en begeleiding behoeven. Waaruit zou deze zorg moeten bestaan wanneer wordt besloten niet te opereren?
Antibiotica lijken geen goed alternatief. Ten eerste omdat de meeste bovenste luchtweginfecties door virussen veroorzaakt worden en ten tweede omdat diverse studies hebben aangetoond dat het effect van antibiotica bij recidiverende bovenste luchtweginfecties beperkt is.
Vaccinaties zouden in de toekomst een belangrijke rol kunnen gaan spelen in de preventie van bovenste luchtweginfecties. **Vaccins** tegen virale pathogenen zijn nog volop in ontwikkeling. Tegen de belangrijkste bacteriële veroorzakers van bovenste luchtweginfecties zijn momenteel slechts vaccins tegen Streptococcus pneumoniae commercieel beschikbaar. Ten aanzien van keelontstekingen is er geen gerandomiseerd onderzoek verricht naar de effectiviteit van deze vaccins. Trials naar de effectiviteit van pneumococcen-vaccins ten aanzien van otitis media hebben aangetoond dat na de vaccinatie een verschuiving optrad van serotypes die in het vaccin waren opgenomen naar andere serotypes die niet in het vaccin waren opgenomen. De effectiviteit van deze vaccins was daardoor beperkt.

Het belangrijkste alternatief is een **afwachtend beleid**, waarbij aan ouders en kinderen wordt uitgelegd dat bovenste luchtweginfecties een gunstig natuurlijk beloop kennen en dat chirurgie op de lange termijn maar weinig extra voordeel biedt. Het is belangrijk dat ouders de mogelijke complicaties van bovenste luchtweginfecties kennen en herkennen. Huisartsen, KNO-artsen en ouders moeten goede afspraken maken over het moment wanneer het kind door een arts gezien moet worden. Het is belangrijk dat het kind adequate pijnstilling ontvangt wanneer er sprake is van een keelontsteking. Tenslotte moeten ouders geïnformeerd worden over het effect van beïnvloedbare factoren, zoals roken en de wijze van kinderopvang, op het ontwikkelen van bovenste luchtweginfecties bij hun kind.

Toekomstig onderzoek

Omdat er geen twijfel over bestaat dat er subgroepen van kinderen zijn bij wie adenotonsillectomie effectief is, zou een van de doelen van toekomstig onderzoek kunnen zijn, het individualiseren van de reeds bestaande behandelingsmogelijkheden – adenotonsillectomie of een niet-chirurgisch beleid –. Omdat de kracht van de huidige beschikbare trials te klein is om subgroepen te identificeren is het wenselijk een **IPD meta-analyse** (individuele-patiënten-data-meta-analyse) uit te voeren. Een dergelijke analyse, waarin de data van alle tot nu toe uitgevoerde trials worden samengevoegd, inclusief die van de NATAN trial, is een efficiënte methode om subgroepen te identificeren die een groter effect van de behandeling kunnen hebben.

Prognostisch onderzoek. Als het mogelijk zou zijn kinderen te identificeren met een hoog risico op het recidiveren van bovenste luchtwegklachten, zouden medische interventies speciaal op deze groep kinderen kunnen worden gericht. Momenteel is het echter nog niet mogelijk aan de hand van een model te voorspellen bij welke kinderen bovenste luchtweginfecties een gunstig natuurlijk beloop hebben en bij welke kinderen de klachten blijven voortduren.

Etiologisch onderzoek. Het is bekend dat recidiverende bovenste luchtweginfecties complex en multifactorieel bepaald zijn en worden veroorzaakt door interactie tussen gastheerfactoren, zoals genetische predispositie, leeftijd en immunologische respons, en omgevingsfactoren, zoals microbiologische belasting (viraal en bacterieel), het aantal broers/zussen, kinderdagverblijf en seizoen. De relatieve invloed van en de interactie tussen de verschillende bekende etiologische factoren is onvoldoende bekend. Het verkrijgen van meer inzicht in de etiologie van bovenste luchtweginfecties is essentieel, om effectievere **preventieve en therapeutische maatregelen** te ontwikkelen die zowel het aantal als de ernst van bovenste luchtweginfecties kunnen doen verminderen. Het meeste succes is te verwachten van interventies die gericht zijn op de interacties tussen verschillende pathogene factoren.

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Antonius Ziekenhuis in Nieuwegein, Vlietland Ziekenhuis in Schiedam en Vlaardingen, Wilhelmina Kinderziekenhuis/UMC Utrecht in Utrecht, IJsselmeer Ziekenhuis in Lelystad, Ziekenhuis Gooi Noord in Blaricum) dank ik voor hun betrokkenheid bij het NATAN project en het verwijzen van kinderen voor deelname.

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Curriculum vitae

Emma Henriëtte van den Akker werd op 16 januari 1970 geboren te Amsterdam. In 1988 behaalde zij het VWO diploma aan het Vossius Gymnasium te Amsterdam. Vervolgens woonde zij een jaar in Londen alwaar zij het Cambridge Proficiency examen haalde.
In 1989 begon zij met de studie Geneeskunde aan de Rijksuniversiteit Gent in België. Het artsexamen werd behaald in 1996. Nadien volgde een korte periode als arts-assistent chirurgie en als poortarts in het St. Barbara ziekenhuis te Lanaken in België (Dr. P. Danneels). De opleiding tot KNO-arts werd van 1997 tot 2004 gevolgd in het Universitair Medisch Centrum Utrecht (Opleiders: Prof. dr. G.J. Hordijk en Prof. dr. E.H. Huizing). De B-opleiding werd gevolgd in de Gelre Ziekenhuizen, locatie Lukas te Apeldoorn (Opleider: J.B. Antvelink). Het onderzoek dat heeft geleid tot dit proefschrift werd tijdens de opleidingstijd uitgevoerd. Sinds april 2004 is de auteur werkzaam als KNO-arts in het Meander Medisch Centrum te Amersfoort, in de maatschap SONOOR.
De auteur is gehuwd met Raphaël Panhuysen. Zij hebben een zoon, genaamd Tijmen.